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(54) Title: TREATMENT OF MIGRAINE AND HEADACHES

(57) **Abstract:** Treatment of migraine and headaches can be performed by the use of potassium channel blockers. The potassium channel blockers block KATp channels and/or BK channels. Also disclosed are the potassium channel blockers in the manufacture of a medicament for the treatment of migraine or headache. In respect of the KATP channels the potassium channel blocker may blocks channels with SUR2B subunits e.g. channels with SUR2B and Kir6.1 subunits. In respect of BKGa channels, any of the α - or β -subunits of the channels may be blocked by a potassium channel blocke in the treatment of migraine and headaches.



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Title

Treatment of migraine and headaches

- 5 All patent and non-patent references cited in the present application, are also hereby incorporated by reference in their entirety.

Field of invention

- 10 The present invention relates to the use of potassium channel blockers in the manufacture of a medicament for the treatment of migraine or headache. The potassium channel blockers block K_{ATP} channels and/or BK channels.

Background of invention

- 15 K_{ATP} and BK channels play key roles in several vital physiological functions. The K_{ATP} channels have a role in insulin secretion by the pancreas; protection of cardiac muscle during ischaemia and hypoxic vasodilatation of arterial smooth muscle; and play an important role in sepsis-induced vascular hyporeactivity as well as the development of septic shock.
- 20

Migraine and other headaches

- 25 A migraine headache is a form of vascular headache. Migraine has been defined by the international headache society in its classification of headache disorders, 2nd edition (IHCD-2). Migraine in this application is defined according to IHCD-2 (Headache_Classification_Subcommittee_of_the_International_Headache_Society (2004). "The International Classification of Headache Disorders: 2nd edition." Cephalalgia 24 Suppl 1: 9-160).

- 30 Migraine headache is caused by a combination of vasodilatation (enlargement of blood vessels) and the release of chemicals from nerve fibres that coil around the blood vessels. During a migraine attack, the temporal, dural and pial arteries enlarge. Enlargement of the arteries stretches the nerves that coil around the arteries and cause the nerves to release chemicals. Among these chemicals are calci-
- 35

tonin gene-related peptide and other peptides and monoamines. They cause inflammation, pain, and further enlargement of the arteries. The increasing enlargement of the arteries magnifies the pain.

- 5 Migraine attacks are commonly associated with nausea, vomiting, diarrhoea and delayed emptying of the stomach into the small intestine which prevents oral medications from entering the intestine and being absorbed. The impaired absorption of oral medications is a common reason for the ineffectiveness of medications taken to treat migraine headaches, to the attack is also associated with pallor of the skin as
10 well as cold hands and feet and increased sensitivity to light and sound sensitivity as well as blurred vision.

Different factors can trigger a migraine or make it worse. Headache inducing or increasing factors can be things a person eat, smell, hear or see. Among headache
15 triggers are:

- Stress and time pressure, major hassles, major losses, anger and conflict.
- Smells and fumes, tobacco smoke, light glare or dazzle, weather changes.
- Monthly periods, birth control pills, oestrogen therapy.
- Too much, too little or interrupted sleep.
- 20 • Hunger, fasting, specific foods or beverages.
- Excessive activity.
- Certain medicines may cause migraine. Among these are Cimetidine (e.g. brand name: Tagamet), Estrogens (including birth control pills), Fenfluramine (e.g. brand name: Pondimin), Indomethacin (e.g. brand name: Indocin),
25 Nifedipine (e.g. brand name: Adalat, Procardia), Nitroglycerin (e.g. brand name: Nitrostat), Pain medicines in general (either overuse or withdrawal from them), Reserpine-containing medicines (e.g. brand names: Ser-ap-Es, Hydropres, Regroton) and Theophylline (e.g. brand name: TheoDur, Theo-24).

30 The ICHD-2 defines, in addition to migraine definitions to all other headaches. When this application refers to other headaches it means all headaches defined in IHCD-2 (Headache_Classification_Subcommittee_of_the_International_Headache_Society (2004). "The International Classification of Headache Disorders: 2nd edition." Cephalalgia 24 Suppl 1: 9-160).

Drug therapy

In migraine, drug therapy can be used in two ways: to prevent the attack or to relieve symptoms after the headache occurs.

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If a person suffers infrequently from migraines, drugs can be taken at the first sign of a headache to stop or ease the pain.

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If a person suffer frequently from migraines, both pain relief and prophylactic measures may be used. For many years ergotamine was the only drug available to address severe migraine pain relief. Now there are newer, more effective drugs available - imitrex, Zomig, Maxalt, Ameg are some choices for relief of the pain of migraine. For headaches that occur three or more times a month, preventive treatment is often recommended. Drugs used to prevent migraine include beta blockers, antiepileptics, NSAID's and amine antagonists e.g. methysergide, which counteracts blood vessels by blocking the activity of serotonin at one type of receptor while mimicking the effect of serotonin at another type of receptor. It is believed that this last effect makes extended blood vessels tighten and migraine symptoms diminishes; propranolol, which stops blood vessel dilation and amitriptyline, an antidepressant.

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The medicaments developed to date to prevent or stop migraine have different effects on different persons, including different side-effects. Therefore there is a continued need to develop new medicaments for treating migraine.

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Potassium channel openers and blockers can be used in the treatment of different diseases.

Summary of invention

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The present invention relates to the use of potassium channel blockers in the manufacture of a medicament for the treatment of migraine or other headaches. The potassium channel blockers block K_{ATP} channels and/or BK_{Ca} channels.

35

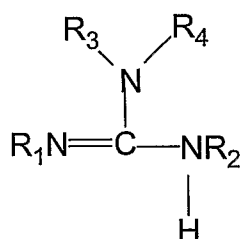
By blocking the K_{ATP} channels and/or BK_{Ca} channels the dilatation of arteries especially within the brain of an individual are reduced or inhibited.

In respect of the K_{ATP} channels the potassium channel blocker preferably blocks channels with SUR2B subunits, and more preferably channels with SUR2B and Kir6.1 subunits.

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Preferred is a specific potassium channel blocker which blocks K_{ATP} channels with SUR2B subunits, but which does not block K_{ATP} channels with other SUR-subunits.

A preferred K_{ATP} channel blocker is a compound of the formula



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wherein R_1 , R_2 , R_3 and R_4 are individually selected from the group of adamantyl, hydrogen, alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, phenyl, phenalkyl where alkyl is one to three carbon atoms, inclusive, and mono- or di-substituted phenyl or phenyl moiety of the phenalkyl

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wherein the substituents are the same or different and are selected from the group consisting of alkyl of one to three carbon atoms, inclusive, halogen, trifluoromethyl and alkoxy of from one to three carbon atoms, inclusive, halo, and trifluoromethyl; hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur. When the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms. When the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof.

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In respect of the BK_{Ca} channels, any of the α - or β -subunits of the channels may be blocked by a potassium channel blocker.

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A preferred BK_{Ca} channel blocker is iberiotoxin or a related compound.

Also disclosed are methods for identifying potassium channel blockers which block K_{ATP} channels and/or BK_{Ca} channels. The methods are based on affecting segments of arteries or homogenised tissue which is known to include K_{ATP} channels and/or BK_{Ca} channels with potassium channel openers followed by affecting with possible blockers of these potassium channels.

K_{ATP} -channel blockers and/or BK_{Ca} -channel blockers can be utilised to produce a pharmaceutical composition comprising an effective amount of at least one K_{ATP} -channel blocker and/or an effective amount of at least one BK_{Ca} -channel blocker where further information of the channel blockers are specified herein. For the pharmaceutical composition also a salt of the at least one K_{ATP} -channel blocker and/or the at least one BK_{Ca} -channel blocker can be used, optionally further comprising a pharmaceutically acceptable carrier substance.

Also disclosed is a method for treating or alleviating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to blockade of the K_{ATP} channels and/or of the BK_{Ca} -channels, the method comprises administering to such a living animal body a therapeutically-effective amount of a K_{ATP} -channel blocker and/or of the BK_{Ca} -channel blocker as further described herein.

Further disclosed is a method for identifying a K_{ATP} -blocker that blocks K_{ATP} -channels or for identifying a BK_{Ca} -channel blocker that blocks BK_{Ca} -channels, where the method comprises: obtaining a compound being a possible K_{ATP} -blocker; obtaining isolated cerebral and/or dural arteries of an animal; dividing said arteries into pre-determined segments; placing said divided arteries into a buffer composition in a tissue bath; affecting said cerebral and/or dural arteries with a K_{ATP} -channel opener by addition of said K_{ATP} -channel opener to the buffer composition, whereby said K_{ATP} -channel opener induce increased diameter/relaxation of the arteries; affecting said K_{ATP} -channel opener induced cerebral and/or dural arteries with said possible K_{ATP} -blocker by addition of said possible K_{ATP} -channel blocker to the buffer composition; determining the effect of said possible K_{ATP} -blocker on the diameter of said K_{ATP} -channel opener induced arteries, and wherein said possible K_{ATP} -blocker is determined to be a K_{ATP} -blocker when the diameter of said K_{ATP} -channel opener induced response in the isolated arteries is reduced by said possible K_{ATP} -blocker.

Yet further disclosed is a method for identifying a K_{ATP} -channel blocker that blocks K_{ATP} -channels or for identifying a BK_{Ca} -channel blocker that blocks BK_{Ca} -channels, where the method comprises: obtaining pancreas, heart and/or cerebral tissues of an animal in respect of identifying K_{ATP} -channel blockers and peripheral arteries or veins, intestine, kidney, pancreas, heart and/or cerebral arteries of an animal in respect of identifying BK_{Ca} -channel blockers; homogenising said tissues; sieving said homogenised tissues to obtain a filtrate; ultra-centrifugating said filtrate to obtain a pellet; resuspending said pellet, to obtain a membrane preparation including membranes from said tissues; incubating said membrane preparation with a ^3H -labelled K_{ATP} -channel agent or a ^3H -labelled BK_{Ca} -channel agent, whereby the ^3H -labelled K_{ATP} -channel agent or ^3H -labelled BK_{Ca} -channel agent binds to said membranes; filtrating under vacuum over a filter said membrane preparation incubated with said ^3H -labelled K_{ATP} -channel agent or ^3H -labelled BK_{Ca} -channel agent, whereby said membranes in said membrane preparation is deposited on said filter; washing said filter; counting the amount of ^3H -labelled K_{ATP} -channel agent or ^3H -labelled BK_{Ca} -channel agent on said filter, hereby obtaining a standard signal; incubating a second membrane with a possible K_{ATP} -channel blocker or a possible BK_{Ca} -channel blocker, performing filtration and washing steps with said second membrane to obtain an inhibition signal; comparing said inhibition signal with said standard signal and hereby determining the displacing properties of said possible K_{ATP} -channel blocker or BK_{Ca} -channel blocker, and wherein said possible K_{ATP} -blocker or BK_{Ca} -channel blocker is determined to be a K_{ATP} -blocker or BK_{Ca} -channel blocker when said inhibition signal is less than said standard signal.

Description of figures

Figure 1. Concentration-response curves for P-1075 in rat basilar and middle cerebral arteries in absence and in presence of PNU37883A 10^{-8} , 3×10^{-8} M and 10^{-7} M. Values are given as means $\pm$ S.E.M.

Detailed description of the invention

In one aspect of the present invention at least one K_{ATP} -channel blocker is used for the manufacture of a medicament for treatment or alleviation of migraine and/or other headaches.

A K_{ATP} -channel blocker is a blocker of a K_{ATP} -channel. The K_{ATP} -channel blockers used for the manufacture of the medicament can be any K_{ATP} -channel blocker, and are not limited to the K_{ATP} -channel blockers mentioned herein. Details of K_{ATP} -channels and K_{ATP} -channel blockers are listed herein below.

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In another aspect of the present invention at least one BK_{Ca} -channel blocker is used for the manufacture of a medicament for treatment or alleviation of migraine and/or other headaches.

10

A BK_{Ca} -channel blocker is a blocker of a BK_{Ca} -channel. The BK_{Ca} -channel blockers used for the manufacture of the medicament can be any BK_{Ca} -channel blocker, and are not limited to the BK_{Ca} -channel blockers mentioned herein. Details of BK_{Ca} -channels and BK_{Ca} -channel blockers are listed herein below.

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Potassium channels

Potassium channels are integral membrane proteins that mediate the passage of potassium ions across lipid membranes down their electrochemical gradients.

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Generally, potassium channels have been grouped into two families: the voltage-gated potassium channels and the inwardly-rectifying potassium channels. Potassium channels are comprised of four pore-lining α -subunits and additional auxiliary β -subunits that may regulate channel function or targeting. Voltage-gated potassium channels have six trans-membrane segments and are intrinsically sensitive to changes in the membrane potential, while inwardly-rectifying potassium channels have two trans-membrane segments and do not contain intrinsic voltage sensors.

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Many peptide toxins from venomous species, together with several drugs act as blockers by plugging the channel pore. Other drugs work by shifting the sensitivity of channels to voltage, calcium concentrations, or other modulating factors. Potassium channel modulators can thus be potassium channel openers or potassium channel blockers.

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Inwardly-rectifying potassium channels

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Inwardly-rectifying potassium channels are tetramers, whose α -subunits each contain two trans-membrane segments, M1 and M2 with a P loop in between. These potassium channels have two main functions, 1) to stabilize the resting membrane potential near E_K and 2) to mediate potassium transport across membranes. Inwardly-rectifying potassium channels, as the name suggests, allow more potassium ions to enter the cell than leave the cell.

Certain subfamilies of inwardly-rectifying potassium channels are specialized to respond to certain effectors.

At least seven families of inwardly-rectifying potassium channels has been identified: Kir1.0, Kir2.0, Kir3.0, Kir4.0, Kir5.0, Kir6.0, and Kir7.0. The Kir6.0 family associates with the sulphonylurea receptor (SUR), a member of the ABC superfamily, to form K_{ATP} -channels.

The ATP-sensitive potassium channels, K_{ATP} -channels, are located in the pancreas, smooth muscle, heart, brain and skeletal muscles.

One key characteristic of ATP-sensitive K^+ channels (K_{ATP}) is that their activity may reflect the metabolic state of the cell. These K^+ channels are sensitive to intracellular ATP, which inhibits channel activity. Dissociation of ATP from the channel results in channel opening and membrane hyperpolarization. Other metabolically related stimuli, including reductions in PO_2 or pH, also open the channel and produce vasorelaxation. It is estimated that a few hundred K_{ATP} channels are present per cell in arteries. The number is much less than that for calcium-activated K^+ channels.

K_{ATP} channels have several physiological roles. The channel is activated by a number of vasodilators, and the associated membrane hyperpolarization causes part of the resulting vasodilation in many cases. The K_{ATP} channel may also be inhibited by vasoconstrictors which would tend to cause depolarization and constriction. The channel is involved in the metabolic regulation of blood flow; it is activated in conditions of increased blood demand, e.g., in hypoxia, either by release of vasodilators from the surrounding tissue or as a direct result of hypoxia on the vascular smooth muscle cells. Finally, the channel may be active in the resting state, because inhibi-

tion of K_{ATP} channels can lead to increased resistance to blood flow in some vascular beds.

In the K_{ATP} channels the Kir6.0 family consists of the two isoforms Kir6.1 or Kir6.2 which are associated with one of the three main isoforms of the sulphonylurea receptor: SUR1, SUR2A or SUR2B. Thus the following composition of Kir and SUR can exist: Kir6.1 associated with SUR1; Kir6.1 associated with SUR2A; Kir6.1 associated with SUR2B; Kir6.2 associated with SUR1; Kir6.2 associated with SUR2A; Kir6.2 associated with SUR2B.

The types of K_{ATP} channels are tissue specific, the pancreatic K_{ATP} channel is Kir6.2/SUR1; the cardiac channel is Kir6.2/SUR2A and the vascular channel is attributed to Kir6.1/SUR2B.

In one embodiment the at least one K_{ATP} -channel blocker blocks K_{ATP} -channels comprising at least one of the subunits SUR1, SUR2A, SUR2B, kir6.1 and kir6.2.

In a preferred embodiment of the present invention at least one K_{ATP} -channel blocker blocks K_{ATP} -channels comprising at least one of the subunits SUR2B, kir6.1 and kir6.2.

In one embodiment the K_{ATP} channel blocker is a blocker of K_{ATP} channels with SUR2A or SUR2B subunits. The compositions can be Kir6.1 associated with SUR2A; Kir6.1 associated with SUR2B; Kir6.2 associated with SUR2A; Kir6.2 associated with SUR2B. Preferred is K_{ATP} channel blockers that blocks SUR2B. SUR2B may be associated with Kir6.1 or Kir6.2. Most preferred is K_{ATP} channel blockers which block channels of Kir6.1 associated to SUR2B.

In an embodiment the K_{ATP} channel blocker has a higher affinity for SUR2A and/or SUR2B than for SUR1. Preferred is when the K_{ATP} channel blocker has a higher affinity for SUR2B than for SUR1A and SUR2A. A low binding effect of the K_{ATP} channel blocker on SUR2B may or may not be accepted.

The K_{ATP} channel blocker described herein may also have a higher affinity for a system of channels comprising a major amount of channels with Kir6.1 associated with

SUR2B and a minor amount of channels with Kir6.1 associated with SUR1. The relation between the amount of channels of Kir6.1 associated with SUR2B and channels of Kir6.1 associated with SUR1 is at least 2:1; e.g. at least 5:1; such as at least 10:1; e.g. at least 15:1; such as at least 20:1; e.g. at least 25:1; such as at least 30:1; e.g. at least 35:1; such as at least 40:1; e.g. at least 45:1; such as at least 50:1; e.g. at least 75:1; such as at least 100:1; e.g. at least 150:1; such as at least 200:1.

A medicament for the treatment of migraine or headache may be a combination of channel blockers. This combination may be at least one K_{ATP} channel blocker and at least one BK-channel blocker. The combination may also be different K_{ATP} channel blockers blocking the same type of K_{ATP} channel, these types are described elsewhere herein, or the combination may be different K_{ATP} channel blockers blocking different types of K_{ATP} channels.

The different types of K_{ATP} channels, on which a combination of channel blockers are effective, may be Kir6.1 associated with SUR2B and Kir6.2 associated with SUR1; or Kir6.1 associated with SUR2B and of Kir6.1 associated with SUR1.

The channel blockers described herein may act upon K_{ATP} channels located to the vascular smooth muscle cells of e.g. middle cerebral and/or basilar arteries. Preferred are channel blockers blocking channels of Kir6.1 associated with SUR2B within the vascular smooth muscle cells of the middle cerebral and/or basilar arteries.

The potassium channel blocker glibenclamide is used in the treatment of diabetes. Glibenclamide in the concentration used for treatment of diabetes does not have an effect on migraine. Glibenclamide has a blocking effect on the K_{ATP} channels, but it has an affinity that is 10-20 folds lower for SUR2B than for SUR1.

In another embodiment the K_{ATP} channel blocker has a higher affinity for SUR2B than for SUR2A and SUR1. A low effect on SUR2A or SUR1 may or may not be accepted. The K_{ATP} channel blocker has an affinity to SUR2B that is higher than to SUR2A and SUR1. The affinity to SUR2B is at least 3 times higher than to SUR2A and/or SUR1, such as equal or above 5, such as equal or above 10, such as equal

or above 15, such as equal or above 20, such as equal or above 25, such as equal or above 30, such as equal or above 35, such as equal or above 40, such as equal or above 45, such as equal or above 50, such as equal or above 55, such as equal or above 60, such as equal or above 65, such as equal or above 70, such as equal or above 75, such as equal or above 80, such as equal or above 85, such as equal or above 90, such as equal or above 95, such as equal or above 100, such as equal or above 105, such as equal or above 110, such as equal or above 115, such as equal or above 120, such as equal or above 125, such as equal or above 150, such as equal or above 175, such as equal or above 200, such as equal or above 225, such as equal or above 250, such as equal or above 275, such as equal or above 300, such as equal or above 325, such as equal or above 350, such as equal or above 375, such as equal or above 400, such as equal or above 425, such as equal or above 450, such as equal or above 475, such as equal or above 500.

15 In a preferred embodiment, in order to avoid side effects, the K_{ATP} -channel blocker should in the doses given, not block SUR1 and SUR2A subunits.

In one embodiment the K_{ATP} channel blocker blocks the K_{ATP} channel by binding to the SUR1, SUR2A or SUR2B subunit alone or one of these SUR-subunits together with Kir6.1 or Kir6.2. Preferred is when the K_{ATP} channel blocker acts by binding to SUR2B alone or to SUR2B and Kir6.1 in combination.

25 In an embodiment the K_{ATP} -channel blocker binds specific to the K_{ATP} -channel with a SUR2B subunit and the K_{ATP} -channel blocker binds at least 3 times more specific than a non-specific K_{ATP} -channel blocker.

A non-specific blocker will bind with equal affinity to K_{ATP} -channels consisting of SUR2B, SUR2A and/or SUR1 subunits in combination with Kir6.1 and/or Kir6.2.

30 In a further embodiment the K_{ATP} -channel blocker inhibits K_{ATP} -channel openers to act with the K_{ATP} -channels.

The inhibition of the K_{ATP} -channel blocker on the capacity of K_{ATP} -channel openers is at least 10% of the binding affinity of the K_{ATP} -channel openers, such as at least 20%, e.g. at least 30%, such as at least 40%, e.g. at least 50%, such as at least

60%, e.g. at least 70%, such as at least 80%, e.g. at least 90%, such as substantially 100%.

5 In an embodiment the K_{ATP} -channel blocker when used reduces or inhibits dilatation of arteries, arterioles, capillary system, and/or veins.

In the artery the K_{ATP} -channel blocker inhibits the vasorelaxation response to a K_{ATP} -channel opener.

10 In a preferred embodiment the K_{ATP} -channel blocker when used reduces or inhibits dilatation of arteries, arterioles, capillary system, veins and/or venaroles within the head of an individual.

15 In an embodiment the K_{ATP} -channel blocker has a tissue selectivity characterised by a higher selectivity to K_{ATP} -channels within the brain than to K_{ATP} -channel in the vascular tissue, pancreatic tissue and cardiac tissue.

20 The affinity to K_{ATP} -channels within the brain than to K_{ATP} -channels in the vascular tissue, pancreatic tissue and/or cardiac tissue is equal or above 3, such as equal or above 5, such as equal or above 10, such as equal or above 15, such as equal or above 20, such as equal or above 25, such as equal or above 30, such as equal or above 35, such as equal or above 40, such as equal or above 45, such as equal or above 50, such as equal or above 55, such as equal or above 60, such as equal or above 65, such as equal or above 70, such as equal or above 75, such as equal or above 80, such as equal or above 85, such as equal or above 90, such as equal or above 95, such as equal or above 100, such as equal or above 105, such as equal or above 110, such as equal or above 115, such as equal or above 120, such as equal or above 125, such as equal or above 150, such as equal or above 175, such as equal or above 200, such as equal or above 225, such as equal or above 250, such as equal or above 275, such as equal or above 300, such as equal or above 325, such as equal or above 350, such as equal or above 375, such as equal or above 400, such as equal or above 425, such as equal or above 450, such as equal or above 475, such as equal or above 500.

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In an embodiment the K_{ATP} -channel blocker binds with a significantly higher affinity equal or above 1.5 to K_{ATP} channels consisting of the SUR2B subunit in combination with Kir6.1 subunits than K_{ATP} -channels consisting of SUR 1 and SUR2A subunits in combination with Kir6.1 and/or Kir6.2. The affinity to the SUR2B/Kir6.1 channel compared to the channels with SUR1 or SUR2A subunits is equal or above 3, such as equal or above 5, such as equal or above 10, such as equal or above 15, such as equal or above 20, such as equal or above 25, such as equal or above 30, such as equal or above 35, such as equal or above 40, such as equal or above 45, such as equal or above 50, such as equal or above 55, such as equal or above 60, such as equal or above 65, such as equal or above 70, such as equal or above 75, such as equal or above 80, such as equal or above 85, such as equal or above 90, such as equal or above 95, such as equal or above 100, such as equal or above 105, such as equal or above 110, such as equal or above 115, such as equal or above 120, such as equal or above 125, such as equal or above 150, such as equal or above 175, such as equal or above 200, such as equal or above 225, such as equal or above 250, such as equal or above 275, such as equal or above 300, such as equal or above 325, such as equal or above 350, such as equal or above 375, such as equal or above 400, such as equal or above 425, such as equal or above 450, such as equal or above 475, such as equal or above 500.

In an embodiment the K_{ATP} channel blocker is used for the manufacture of a medicament, where the K_{ATP} channel blocker is in a concentration corresponding to a concentration of between 1 nM ml^{-1} serum and $500\text{ }\mu\text{M ml}^{-1}$ serum of the individual to be treated with the medicament. The concentration may be between 1 nM ml^{-1} and 10 nM ml^{-1} , such as between 10 nM ml^{-1} and 100 nM ml^{-1} , such as between 100 nM ml^{-1} and 200 nM ml^{-1} , such as between 200 nM ml^{-1} and 300 nM ml^{-1} , such as between 300 nM ml^{-1} and 400 nM ml^{-1} , such as between 400 nM ml^{-1} and 500 nM ml^{-1} , such as between 500 nM ml^{-1} and 600 nM ml^{-1} , such as between 600 nM ml^{-1} and 700 nM ml^{-1} , such as between 700 nM ml^{-1} and 800 nM ml^{-1} , such as between 800 nM ml^{-1} and 1000 nM ml^{-1} , such as between $1\text{ }\mu\text{M ml}^{-1}$ and $100\text{ }\mu\text{M ml}^{-1}$, such as between $100\text{ }\mu\text{M ml}^{-1}$ and $200\text{ }\mu\text{M ml}^{-1}$, such as between $200\text{ }\mu\text{M ml}^{-1}$ and $300\text{ }\mu\text{M ml}^{-1}$, such as between $300\text{ }\mu\text{M ml}^{-1}$ and $400\text{ }\mu\text{M ml}^{-1}$, such as between $400\text{ }\mu\text{M ml}^{-1}$ and $500\text{ }\mu\text{M ml}^{-1}$.

The K_{ATP} channel blocker used for the manufacture of a medicament for the treatment or alleviation of migraine and/or headache can be selected from the list: 2,3-Butanedione monoxime; 4-aminopyridine (4-AP); 5-Hydroxydecanoate; 7-nitroindazole; 8-oxo-berberine; A-184209; Acecainide; Adenosine (ATP); Aflatrem; Agatoxin, ω -type (ω -Agatoxin); Agitoxin-1; Agitoxin-2; Agitoxin-3; AL 275; Alinidine ST 567; Almokalant H 234/09; Alpha-dendrotoxin; AM 92016; Ambasilide; Ambasilide LU 47110; AN 132; Antioxidants; Apamin; ARH 050642; ATI 2042; ATP; AWD 12-260; AWD 160275; AWD 23-111; AZD 7009; AZDF 265; Azimilide; Barium chloride; Bay K8644 (R)-(+)-form; BDS-I; BDS-II; Bepridil; Berlambine; Bertosamil; Beta-bungarotoxin (beta-BuTX); Beta-dendrotoxin; BIIA 0388; BMS 208782; BMS 208783; BRBI 28; Bretylium; BRL 32872; Bromide dendrotoxin; BTS 67582; Bupivacaine; Carsatrin Succinate RWJ 24517; Caryachine; CGX 1007; Changrolin pyro-
 zoline; Charybdotoxin; Charylotoxin; CHF 1522 Cyclo-dextrin complex of glibenclamide; Chlorpropamide; Chromanol 293 isomer; Chromanol 293B; Cibenzoline; Ciclazindol; Clamikalant HMR 1098; Clamikalant HMR 1883; Clausenamide (- form); Clausenamide (racemic); Clofilium LY 150378; Clofilium tosylate; Clotrimazole; Clotrimazole; CNS 1237; CP 308408; CP 339818; CP 366660; CP 92713; CPU 86017; Cyanoguanidine; Dendrotoxin (DTX); Dendrotoxin I (DTX-I); Dendrotoxin K (DTX-K); Dequalinium chloride; Dexsotalol BMY; 057631D d-sotalol; Dicentrine; Dimethyl sulfoxide; DKAH 269; DMP 543; Dofetilide; DPC 543; DPI 201106; Drone-
 darone SR 33589; DTX, α -type (α -DTX); DTX, β -type (β -DTX); DTX, γ -type (γ -DTX); DTX, δ -type (δ -DTX); E-4031; Efaroxan; EGIS 7229; Englitazone; Ersentilide (+/- form); Ersentilide (S-form); Ethanol; Evodiamine (S); Fampridine 4-
 aminopyridine EL 970; Fosinoprilat; Gamma-dendrotoxin; GEA 857; Glemanserin MDL 11939; GLG V 13; Glibenclamide; Glimepiride; Glipizide (GLP); Glipizide K 4024; Glipizide TK 1320; Glucagons antagonists; Glybenclamide; Glyburide; Guanethidine; Guanidinium moieties; GYKI 16638; HA 7; HMR 1372; HMR 1402; HMR 1556; HMR 1883; Hydroxy; Iberiotoxin; Ibutilide; Ibutilide U 70226; ICA 17043; ICI 181037; IK Channel Blocker; IMID-1M; IMID-26F; IMID-4F; IMID-4F hydrochlo-
 ride; Imidazoline moieties; Ipazilide WIN 54177; Ipidacrine NIK 247; Ivabradine; JKL 1073A oxy-berberine; JTV 519; Kaliotoxin; KCB 328; KMC IV 84; KW 3407; L 691121; L 702958; L 706000; L 735821; L 742084; L 768673; L755860 and related compounds; Levosemotiadil SA 3212; Levosemotiadil SD 3212; Limbatoxin; Limbatustoxin; Liriodenine; Lq2; LQE 908 Pinokalant; LY 190147; LY 97241; Margatoxin;

Mitiglinide KAD 1229 S-21403; MK 499; N 3601; N-allyl secoboldine; Nateglinide; Nateglinide AY 4166; Neuropeptide Y; Nibentan; Nifekalant MS 551; Niguldipine hydrochloride S(+)-form; NIP 142; NOS inhibitors; Noxiustoxin; NS 004; NS 1546; OPC 88117; ORG 20781; Pandinotoxin-K α ; Paspalitrem; Paxilline; PD 157667; 5 Penitrem A; PGE 844384; Phencyclidine; Phentolamine; Phentolamine; Pirmenol Cl 845; Pirocixan; PNU 18177A; PNU 37883A; PNU 89692; PNU 94126; PNU 94158; PNU 94563; PNU 94750; PNU 96179; PNU 96293; PNU 97025E; PNU 99963; Pyrido triazoles; Quinidine; Quinine; Quinine hemisulfate salt; Repaglinide AGEE 623; Repaglinide NN 623; Repaglinide; Rimonabant SR 141716; Risotilide; Ro- 10 034563; Ropivacaine AL 281; Ropivacaine LEA 103; RP 58866; RP 66784 RSD 1000; RSD 1019; Rutaecarpine; RWJ 28810; RX 871024; S 16260; S 9947; Salicylaldoxime; Saxitoxin; SB 237376; Scyllatoxin; SDZ DNJ 608; Sematilide; Sematilide CK 1752; Sematilide ZK 110516; Sinominine; Sodium 5-hydroxydecanoate; Sotalol; SPM 928; Spriadoiline; SSR 149744B; Stichodactyla toxin; Sulfonylureas; TEA (tetraethylammonium); Tedisamil; Tedisamil KC 8857; Terikalant RP 62719; Tertiapin; 15 Tertiapin-Q; Tetraethylammonium chloride; Tetraethylammonium ions; Tetrodotoxin; TH 9121; TH 9122; Tityustoxin K; Tityustoxin-K α ; TMB-8; TN 871; Tolazamide; Tolbutamide; Toxin based therapeutics BRI 6906; TRAM 30; Troglitazone; U 37883A; U 50488H; U-37883A; U-45194A; UCL 1439; UCL 1530; UCL 1559; UCL 1608; UCL 1684; UK 66914; UK 78282; WAY 123223; WAY 123398; WIN 17317-3; 20 WIN 61773; XE 991; Y 39677; YM 026; YM 19348 Racemate; YM 193489-R; YM 193489-S; YT 1; Zatebradine; ZM 181037; ZM 181037; ZM 244085.

25 The medicament may be formulated in any suitable manner as described below.

The compounds mentioned above can be used individually as the K_{ATP}-channel blocker or two or more compounds can be incorporated into the medicament.

30 In one embodiment the K_{ATP} channels to be blocked by the K_{ATP}-channel blocker as described herein, are located in or in connection to vascular tissue.

In a preferred embodiment K_{ATP} channels to be blocked by the K_{ATP}-channel blocker are located in or in connection to blood vessels. Blood vessels of the brain are preferred.

The K_{ATP} channels to be blocked by the K_{ATP} -channel blocker are located in or in connection to blood vessels in the brain, these blood vessels may be selected from, but are not limited to the group of vertebral arteries, common carotid arteries, external carotid arteries, internal carotid arteries, anterior communicating arteries, anterior cerebral arteries, middle cerebral arteries, posterior communicating arteries, posterior cerebral arteries, superior cerebellar arteries, anterior inferior cerebellar arteries, basilar arteries, precuneal arteries, paracentral artery, pericallosal arteries, callosomarginal arteries, frontopolar arteries, medial orbitofrontal arteries, posterior temporal arteries, angular arteries, posterior parietal arteries, anterior parietal arteries, central arteries, precentral arteries, ascending frontal arteries, lateral orbitofrontal arteries, anterior temporal arteries, middle temporal arteries, anterior inferior cerebellar arteries, posterior temporal arteries, calcarine arteries, parietooccipital arteries, posterior pericallosal arteries, medial lenticulostriate arteries, lateral lenticulostriate arteries.

15

In one embodiment the K_{ATP} channels to be blocked by the K_{ATP} -channel blocker are located in or in connection to any kind of cerebral and/or dural arteries.

20

In another embodiment the K_{ATP} channels are located in or in connection to arteries, arterioles, capillary system, veins and/or venaroles within the head of an individual.

25

In a preferred embodiment the K_{ATP} channels to be blocked by the K_{ATP} -channel blocker are located in or in connection to any kind of arteries within the brain, preferred are cerebral and/or dural arteries within the brain.

30

In a preferred embodiment the K_{ATP} channels to be blocked by the K_{ATP} -channel blocker are located to the smooth muscle cells of the vessels, and/or to the endothelial cells and/or perivascular nerve endings.

The perivascular nerve endings may be of sympathetic, parasympathetic or sensory origin.

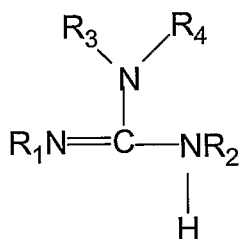
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In one embodiment of the invention the K_{ATP} -channel blocker is used for treatment of migraine, where said treatment is prophylactic and/or acute. The person skilled in the art knows of prophylactic and/or acute treatment of migraine.

In another embodiment of the invention the K_{ATP} -channel blocker is used for treatment of migraine, where said treatment is systemic.

5 In an embodiment the K_{ATP} -channel blocker is a morpholinoguanidine.

In a preferred embodiment the said K_{ATP} -channel blocker is a compound of the formula



10 wherein R_1 , R_2 , R_3 and R_4 are individually selected from the group of adamantyl, hydrogen, alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, phenyl, phenalkyl where alkyl is one to three carbon atoms, inclusive, and mono- or di-substituted phenyl or phenyl moiety of the phenalkyl
 15 wherein the substituents are the same or different and are selected from the group consisting of alkyl of one to three carbon atoms, inclusive, halogen, trifluoromethyl and alkoxy of from one to three carbon atoms, inclusive, halo, and trifluoromethyl; hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen
 20 coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur. When the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms. When the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof.

25

In a preferred embodiment

- R_1 is adamantyl,
 - R_2 is selected from the group consisting of hydrogen, alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, phenyl, phenalkyl where alkyl is one to three carbon atoms, inclusive, and monosubstituted phenyl wherein the substituent is selected from the group
- 30

consisting of alkyl of one to three carbon atoms, inclusive, alkoxy of one to three carbon atoms, inclusive, halo, and trifluoromethyl,

- R_3 is selected from the group consisting of hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur, and

when the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms and,

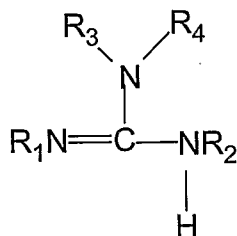
when the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof, and

- R_4 is selected from the group consisting of hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur, and

when the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms, and

when the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof.

Preferred compounds are listed in Table 1 by indicating R_1 , R_2 , R_3 and R_4 of the formula



R_3 and R_4 are the same or different and are selected from the group consisting of hydrogen, alkyl of from one to eight carbon atoms, inclusive, cycloalkyl of from five

to eight carbon atoms, inclusive, phenalkyl wherein alkyl is from one to three carbon atoms, phenyl, and mono and di-substituted phenyl or the phenyl moiety of the phenalkyl wherein the substituents are the same or different and are selected from the group consisting of alkyl of from one to three carbon atoms, alkoxy of from one to three carbon atoms, halogen and trifluoromethyl, and when R3 and R4 are taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring (Z_N) wherein Z is selected from the group consisting of methylene, NA where N is nitrogen and A is selected from the group consisting of hydrogen and alkyl of one to three carbon atoms, inclusive, oxygen, and sulfur, and when Z is methylene, (Z_N) has from four to six carbon atoms and when Z is NA as previously defined, oxygen, or sulfur, (Z_N) is, respectively, piperazino, N-alkylpiperazino, morpholino and thiomorpholino; and pharmaceutically acceptable acid addition salts thereof in association with a pharmaceutical carrier.

Another group of compounds, hereinafter referred to as Group A, for systemic administration comprises compounds where R1 and R2 are the same or different and are selected from the group consisting of alkyl of from four to seven carbon atoms, inclusive, cycloalkyl of from five to seven atoms, inclusive, phenyl, phenalkyl with alkyl of from one to three carbon atoms, inclusive, phenyl and mono-substituted phenyl and phenyl moiety of the phenalkyl wherein the substituent is selected from the group consisting of alkyl of one to three carbon atoms, inclusive, alkoxy of from one to three carbon atoms, inclusive, halogen, and trifluoromethyl;

R3 and R4 are the same or different and are selected from the group consisting of alkyl of from one to eight carbon atoms, inclusive, cycloalkyl of from five to seven carbon atoms, inclusive, phenyl, phenalkyl with alkyl of from one to three carbon atoms, inclusive, and mono-substituted phenyl and phenyl moiety of the phenalkyl wherein the substituent is selected from the group consisting of one to three carbon atoms, inclusive, alkoxy with one to three carbon atoms, inclusive, halogen and trifluoromethyl, and when R3 and R4 are taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring, (Z_N) wherein Z is selected from the group consisting of methylene, NA as defined previously, oxygen and sulfur and when Z is methylene, (Z_N) has from four to six carbon atoms, and when Z is NA, oxygen, or sulfur, (Z_N) is, respectively, piperazino, N-alkylpiperazino, morpholino and thiomorpholino.

A further group of compounds, hereinafter referred to as Group B, for systemic administration comprises compounds where R1 and R2 are the same or different and are selected from the group consisting of alkyl of from four to six carbon atoms, inclusive, cycloalkyl of five to seven carbon atoms, inclusive, phenyl, phenalkyl with alkyl of one to three carbon atoms, inclusive, mono-substituted phenyl or phenyl moiety of phenalkyl, the substituent selected from the group consisting of alkyl of one to three carbon atoms, inclusive, alkoxy of one to three carbon atoms, inclusive, halogen, and trifluoromethyl with the proviso that when R1 is phenyl, phenalkyl or the mono-substituted phenyl or phenyl moiety of the phenalkyl, R2 is selected from the group consisting of alkyl of four to six carbon atoms, inclusive, and cycloalkyl of five to seven carbon atoms, inclusive;

R3 and R4 are the same or different and are selected from the group consisting of alkyl of from four to six carbon atoms, inclusive, cycloalkyl of from five to seven carbon atoms, and R3 and R4 when taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring, (^Z_N) wherein Z is selected from the group consisting of methylene, NA as previously defined, oxygen, and sulfur, and when Z is methylene, (^Z_N) is from four to six carbon atoms, and when Z is NA oxygen, or sulfur, (^Z_N) is, respectively, piperazino, N-alkylpiperazino, morpholino or thiomorpholino.

A further group of compounds, hereafter referred to as Group C, for systemic administration and composition compounding, comprise compounds where R1 and R2 are the same or different and are selected from the group consisting of alkyl of from four to six carbon atoms, inclusive, and cycloalkyl of from five to seven carbon atoms, inclusive;

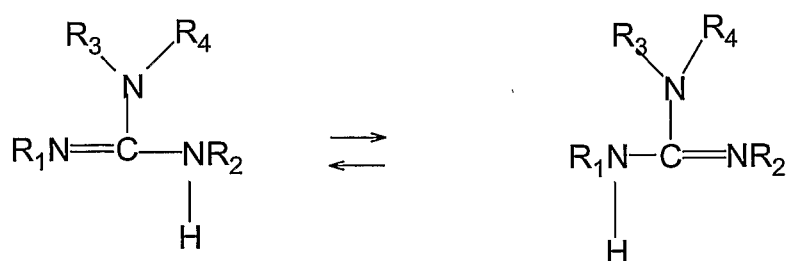
R3 and R4, when taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring, (^Z_N) wherein Z is selected from the group consisting of methylene, nitrogen, oxygen and sulfur and when Z is methylene, (^Z_N) has from four to six carbon atoms, and when Z is nitrogen, oxygen, or sulfur, (^Z_N) is, respectively, piperazino, morpholino, or thiomorpholino.

Preferred compounds to be used in the medicament and methods of using these medicaments are:

- N,N'-dicyclohexyl-4-morpholinecarboxamidine and hydrochloride salt,
- N,N'-diphenyl-4-morpholinecarboxamidine and maleate salt,
- 5 • N,N'-bis-(p-fluorophenyl)-4-morpholinecarboxamidine and hydrochloride salt,
- N,N'-bis(2,6-diethylphenyl)-4-morpholinecarboxamidine and sulfate salt,
- N-cyclohexyl-N'-(3,4-dichlorophenyl)-4-morpholinecarboxamidine and hydrochloride or nitrate salt.

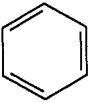
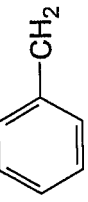
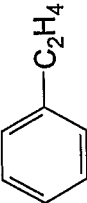
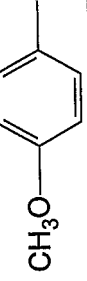
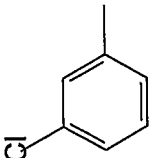
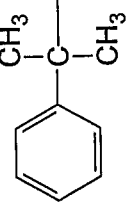
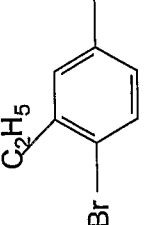
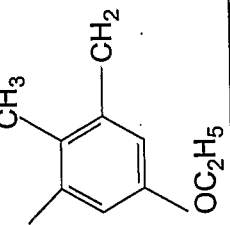
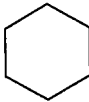
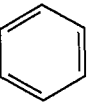
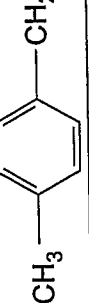
- 10 As employed in the above disclosure and throughout the specification, the term "halogen" includes fluorine, chlorine, bromine and iodine. The term "alkyl" includes methyl, ethyl, propyl, and isomers thereof when limited to three carbon atoms. When limited to a higher number of carbon atoms, the term encompasses compounds through that number of carbon atoms and isomers thereof. "Pharmaceutically
- 15 acceptable acid addition salts" include the hydrochloric, hydrobromic, hydriodic, nitric, sulfuric, phosphoric, acetic, lactic, citric, succinic, benzoic, salicylic, palmitic, oxalic, cyclohexanesulfamic and the like. "Cycloalkyl" of from five to eight carbon atoms includes cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

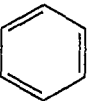
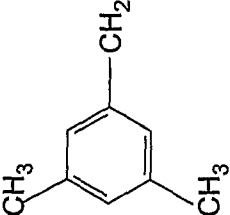
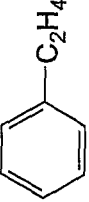
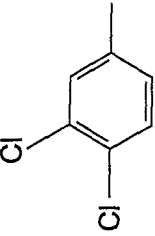
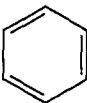
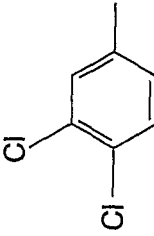
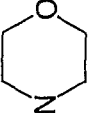
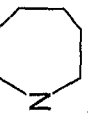
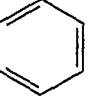
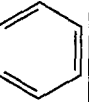
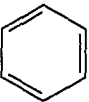
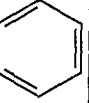
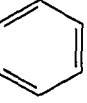
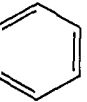
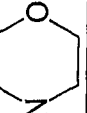
- 20 When R₁ and R₂ are different, tautomers exist when the amine is added to the carbodiimide due to the mobility of the double bond. These tautomers are represented by the following equilibrium:

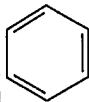
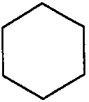
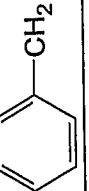
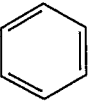
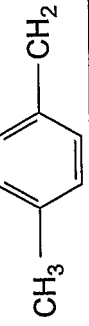
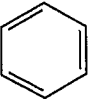
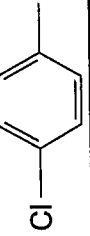
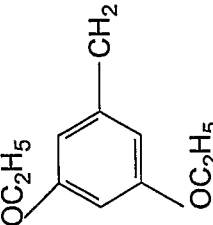
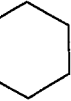
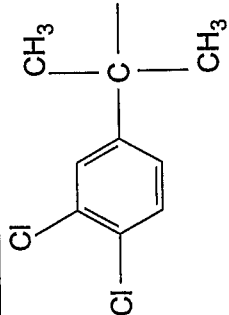
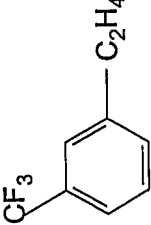
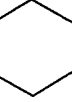


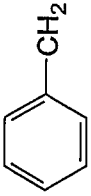
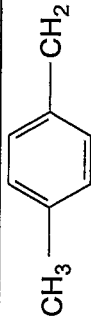
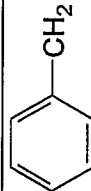
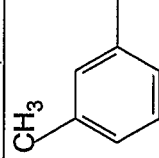
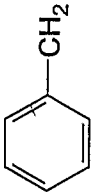
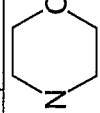
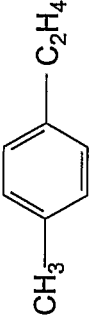
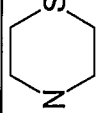
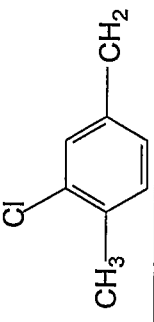
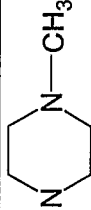
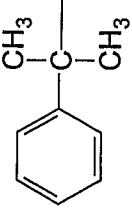
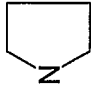
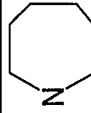
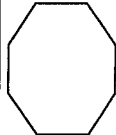
- 25 Each of the tautomers can be used as a K_{ATP}-channel blocker for the manufacture of a medicament for treatment or alleviation of migraine and/or other headaches. Also mixtures of the tautomers can be used for the preparation of the medicament.

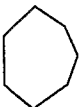
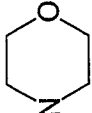
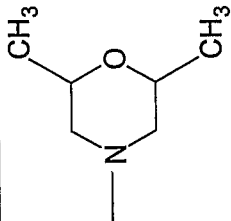
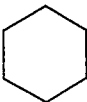
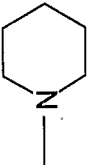
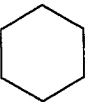
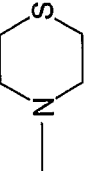
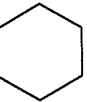
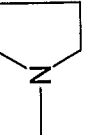
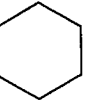
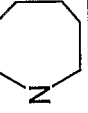
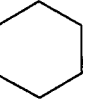
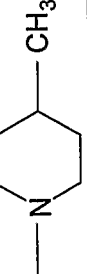
Table 1

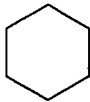
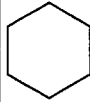
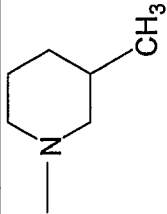
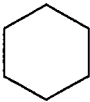
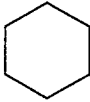
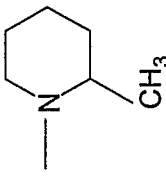
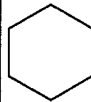
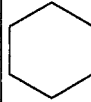
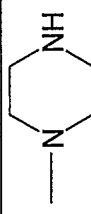
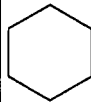
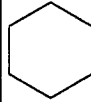
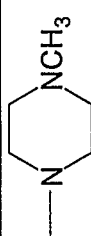
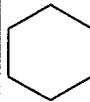
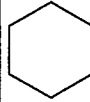
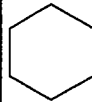
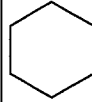
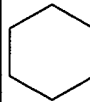
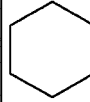
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2	C ₂ H ₅	tC ₄ H ₉		
3	C ₃ H ₇	C ₆ H ₁₃		
4	iC ₄ H ₉	C ₈ H ₁₇		
5	CH ₃			

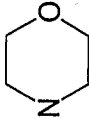
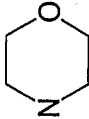
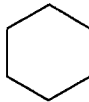
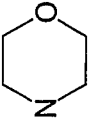
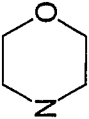
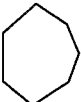
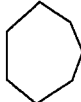
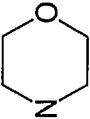
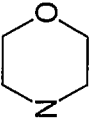
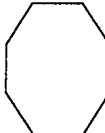
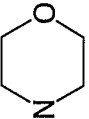
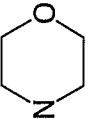
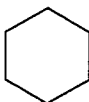
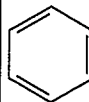
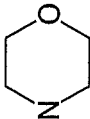
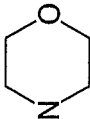
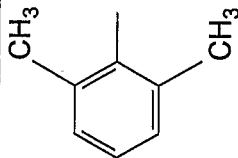
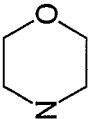
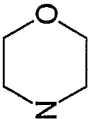
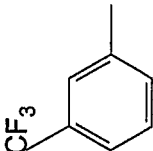
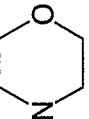
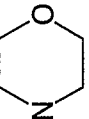
Formular No.	R ₁	R ₂	R ₃	R ₄
6	iC ₃ H ₇			
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8	C ₆ H ₁₃			
9	C ₄ H ₉			
10				
11				

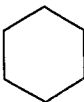
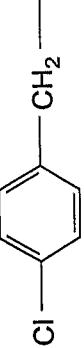
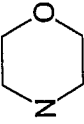
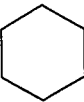
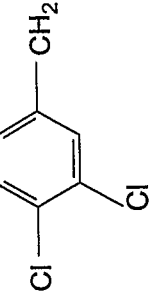
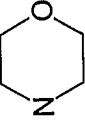
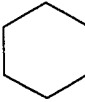
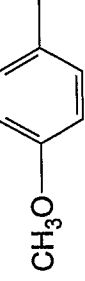
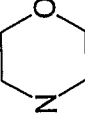
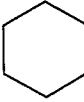
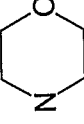
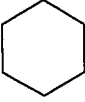
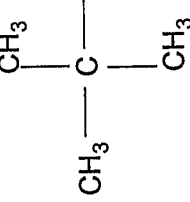
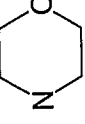
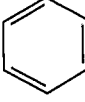
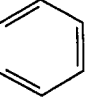
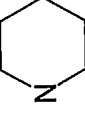
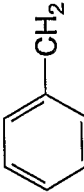
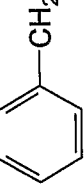
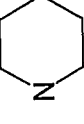
Formular No.	R ₁	R ₂	R ₃	R ₄
12			H	
13				
14			C ₃ H ₇	CH ₃
15			H	
16		C ₂ H ₅	C ₃ H ₇	
17				

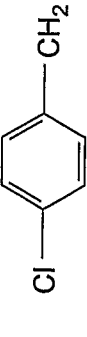
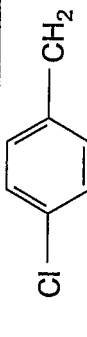
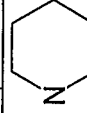
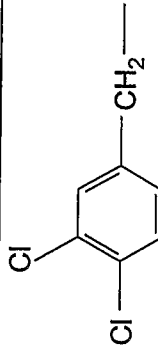
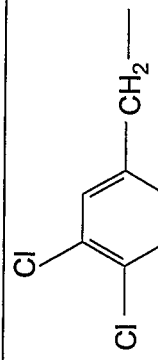
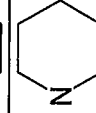
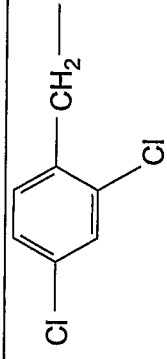
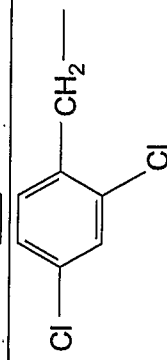
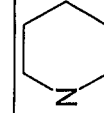
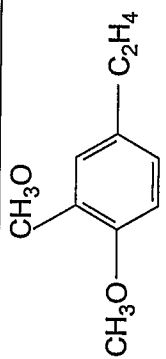
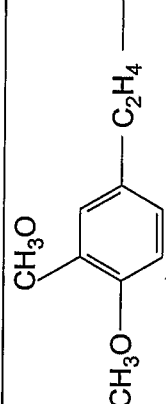
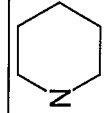
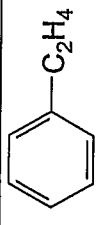
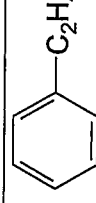
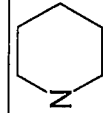
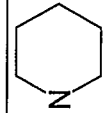
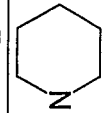
Formular No.	R ₁	R ₂	R ₃	R ₄
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19		CH ₃		
20				
21				
22				
23				
24			CH ₃	C ₅ H ₁₁

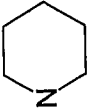
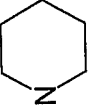
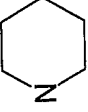
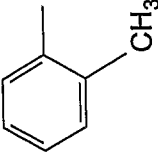
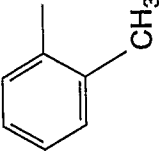
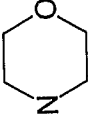
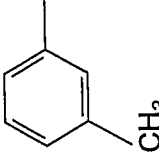
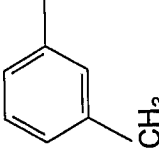
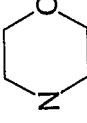
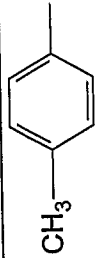
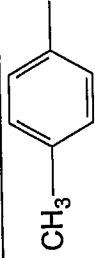
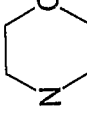
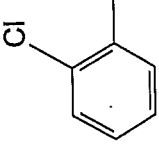
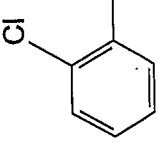
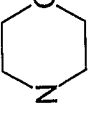
Formular No.	R ₁	R ₂	R ₃	R ₄
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26				
27				
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31				

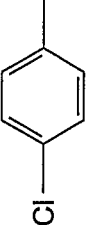
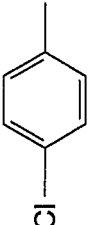
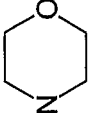
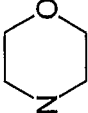
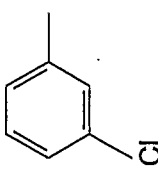
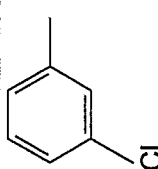
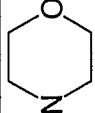
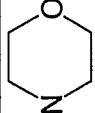
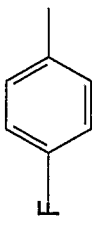
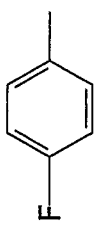
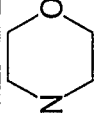
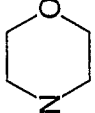
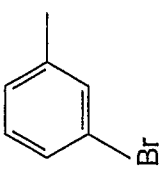
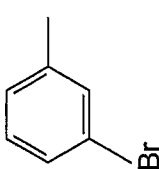
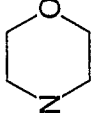
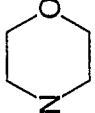
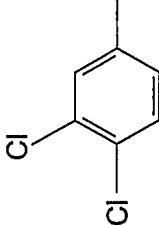
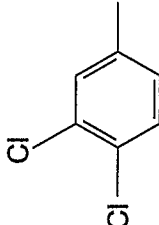
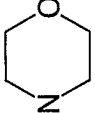
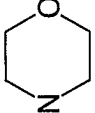
Formular No.	R ₁	R ₂	R ₃	R ₄
32				
33				
34				
35				
36			CH ₃	CH ₃
37			C ₂ H ₅	C ₂ H ₅
38			H	C ₄ H ₉

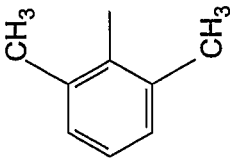
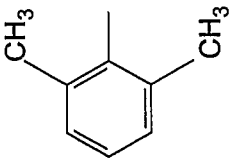
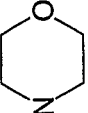
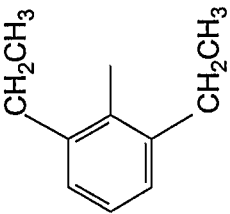
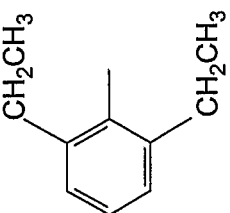
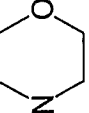
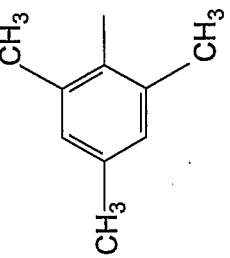
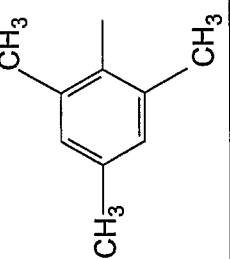
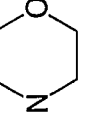
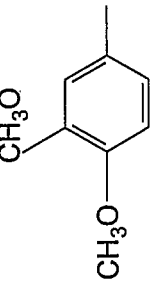
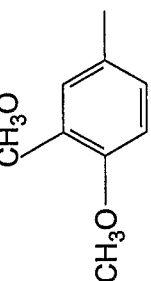
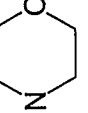
Formular No.	R ₁	R ₂	R ₃	R ₄
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45				

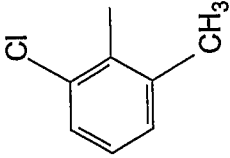
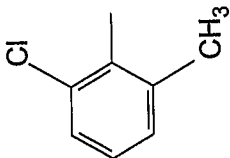
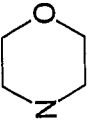
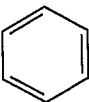
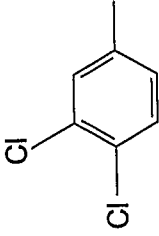
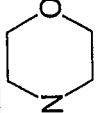
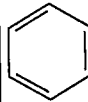
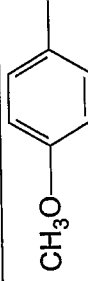
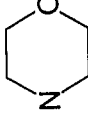
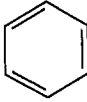
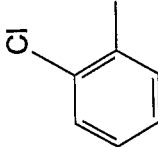
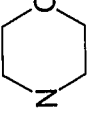
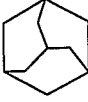
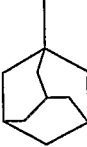
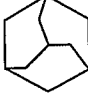
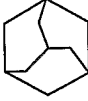
Formular No.	R ₁	R ₂	R ₃	R ₄
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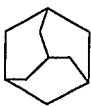
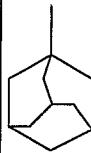
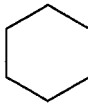
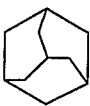
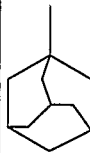
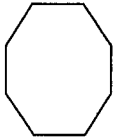
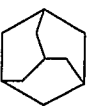
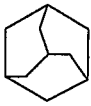
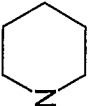
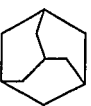
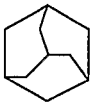
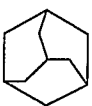
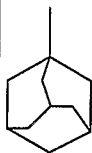
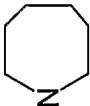
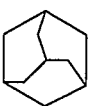
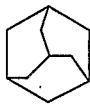
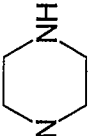
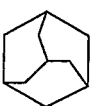
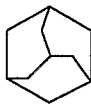
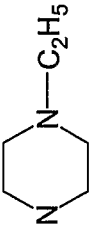
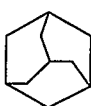
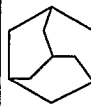
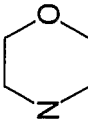
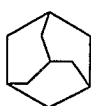
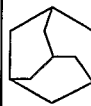
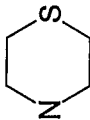
Formular No.	R ₁	R ₂	R ₃	R ₄
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59				

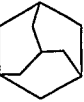
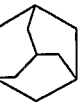
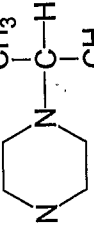
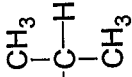
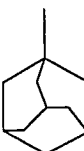
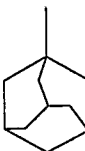
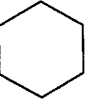
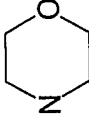
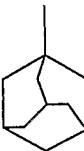
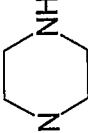
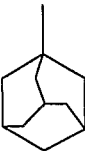
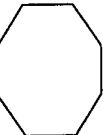
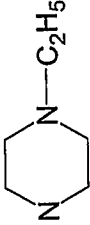
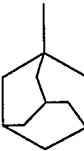
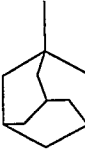
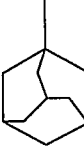
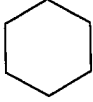
Formular No.	R ₁	R ₂	R ₃	R ₄
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61	CH ₃ (CH ₂) ₅ —	CH ₃ (CH ₂) ₄ —		
62	CH ₃ CH ₂ CHCH ₂ — CH ₃	CH ₃ CH ₂ CHCH ₂ — CH ₃		
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66				

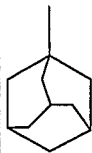
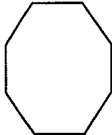
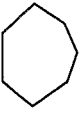
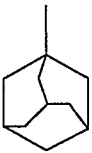
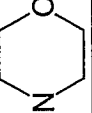
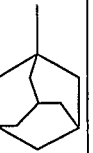
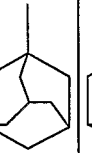
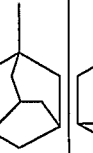
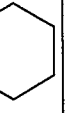
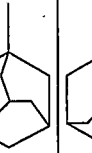
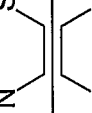
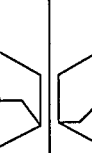
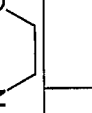
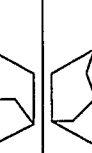
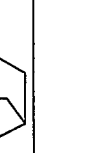
Formular No.	R ₁	R ₂	R ₃	R ₄
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70				
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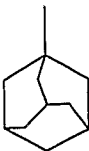
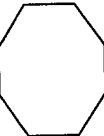
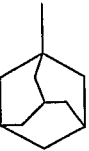
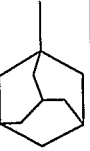
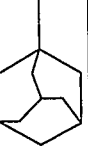
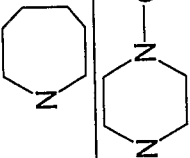
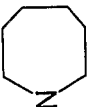
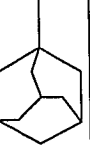
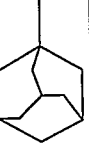
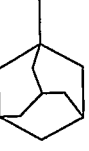
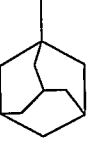
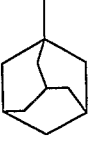
Formular No.	R ₁	R ₂	R ₃	R ₄
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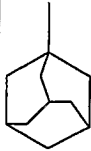
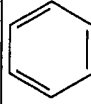
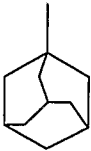
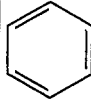
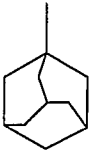
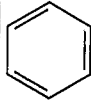
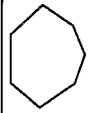
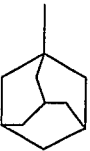
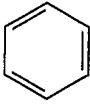
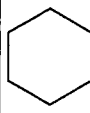
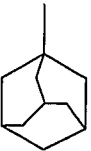
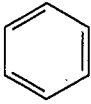
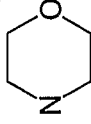
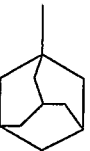
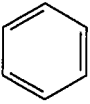
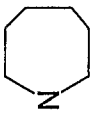
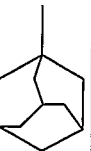
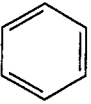
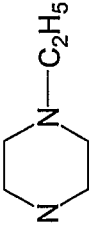
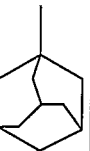
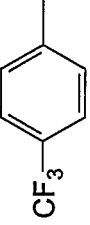
Formular No.	R ₁	R ₂	R ₃	R ₄
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77				
78				
79				
80			H	H
81			C ₂ H ₅	iC ₇ H ₁₅

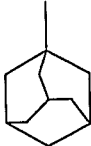
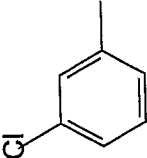
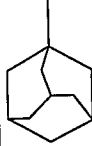
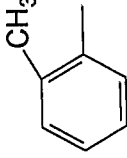
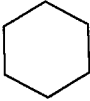
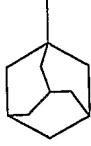
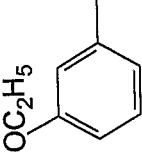
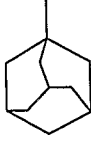
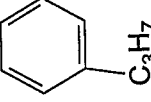
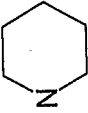
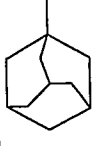
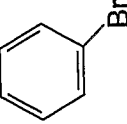
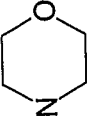
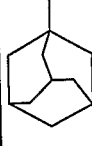
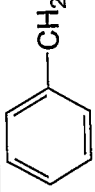
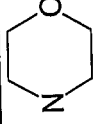
Formular No.	R ₁	R ₂	R ₃	R ₄
82			H	
83			CH ₃	
84				
85				
86				
87				
88				
89				
90				

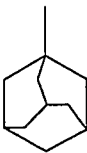
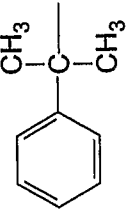
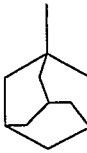
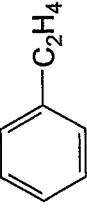
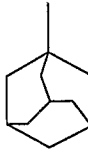
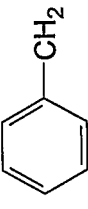
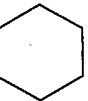
Formular No.	R ₁	R ₂	R ₃	R ₄
91				
92				
93				
94				
95				
96			H	C ₄ H ₉
97			C ₂ H ₅	C ₇ H ₁₅
98			CH ₃	

Formular No.	R ₁	R ₂	R ₃	R ₄
99			H	
100		H		
101		H	H	H
102		H	H	C ₅ H ₁₁
103		H	iC ₃ H ₇	
104		H		
105		CH ₃		
106		C ₂ H ₅	H	H
107		C ₃ H ₇	H	iC ₈ H ₁₇

Formular No.	R ₁	R ₂	R ₃	R ₄
108		tC ₄ H ₉	H	
109		C ₅ H ₁₁	C ₂ H ₅	
110		C ₆ H ₁₃	iC ₃ H ₇	tC ₅ H ₁₁
111		C ₇ H ₁₅		
112		C ₈ H ₁₇		
113			H	H
114			H	C ₃ H ₇
115			H	
116			C ₂ H ₅	C ₈ H ₁₇

Formular No.	R ₁	R ₂	R ₃	R ₄
117			$t\text{-C}_4\text{H}_9$	C_5H_{11}
118			$i\text{-C}_3\text{H}_7$	
119			C_4H_9	
120				
121				
122				
123				
124			H	$t\text{-C}_4\text{H}_9$

Formular No.	R ₁	R ₂	R ₃	R ₄
125			C_2H_5	C_5H_{11}
126			C_3H_7	
127				
128				
129				
130				

Formular No.	R ₁	R ₂	R ₃	R ₄
131			H	C ₂ H ₁₅
132			C ₃ H ₇	C ₇ H ₁₅
133				CH ₃

Further preferred compounds for use as K_{ATP} -channel blocker are N-1-adamantyl-N'-cyclohexyl-4-morpholinecarboxamidinium and hydrochloride (PNU 37883A), N,N'-di-1-
5 adamantyl-4-morpholinecarboxamidinium and hydrochloride N,N'-di-2-adamantyl-4-morpholinecarboxamidinium.

In an embodiment the K_{ATP} -channel blocker is selected from a mixture of the (R)-enantiomer and the (S)-enantiomer or substantially pure (R)-enantiomer or
10 substantially pure (S)-enantiomer.

An aspect of the invention is a pharmaceutical composition comprising an effective amount of at least one K_{ATP} -channel blocker as defined herein or a salt thereof, optionally further comprising a pharmaceutically acceptable carrier substance.
15

Another aspect of the invention is a method for treating or alleviating a disorder or disease of a living animal body, including a human, where the disorder or disease is responsive to blockade of the K_{ATP} channel, and where the method comprises administering to such a living animal body a therapeutically-effective amount of a
20 K_{ATP} -channel blocker as defined elsewhere herein.

A further aspect of the invention is a method for identifying a K_{ATP} -blocker that blocks a K_{ATP} -channel comprising at least one of the subunits SUR2B, kir6.1 and kir6.2, said method comprises:
25

- a. obtaining a compound being a possible K_{ATP} -blocker,
- b. obtaining isolated cerebral and/or dural arteries of an animal,
- 30 c. dividing said arteries into pre-determined segments,
- d. placing said divided arteries into a buffer composition in a tissue bath,
- e. affecting said cerebral and/or dural arteries with a K_{ATP} -channel
35 opener by addition of said K_{ATP} -channel opener to the buffer

composition, whereby said K_{ATP} -channel opener induce increased diameter/relaxation of the arteries,

5 f. affecting said K_{ATP} -channel opener induced cerebral and/or dural arteries with said possible K_{ATP} -blocker by addition of said possible K_{ATP} -channel blocker to the buffer composition,

10 g. determining the effect of said possible K_{ATP} -blocker on the diameter of said K_{ATP} -channel opener induced response in isolated arteries, and

h. wherein said possible the K_{ATP} -blocker is determined to be a K_{ATP} -blocker when the diameter of said K_{ATP} -channel opener induced response in isolated arteries is reduced by said possible K_{ATP} -blocker.

15 Studies of the inhibiting effect of the K_{ATP} blocker on K_{ATP} opener induced effects on isolated cerebral and dural arteries using a sensitive in vitro system is further described in the paper Gozalov, et al., "Role of K_{ATP} channels in the regulation of rat dura and pia artery diameter" in Cephalalgia, 2004, 24, 249-260.

20 Another aspect of the invention is a method for identifying a K_{ATP} -blocker that blocks the K_{ATP} -channel comprising at least one of the subunits SUR2B, kir6.1 and kir6.2, said method comprises

a. obtaining pancreas, heart and/or cerebral tissue of an animal,

b. homogenising said tissue,

25 c. sieving said homogenised tissue to obtain a filtrate,

d. ultra-centrifugating said filtrate to obtain a pellet,

e. resuspending said pellet, to obtain a membrane preparation including membranes from said tissue,

30 f. incubating said membrane preparation with a ^3H -labelled K_{ATP} -channel agent, whereby said ^3H -labelled K_{ATP} -channel agent binds to said membranes,

- g. filtrating under vacuum over a filter said membrane preparation incubated with said ^3H -labelled K_{ATP} -channel agent, whereby said membranes in said membrane preparation is deposited on said filter,
 - h. washing said filter,
 - 5 i. counting the amount of ^3H -labelled K_{ATP} -channel agent on said filter, hereby obtaining a standard signal,
 - j. incubating a second membrane obtained from step f with possible K_{ATP} -blocker, performing step g-i with said second membrane to obtain an inhibition signal,
 - 10 k. comparing said inhibition signal with said standard signal and hereby determining the displacing properties of said possible K_{ATP} -blocker,
 - l. wherein said possible K_{ATP} -blocker is determined to be a K_{ATP} -blocker when said inhibition signal is less than said standard signal.
- 15 Binding studies using a ^3H -labelled K_{ATP} channel agent (P-1075) and study the displacing properties of the new potential K_{ATP} blocker is further described by Loffler-Walz and Quast "Binding of K_{ATP} channel modulators in rat cardiac membranes" in British Journal of Pharmacology 1998, 123, 1395-1402.
- 20 In an embodiment the K_{ATP} -channel agent used in the method for identifying a K_{ATP} -blocker that blocks the K_{ATP} -channel is a K_{ATP} -channel opener.
- In a preferred embodiment the K_{ATP} -channel opener is selected from the group of P1075, levromakalim, cromakalim, pinacidil, nicorandil, ZM226600, diazoxide,
- 25 ZD6169, celikalim, bimakalim, WAY-133537, Y26763, Y27152, BMS-180448, JTV-506, KR-30450, SDZ PCO 400, YM 934, KC-399, BRL 55834, rilimakalim and SDZ 217-744.

Voltage-gated potassium channels

30

Voltage-gated potassium channels include α -subunits with six trans-membrane segments, S1-S6, with a H5 or P loop between S5 and S6.

Of the voltage-gated potassium channels BK_{Ca} , IK_{Ca} and SK_{Ca} channels constitute a group of potassium channels that are activated by intracellular calcium and each subfamily has taken their names from their single channel conductance: BK_{Ca} ("big") has a conductance of 100-300 pS; IK_{Ca} ("intermediate") 20-80 pS and SK_{Ca} ("small") 5-20 pS. IK_{Ca} and SK_{Ca} resemble the voltage-gated potassium channels in membrane topology with six trans-membrane segments; however, BK_{Ca} is unique in that it contains a seventh trans-membrane segment (S0) which is located before the six trans-membrane segments and with its N-terminus on the extra-cellular side.

BK_{Ca} channels are also unique in their pharmacological profile compared to IK_{Ca} and SK_{Ca} channels. BK_{Ca} channels are sensitive to iberiotoxin, charybdotoxin and TEA whereas SK_{Ca} and IK_{Ca} channels are not blocked by iberiotoxin and TEA.

One aspect of the present invention is the use of a BK_{Ca} -channel blocker for the manufacture of a medicament for treatment or alleviation of migraine and/or other headaches.

In one embodiment the BK_{Ca} -channel blocker blocks BK_{Ca} -channels comprising the pore-forming alpha subunit and the accessory beta subunit.

The alpha-subunits are derived from a single gene that undergoes extensive alternative pre-mRNA splicing. The alpha-subunits are assembled as tetramers.

Intracellular calcium regulates the physical association between the alpha and beta subunits. Differences in biophysical and pharmacological properties of BK_{Ca} -channels can be explained by exon splice variants of the gene Slo and by regulation of the β subunit. The β subunit is classified into four distinct subtypes $\beta 1$ - $\beta 4$, which are encoded by distinct genes.

The BK_{Ca} -channel blocker should act by binding to the α subunit either alone or in combination with the β subunits. The BK_{Ca} -channel blocker could also act by binding to any of the β subunits alone.

In one embodiment the BK_{Ca}-channel blocker blocks BK_{Ca}-channels comprising at least one of the α -subunits coded by the genes KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4.

5 In another embodiment the BK_{Ca}-channels are located in connection to vascular tissue. Preferred is when the BK_{Ca}-channels are located in or in connection to smooth muscle and/or to the endothelial cells and/or perivascular nerve endings. The BK_{Ca}-channels can be located in or in connection to arteries, arterioles, capillary system, and/or veins. Preferred is when the BK_{Ca}-channels are located in a system
10 which is located within the head of an individual. Also preferred is when the BK_{Ca}-channels are located in connection to basilar arteries, cerebral arteries, pial arteries and/or dural arteries.

In an embodiment the arteries are selected from the group of vertebral arteries,
15 common carotid arteries, external carotid arteries, internal carotid arteries, anterior communicating arteries, anterior cerebral arteries, middle cerebral arteries, posterior communicating arteries, posterior cerebral arteries, superior cerebellar arteries, anterior inferior cerebellar arteries, basilar arteries, precuneal arteries, paracentral artery, pericallosal arteries, callosomarginal arteries, frontopolar arteries, medial
20 orbitofrontal arteries, posterior temporal arteries, angular arteries, posterior parietal arteries, anterior parietal arteries, central arteries, precentral arteries, ascending frontal arteries, lateral orbitofrontal arteries, anterior temporal arteries, middle temporal arteries, anterior inferior cerebellar arteries, posterior temporal arteries, calcarine arteries, parietooccipital arteries, posterior pericallosal arteries, midial
25 lenticulostriate arteries, lateral lenticulostriate arteries.

In an embodiment the treatment is prophylactic and/or acute. Also the treatment can be systemic. Preferred is a systemic treatment.

30 In an embodiment the BK_{Ca}-channel blocker blocks a α -subunit of the BK_{Ca}-channel.

In an embodiment the BK_{Ca}-channel blocker specifically binds to the BK_{Ca}-channel with an α -subunit coded by the gene slo1 and where said BK_{Ca}-channel binds at least 3 times more specific than a non-specific BK_{Ca}-channel blocker.

In a preferred embodiment the BK_{Ca}-channel blocker is a specific BK_{Ca}-channel which blocks BK_{Ca}-channels with one of the β -subtypes $\beta 1$, $\beta 2$, $\beta 3$, or $\beta 4$ more than BK_{Ca}-channels with the other subunits.

5 In another embodiment BK_{Ca}-channel blocker binds to the β -subunit of the BK_{Ca}-channel. Preferred is when the BK_{Ca}-channel blocker binds specific to the BK_{Ca}-channel with one predetermined beta subunit and where said BK_{Ca}-channel binds at least 3 times more specific than to the other beta subunits hereby being a non-specific BK_{Ca}-channel blocker in respect of these other beta subunits. The
10 predetermined beta subunits can be any beta subunits e.g. subtypes $\beta 1$, $\beta 2$, $\beta 3$, or $\beta 4$. The BK_{Ca}-channel blocker may bind more specific to $\beta 1$ - and $\beta 4$ -subunits than the other β -subunits. The BK_{Ca}-channel blocker may further bind more specific to $\beta 4$ -subunits than the other β -subunits.

15 In an embodiment the BK_{Ca}-channel blocker inhibits BK_{Ca}-channel openers to act with the BK_{Ca}-channels. Furthermore the BK_{Ca}-channel blocker reduces or inhibits dilatation of arteries.

A non-specific blocker will bind with equal affinity to BK_{Ca}-channels consisting of $\beta 1$,
20 $\beta 2$, $\beta 3$, or $\beta 4$ subunits in combination with any α -subunit.

In a preferred embodiment the BK_{Ca}-channel blocker has a tissue selectivity characterised by a higher selectivity to BK_{Ca}-channels within blood vessels and associated nerves in the cranial circulation than to BK_{Ca}-channel in the CNS and
25 other tissue of peripheral organs, such as in peripheral vascular tissue, intestinal tissue, kidney tissue, pancreatic tissue and/or cardiac tissue.

The blood vessels and associated nerves in the cranial circulation may be in the brain and dura mater.

30 The specificity mentioned above is characterised by a higher affinity to BK_{Ca}-channels within blood vessels and associated nerves in the brain and dura mater than to the BK_{Ca}-channel of the other mentioned tissue types. The BK_{Ca}-channel blocker has an affinity that is equal or above 3 the affinity of the BK_{Ca}-channel
35 blocker to the BK_{Ca}-channels of the other mentioned tissue types, such as equal or

above 5, such as equal or above 10, such as equal or above 15, such as equal or above 20, such as equal or above 25, such as equal or above 30, such as equal or above 35, such as equal or above 40, such as equal or above 45, such as equal or above 50, such as equal or above 55, such as equal or above 60, such as equal or above 65, such as equal or above 70, such as equal or above 75, such as equal or above 80, such as equal or above 85, such as equal or above 90, such as equal or above 95, such as equal or above 100, such as equal or above 105, such as equal or above 110, such as equal or above 115, such as equal or above 120, such as equal or above 125, such as equal or above 150, such as equal or above 175, such as equal or above 200, such as equal or above 225, such as equal or above 250, such as equal or above 275, such as equal or above 300, such as equal or above 325, such as equal or above 350, such as equal or above 375, such as equal or above 400, such as equal or above 425, such as equal or above 450, such as equal or above 475, such as equal or above 500.

The BK_{Ca}-channel blocker used to make a medicament to treat or alleviate migraine or other headaches can be a medicament which is formulated in any suitable manner as described below..

In an embodiment the BK_{Ca}-channel blocker is selected from the group of 2,3-Butanedione monoxime; 4-aminopyridine (4-AP); 5-Hydroxydecanoate; 7-nitroindazole; 8-oxo-berberine; A-184209; Acecainide; Adenosine (ATP); Aflatrem; Agatoxin, ω -type (ω -Agatoxin); Agitoxin-1; Agitoxin-2; Agitoxin-3; AL 275; Alinidine ST 567; Almokalant H 234/09; Alpha-dendrotoxin; AM 92016; Ambasilide; Ambasilide LU 47110; AN 132; Antioxidants; Apamin; ARH 050642; ATI 2042; ATP; AWD 12-260; AWD 160275; AWD 23-111; AZD 7009; AZDF 265; Azimilide; Barium chloride; Bay K8644 (R)-(+)-form; BDS-I; BDS-II; Bepridil; Berlambine; Bertosamil; Beta-bungarotoxin (beta-BuTX); Beta-dendrotoxin; BIIA 0388; BMS 208782; BMS 208783; BRBI 28; Bretylium; BRL 32872; Bromide dendrotoxin; BTS 67582; Bupivacaine; Carsatrin Succinate RWJ 24517; Caryachine; CGX 1007; Changrolin pyro-
zoline; Charybdotoxin; Charylotoxin; CHF 1522 Cyclo-dextrin complex of glibenclamide; Chlorpropamide; Chromanol 293 isomer; Chromanol 293B; Cibenzoline; Ciclazindol; Clamikalant HMR 1098; Clamikalant HMR 1883; Clausenamide (- form); Clausenamide (racemic); Clofilium LY 150378; Clofilium tosylate; Clotrimaxole; Clotrimazole; CNS 1237; CP 308408; CP 339818; CP 366660; CP 92713; CPU

- 86017; Cyanoguanidine; Dendrotoxin (DTX); Dendrotoxin I (DTX-I); Dendrotoxin K (DTX-K); Dequalinium chloride; Dexsotalol BMY; 057631D d-sotalol; Dicentrine; Dimethyl sulfoxide; DKAH 269; DMP 543; Dofetilide; DPC 543; DPI 201106; Drone-darone SR 33589; DTX, α -type (α -DTX); DTX, β -type (β -DTX); DTX, γ -type (γ -DTX); DTX, δ -type (δ -DTX); E-4031; Efaroxan; EGIS 7229; Englitazone; Ersentilide (+/- form); Ersentilide (S-form); Ethanol; Evodiamine (S); Fampridine 4-aminopyridine EL 970; Fosinoprilat; Gamma-dendrotoxin; GEA 857; Glemanserin MDL 11939; GLG V 13; Glibenclamide; Glimepiride; Glipizide (GLP); Glipizide K 4024; Glipizide TK 1320; Glucagons antagonists; Glybenclamide; Glyburide;
- 10 Guanethidine; Guanidinium moieties; GYKI 16638; HA 7; HMR 1372; HMR 1402; HMR 1556; HMR 1883; Hydroxy; Iberiotoxin; Ibutilide; Ibutilide U 70226; ICA 17043; ICI 181037; IK Channel Blocker; IMID-1M; IMID-26F; IMID-4F; IMID-4F hydrochloride; Imidazoline moieties; Ipazilide WIN 54177; Ipidacrine NIK 247; Ivabradine; JKL 1073A oxy-berberine; JTV 519; Kaliotoxin; KCB 328; KMC IV 84; KW 3407; L
- 15 691121; L 702958; L 706000; L 735821; L 742084; L 768673; L755860 and related compounds; Levosemetiadil SA 3212; Levosemetiadil SD 3212; Limbatoxin; Limbatustoxin; Liriodenine; Lq2; LQE 908 Pinokalan; LY 190147; LY 97241; Margatoxin; Mitiglinide KAD 1229 S-21403; MK 499; N 3601; N-allyl secoboldine; Nateglinide; Nateglinide AY 4166; Neuropeptide Y; Nibentan; Nifekalan MS 551; Niguldipine
- 20 hydrochloride S(+)-form; NIP 142; NOS inhibitors; Noxiustoxin; NS 004; NS 1546; OPC 88117; ORG 20781; Pandinotoxin-K α ; Paspalitrem; Paxilline; PD 157667; Penitrem A; PGE 844384; Phencyclidine; Phentolamine; Phentolamine; Pirmenol CI 845; Pirocixan; PNU 18177A; PNU 37883A; PNU 89692; PNU 94126; PNU 94158; PNU 94563; PNU 94750; PNU 96179; PNU 96293; PNU 97025E; PNU 99963;
- 25 Pyrido triazoles; Quinidine; Quinine; Quinine hemisulfate salt; Repaglinide AGEE 623; Repaglinide NN 623; Repaglinide; Rimonabant SR 141716; Risotilide; Ro-034563; Ropivacaine AL 281; Ropivacaine LEA 103; RP 58866; RP 66784 RSD 1000; RSD 1019; Rutaecarpine; RWJ 28810; RX 871024; S 16260; S 9947; Salicylaldehyde; Saxitoxin; SB 237376; Scyllatoxin; SDZ DNJ 608; Sematilide; Sematilide
- 30 CK 1752; Sematilide ZK 110516; Sinominine; Sodium 5-hydroxydecanoate; Sotalol; SPM 928; Spriadoilne; SSR 149744B; Stichodactyla toxin; Sulfonylureas; TEA (tetraethylammonium); Tedisamil; Tedisamil KC 8857; Terikalant RP 62719; Tertipin; Tertipin-Q; Tetraethylammonium chloride; Tetraethylammonium ions; Tetrodotoxin; TH 9121; TH 9122; Tityustoxin K; Tityustoxin-K α ; TMB-8; TN 871; Tolazamide;
- 35 Tolbutamide; Toxin based therapeutics BRI 6906; TRAM 30; Troglitazone; U

37883A; U 50488H; U-37883A; U-45194A; UCL 1439; UCL 1530; UCL 1559; UCL 1608; UCL 1684; UK 66914; UK 78282; WAY 123223; WAY 123398; WIN 17317-3; WIN 61773; XE 991; Y 39677; YM 026; YM 19348 Racemate; YM 193489-R; YM 193489-S; YT 1; Zatebradine; ZM 181037; ZM 181037; and/or ZM 244085.

5

The medicament may be formulated in any suitable manner as described below.

The BK_{Ca}-channel blocker can be a protein comprising at least a sequence of amino acids characterised as Pyr-Phe-Thr-Asp-Val-Asp-Cys-Ser-Val-Ser-Lys-Glu-Cys-Trp-
10 Ser-Val-Cys-Lys-Asp-Leu-Phe-Gly-Val-Asp-Arg-Gly-Lys-Cys-Met-Gly-Lys-Lys-Cys-Arg-Cys-Tyr-Gln.

The protein may have a configuration characterised by Pyr-Phe-Thr-Asp-Val-Asp-Cys⁷-Ser-Val-Ser-Lys-Glu-Cys¹³-Trp-Ser-Val-Cys¹⁷-Lys-Asp-Leu-Phe-Gly-Val-Asp-
15 Arg-Gly-Lys-Cys²⁸-Met-Gly-Lys-Lys-Cys³³-Arg-Cys³⁵-Tyr-Gln-OH wherein there are disulfide bonds between amino acids 7 → 28; 13 → 35; and 17 → 33.

In another embodiment the BK_{Ca}-channel blocker is a protein comprising a homology of at least 50% of the protein mentioned above, such as at least 60%,
20 such as at least 70%, such as at least 80%, such as at least 85%, such as at least 87%, such as at least 90%, such as at least 92%, such as at least 94%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as at least 99.5% in respect of the corresponding amino acid sequences.

25 Preferred is when the BK_{Ca}-channel blocker is selected from the group of Iberitoxin, Aflatrem, Charybdotoxin, Kaliotoxin, Limbatoxin, Paspalitrem, Paxilline, and/or Penitrem A.

Another aspect of the invention is a pharmaceutical composition comprising an
30 effective amount of at least one BK_{Ca}-channel blocker as defined herein above or a salt thereof, optionally further comprising a pharmaceutically acceptable carrier substance.

Yet another aspect of the invention is a method for treating or alleviating a disorder
35 or disease of a living animal body, including a human, which disorder or disease is

responsive to blockade of the BK_{Ca}-channel, and which method comprises administering to such a living animal body a therapeutically-effective amount of a BK_{Ca}-channel blocker as defined herein above.

5 A further aspect of the invention is a method for identifying a compound that blocks BK_{Ca}-channels, the method comprises:

- a. obtaining a compound being a possible BK_{Ca}-channel blocker,
- 10 b. obtaining isolated cerebral and/or dural arteries of an animal,
- c. dividing said arteries into pre-determined segments,
- d. placing said divided arteries into a buffer composition in a tissue bath,
- 15 e. affecting said cerebral and/or dural arteries with a BK_{Ca}-channel opener by addition of said BK_{Ca}-channel opener to the buffer composition, whereby said BK_{Ca}-channel opener induce increased diameter/relaxation of the arteries,
- 20 f. affecting said BK_{Ca}-channel opener induced cerebral and/or dural arteries with said possible BK_{Ca}-channel blocker by addition of said possible BK_{Ca}-channel blocker to the buffer composition,
- 25 g. determining the effect of said possible BK_{Ca}-channel blocker on the diameter of said BK_{Ca}-channel opener induced response in the isolated arteries, and
- 30 h. wherein said possible BK_{Ca}-channel blocker is determined to be a BK_{Ca}-channel blocker when the diameter of said BK_{Ca}-channel opener induced response in the isolated arteries is reduced by said possible BK_{Ca}-channel blocker.

Another aspect of the invention is a method for identifying a BK_{Ca}-channel blocker that blocks the BK_{Ca}-channel, the method comprises

- a. obtaining peripheral arteries or veins, intestine, kidney, pancreas, heart and/or cerebral arteries of an animal,
- b. homogenising said tissue,
- c. sieving said homogenised tissue to obtain a filtrate,
- 5 d. ultra-centrifugating said filtrate to obtain a pellet,
- e. resuspending said pellet, to obtain a membrane preparation including membranes from said tissue,
- f. incubating said membrane preparation with a ^{125}I -labelled BK_{Ca} -channel agent, whereby said ^{125}I -labelled BK_{Ca} -channel agent binds to said membranes,
- 10 g. filtrating under vacuum over a filter said membrane preparation incubated with said ^{125}I -labelled BK_{Ca} -channel agent, whereby said membranes in said membrane preparation is deposited on said filter,
- h. washing said filter,
- 15 i. counting the amount of ^{125}I -labelled BK_{Ca} -channel agent on said filter, hereby obtaining a standard signal,
- j. incubating a second membrane obtained from step f with possible BK_{Ca} -channel blocker, performing step g-i with said second membrane to obtain an inhibition signal,
- 20 k. comparing said inhibition signal with said standard signal and hereby determining the displacing properties of said possible BK_{Ca} -channel blocker,
- l. wherein said possible BK_{Ca} -channel blocker is determined to be a BK_{Ca} -channel blocker when said inhibition signal is less than said standard signal.
- 25

In an embodiment the BK_{Ca}-channel agent is a protein or a fusion protein of any of the proteins selected from the group of Iberitoxin, Aflatrem, Charybdotoxin, Kaliotoxin, Limbatoxin, Paspalitrem, Paxilline, Penitrem A.

5 A fusion protein can be produced according to the description of Koschak et al., "[¹²⁵Iberitoxin-D19Y/Y36F, the first selective, high specific activity radioligand for high-conductance calcium-activated potassium channels" in Biochemistry 1997, 36, 1943-1952. In this article further information can be obtained for method for identifying a BK_{Ca}-channel blocker that blocks the BK_{Ca}-channel.

10

Administration forms

The administration forms described below apply to both a blocker of the K_{ATP}-channels and to a blocker of the BK_{Ca}-channels.

15

The main routes of drug delivery, in the treatment method are intravenous, oral, and topical, as will be described below. Other drug-administration methods, such as subcutaneous injection or via inhalation, which are effective to deliver the drug to a target site or to introduce the drug into the bloodstream, are also contemplated.

20

The mucosal membrane to which the pharmaceutical preparation of the invention is administered may be any mucosal membrane of the mammal to which the biologically active substance is to be given, e.g. in the nose, vagina, eye, mouth, genital tract, lungs, gastrointestinal tract, or rectum, preferably the mucosa of the nose, mouth or vagina.

25

Compounds of the invention may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. The compounds may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

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35

The compounds according to the invention may be administered with at least one other compound. The compounds may be administered simultaneously, either as separate formulations or combined in a unit dosage form, or administered sequentially.

5

Dosing regimes

The dosage requirements will vary with the particular drug composition employed, the route of administration and the particular subject being treated. Ideally, a patient to be treated by the present method will receive a pharmaceutically effective amount of the compound in the maximum tolerated dose, generally no higher than that required before drug resistance develops.

For all methods of use disclosed herein for the compounds, the daily oral dosage regimen will preferably be from about 0.01 to about 80 mg/kg of total body weight. The daily parenteral dosage regimen about 0.001 to about 80 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The term "unit dosage form" as used herein refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of a compound, alone or in combination with other agents, calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier, or vehicle. The specifications for the unit dosage forms of the present invention depend on the particular compound or

compounds employed and the effect to be achieved, as well as the pharmacodynamics associated with each compound in the host. The dose administered should be an "effective amount" or an amount necessary to achieve an "effective level" in the individual patient.

5

Since the "effective level" is used as the preferred endpoint for dosing, the actual dose and schedule can vary, depending on interindividual differences in pharmacokinetics, drug distribution, and metabolism. The "effective level" can be defined, for example, as the blood or tissue level desired in the patient that corresponds to a concentration of one or more compounds according to the invention.

10

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pa. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

15

Formulations

20

Whilst it is possible for the compounds or salts of the present invention to be administered as the raw chemical, it is preferred to present them in the form of a pharmaceutical formulation. Accordingly, the present invention further provides a pharmaceutical formulation, for medicinal application, which comprises a compound of the present invention or a pharmaceutically acceptable salt thereof, as herein defined, and a pharmaceutically acceptable carrier therefore.

25

30

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise the compounds of the invention or its pharmaceutically acceptable salt or a crystal form thereof as the active component. The pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring

agents, solubilizers, lubricants, suspending agents, binders, preservatives, wetting agents, tablet disintegrating agents, or an encapsulating material.

5 Preferably, the composition will be about 0.5% to 75% by weight of a compound or compounds of the invention, with the remainder consisting of suitable pharmaceutical excipients. For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like.

10 In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from one to about seventy percent of the active compound. Suitable carriers are magnesium
15 carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included.
20 Tablets, powders, capsules, pills, cachets, and lozenges can be as solid forms suitable for oral administration.

25 Drops according to the present invention may comprise sterile or non-sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving
30 or maintaining at 98-100.degree C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container aseptically. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include
35 glycerol, diluted alcohol and propylene glycol.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, toothpaste, gel dentrifice, chewing gum, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid

or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

5 Oils useful in parenteral formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils useful in such formulations include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

10 Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides; (b) anionic detergents such as, for example, alkyl, aryl, and olefin sul-
15 fonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl- β -aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

20 The parenteral formulations typically will contain from about 0.5 to about 25% by weight of the active ingredient in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations
25 will typically range from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and
30 vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

The compounds of the invention can also be delivered topically. Regions for topical administration include the skin surface and also mucous membrane tissues of the vagina, rectum, nose, mouth, and throat. Compositions for topical administration via the skin and mucous membranes should not give rise to signs of irritation, such as swelling or redness.

The topical composition may include a pharmaceutically acceptable carrier adapted for topical administration. Thus, the composition may take the form of a suspension, solution, ointment, lotion, sexual lubricant, cream, foam, aerosol, spray, suppository, implant, inhalant, tablet, capsule, dry powder, syrup, balm or lozenge, for example. Methods for preparing such compositions are well known in the pharmaceutical industry.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sor-

bitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

5 Transdermal Delivery

The pharmaceutical agent-chemical modifier complexes described herein can be administered transdermally. Transdermal administration typically involves the delivery of a pharmaceutical agent for percutaneous passage of the drug into the systemic circulation of the patient. The skin sites include anatomic regions for transdermally administering the drug and include the forearm, abdomen, chest, back, buttock, mastoidal area, and the like.

Transdermal delivery is accomplished by exposing a source of the complex to a patient's skin for an extended period of time. Transdermal patches have the added advantage of providing controlled delivery of a pharmaceutical agent-chemical modifier complex to the body. See *Transdermal Drug Delivery: Developmental Issues and Research Initiatives*, Hadgraft and Guy (eds.), Marcel Dekker, Inc., (1989); *Controlled Drug Delivery: Fundamentals and Applications*, Robinson and Lee (eds.), Marcel Dekker Inc., (1987); and *Transdermal Delivery of Drugs*, Vols. 1-3, Kydonieus and Berner (eds.), CRC Press, (1987). Such dosage forms can be made by dissolving, dispersing, or otherwise incorporating the pharmaceutical agent-chemical modifier complex in a proper medium, such as an elastomeric matrix material. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate-controlling membrane or dispersing the compound in a polymer matrix or gel.

Passive Transdermal Drug Delivery

A variety of types of transdermal patches will find use in the methods described herein. For example, a simple adhesive patch can be prepared from a backing material and an acrylate adhesive. The pharmaceutical agent-chemical modifier complex and any enhancer are formulated into the adhesive casting solution and allowed to mix thoroughly. The solution is cast directly onto the backing material and

the casting solvent is evaporated in an oven, leaving an adhesive film. The release liner can be attached to complete the system.

Alternatively, a polyurethane matrix patch can be employed to deliver the pharmaceutical agent-chemical modifier complex. The layers of this patch comprise a backing, a polyurethane drug/enhancer matrix, a membrane, an adhesive, and a release liner. The polyurethane matrix is prepared using a room temperature curing polyurethane prepolymer. Addition of water, alcohol, and complex to the prepolymer results in the formation of a tacky firm elastomer that can be directly cast only the backing material.

A further embodiment of this invention will utilize a hydrogel matrix patch. Typically, the hydrogel matrix will comprise alcohol, water, drug, and several hydrophilic polymers. This hydrogel matrix can be incorporated into a transdermal patch between the backing and the adhesive layer.

The liquid reservoir patch will also find use in the methods described herein. This patch comprises an impermeable or semipermeable, heat sealable backing material, a heat sealable membrane, an acrylate based pressure sensitive skin adhesive, and a siliconized release liner. The backing is heat sealed to the membrane to form a reservoir which can then be filled with a solution of the complex, enhancers, gelling agent, and other excipients.

Foam matrix patches are similar in design and components to the liquid reservoir system, except that the gelled pharmaceutical agent-chemical modifier solution is constrained in a thin foam layer, typically a polyurethane. This foam layer is situated between the backing and the membrane which have been heat sealed at the periphery of the patch.

For passive delivery systems, the rate of release is typically controlled by a membrane placed between the reservoir and the skin, by diffusion from a monolithic device, or by the skin itself serving as a rate-controlling barrier in the delivery system. See U.S. Pat. Nos. 4,816,258; 4,927,408; 4,904,475; 4,588,580, 4,788,062; and the like. The rate of drug delivery will be dependent, in part, upon the nature of the membrane. For example, the rate of drug delivery across membranes within the

body is generally higher than across dermal barriers. The rate at which the complex is delivered from the device to the membrane is most advantageously controlled by the use of rate-limiting membranes which are placed between the reservoir and the skin. Assuming that the skin is sufficiently permeable to the complex (i.e., absorption
5 through the skin is greater than the rate of passage through the membrane), the membrane will serve to control the dosage rate experienced by the patient.

Suitable permeable membrane materials may be selected based on the desired degree of permeability, the nature of the complex, and the mechanical considerations related to constructing the device. Exemplary permeable membrane materials
10 include a wide variety of natural and synthetic polymers, such as polydimethylsiloxanes (silicone rubbers), ethylenevinylacetate copolymer (EVA), polyurethanes, polyurethane-polyether copolymers, polyethylenes, polyamides, polyvinylchlorides (PVC), polypropylenes, polycarbonates, polytetrafluoroethylenes (PTFE), cellulosic
15 materials, e.g., cellulose triacetate and cellulose nitrate/acetate, and hydrogels, e.g., 2-hydroxyethylmethacrylate (HEMA).

Other items may be contained in the device, such as other conventional components of therapeutic products, depending upon the desired device characteristics.
20 For example, the compositions according to this invention may also include one or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, and the like. These pharmaceutical compositions also can contain other active ingredients such as antimicrobial agents, particularly antibiotics, anesthetics, analgesics, and antipruritic
25 agents.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient
30 sized molds, allowed to cool, and to solidify.

The active compound may be formulated into a suppository comprising, for example, about 0.5% to about 50% of a compound of the invention, disposed in a polyethylene glycol (PEG) carrier (e.g., PEG 1000 [96%] and PEG 4000 [4%]).
35

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g., gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a cap-

sule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Pharmaceutically acceptable salts

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Pharmaceutically acceptable salts of the instant compounds, where they can be prepared, are also intended to be covered by this invention. These salts will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant that the salt will retain the biological activity of the parent compound and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

10

Pharmaceutically acceptable salts are prepared in a standard manner. If the parent compound is a base it is treated with an excess of an organic or inorganic acid in a suitable solvent. If the parent compound is an acid, it is treated with an inorganic or organic base in a suitable solvent.

15

The compounds of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective amount.

20

Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

25

Examples of a typical tablet

A typical tablet which may be prepared by conventional tableting techniques may contain:

5

Core:

	Active compound (as free compound or salt thereof)
	100 mg
10	Colloidal silicon dioxide (Aerosil)
	1.5 mg
	Cellulose, microcryst. (Avicel)
	70 mg
	Modified cellulose gum (Ac-Di-Sol)
15	7.5 mg
	Magnesium stearate

Coating:

20

	HPMC approx. 9 mg
	*Mywacett 9-40 T approx.
25	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The pharmaceutical carrier

30

Illustrative solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. A solid carrier can include one or more substances which may also act as flavouring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the car-

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rier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions, and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active
5 ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

10 Illustrative liquid carriers include syrup, peanut oil, olive oil, water, etc. Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain
15 other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl
20 cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous
25 injection. Sterile solutions can also be administered intravenously. The compound can also be administered orally either in liquid or solid composition form.

30 The carrier or excipient may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate along or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like. When formulated for oral administration, 0.01% Tween 80 in PHOSAL PG-50 (phospholipid concentrate
35 with 1,2-propylene glycol, A. Nattermann & Cie. GmbH) has been recognized as

providing an acceptable oral formulation for other compounds, and may be adapted to formulations for various compounds of this invention.

Controlled release formulations

5 The following terms may be considered to be substantially equivalent to controlled release, for the purposes of the present invention: continuous release, controlled release, delayed release, depot, gradual release, long-term release, programmed release, prolonged release, proportionate release, protracted release, repository, retard, slow release, spaced release, sustained release, time coat, timed release,
10 delayed action, extended action, layered-time action, long acting, prolonged action, repeated action, slowing acting, sustained action, sustained-action medications, and extended release. Further discussions of these terms may be found in Lesczek Krowczynski, Extended-Release Dosage Forms, 1987 (CRC Press, Inc.).

15 The various controlled release technologies cover a very broad spectrum of drug dosage forms. Controlled release technologies include, but are not limited to physical systems and chemical systems.

Physical systems include, but not limited to, reservoir systems with rate-controlling
20 membranes, such as microencapsulation, macroencapsulation, and membrane systems; reservoir systems without rate-controlling membranes, such as hollow fibers, ultra microporous cellulose triacetate, and porous polymeric substrates and foams; monolithic systems, including those systems physically dissolved in non-porous, polymeric, or elastomeric matrices (e.g., non-erodible, erodible, environmental agent
25 ingress, and degradable), and materials physically dispersed in non-porous, polymeric, or elastomeric matrices (e.g., non-erodible, erodible, environmental agent ingress, and degradable); laminated structures, including reservoir layers chemically similar or dissimilar to outer control layers; and other physical methods, such as osmotic pumps, or adsorption onto ion-exchange resins.

30 Chemical systems include, but are not limited to, chemical erosion of polymer matrices (e.g., heterogeneous, or homogeneous erosion), or biological erosion of a polymer matrix (e.g., heterogeneous, or homogeneous). Additional discussion of catego-

ries of systems for controlled release may be found in Agis F. Kydonieus, *Controlled Release Technologies: Methods, Theory and Applications*, 1980 (CRC Press, Inc.).

5 Controlled release drug delivery systems may also be categorized under their basic technology areas, including, but not limited to, rate-preprogrammed drug delivery systems, activation-modulated drug delivery systems, feedback-regulated drug delivery systems, and site-targeting drug delivery systems.

10 In rate-preprogrammed drug delivery systems, release of drug molecules from the delivery systems "preprogrammed" at specific rate profiles. This may be accomplished by system design, which controls the molecular diffusion of drug molecules in and/or across the barrier medium within or surrounding the delivery system. Fick's laws of diffusion are often followed.

15 In activation-modulated drug delivery systems, release of drug molecules from the delivery systems is activated by some physical, chemical or biochemical processes and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied, or energy input.

20 In feedback-regulated drug delivery systems, release of drug molecules from the delivery systems may be activated by a triggering event, such as a biochemical substance, in the body. The rate of drug release is then controlled by the concentration of triggering agent detected by a sensor in the feedback regulated mechanism.

25 In a site-targeting controlled-release drug delivery system, the drug delivery system targets the active molecule to a specific site or target tissue or cell. This may be accomplished, for example, by a conjugate including a site specific targeting moiety that leads the drug delivery system to the vicinity of a target tissue (or cell), a solubilizer that enables the drug delivery system to be transported to and preferentially
30 taken up by a target tissue, and a drug moiety that is covalently bonded to the polymer backbone through a spacer and contains a cleavable group that can be cleaved only by a specific enzyme at the target tissue.

35 While a preferable mode of controlled release drug delivery will be oral, other modes of delivery of controlled release compositions according to this invention may be

used. These include mucosal delivery, nasal delivery, ocular delivery, transdermal delivery, parenteral controlled release delivery, vaginal delivery, rectal delivery and intrauterine delivery. All of these dosage forms may be manufactured using conventional techniques, together with the techniques discussed herein.

5

There are a number of controlled release drug formulations that are developed preferably for oral administration. These include, but are not limited to, osmotic pressure-controlled gastrointestinal delivery systems; hydrodynamic pressure-controlled gastrointestinal delivery systems; membrane permeation-controlled gastrointestinal delivery systems, which include microporous membrane permeation-controlled gastrointestinal delivery devices; gastric fluid-resistant intestine targeted controlled-release gastrointestinal delivery devices; gel diffusion-controlled gastrointestinal delivery systems; and ion-exchange-controlled gastrointestinal delivery systems, which include cationic and anionic drugs. Additional information regarding controlled release drug delivery systems may be found in Yie W. Chien, Novel Drug Delivery Systems, 1992 (Marcel Dekker, Inc.). Some of the formulations will now be discussed in more detail.

Enteric coatings may be applied to tablets to prevent the release of drugs in the stomach either to reduce the risk of unpleasant side effects or to maintain the stability of the drug which might otherwise be subject to degradation or exposure to the gastric environment. Most polymers that are used for this purpose are polyacids that function by virtue of the fact that their solubility in aqueous medium is pH-dependent, and they require conditions with a pH higher than normally encountered in the stomach.

Enteric coatings may be used to coat a solid or liquid dosage form of the compounds according to the invention. Enteric coatings promote the inventive compounds remaining physically incorporated in the dosage form for a specified period when exposed to gastric juice. Yet the enteric coatings are designed to disintegrate in intestinal fluid for ready absorption. Delay of the compounds' absorption is dependent on the rate of transfer through the gastrointestinal tract, and so the rate of gastric emptying is an important factor. Some investigators have reported that a multiple-unit type dosage form, such as granules, may be superior to a single-unit type. Therefore, in a preferable embodiment, the compounds according to the inven-

tion may be contained in an enterically coated multiple-unit dosage form. In a more preferable embodiment, the dosage form of the compounds according to the invention is prepared by spray-coating granules of an compounds -enteric coating agent solid dispersion on an inert core material. These granules can result in prolonged
5 absorption of the drug with good bioavailability.

Typical enteric coating agents include, but are not limited to, hydroxypropylmethyl-cellulose phthalate, methacrylic acid-methacrylic acid ester copolymer, polyvinyl acetate-phthalate and cellulose acetate phthalate. Akihiko Hasegawa, Application of
10 solid dispersions of Nifedipine with enteric coating agent to prepare a sustained-release dosage form, Chem. Pharm. Bull. 33: 1615-1619 (1985). Various enteric coating materials may be selected on the basis of testing to achieve an enteric coated dosage form designed ab initio to have a preferable combination of dissolution time, coating thicknesses and diametral crushing strength. S. C. Porter et al.,
15 The Properties of Enteric Tablet Coatings Made From Polyvinyl Acetate-phthalate and Cellulose acetate Phthalate, J. Pharm. Pharmacol. 22:42p (1970).

On occasion, the performance of an enteric coating may hinge on its permeability. S. C. Porter et al., The Permeability of Enteric Coatings and the Dissolution Rates of
20 Coated Tablets, J. Pharm. Pharmacol. 34: 5-8 (1981). With such oral drug delivery systems, the drug release process may be initiated by diffusion of aqueous fluids across the enteric coating. Investigations have suggested osmotic driven/rupturing affects as important release mechanisms from enteric coated dosage forms. Roland Bodmeier et al., Mechanical Properties of Dry and Wet Cellulosic and Acrylic Films
25 Prepared from Aqueous Colloidal Polymer Dispersions used in the Coating of Solid Dosage Forms, Pharmaceutical Research, 11: 882-888 (1994).

Another type of useful oral controlled release structure is a solid dispersion. A solid dispersion may be defined as a dispersion of one or more active ingredients in an
30 inert carrier or matrix in the solid state prepared by the melting (fusion), solvent, or melting-solvent method. Akihiko Hasegawa, Super Saturation Mechanism of Drugs from Solid Dispersions with Enteric Coating Agents, Chem. Pharm. Bull. 36: 4941-4950 (1998). The solid dispersions may be also called solid-state dispersions. The term "coprecipitates" may also be used to refer to those preparations obtained by
35 the solvent methods.

Solid dispersions may be used to improve the solubilities and/or dissolution rates of compounds according to the invention that may be poorly water-soluble. See generally Hiroshi Yuasa, et al., Application of the Solid Dispersion Method to the Controlled Release Medicine. III. Control of the Release Rate of Slightly Water-Soluble Medicine From Solid Dispersion Granules, Chem. Pharm. Bull. 41:397-399 (1993). The solid dispersion method was originally used to enhance the dissolution rate of slightly water-soluble medicines by dispersing the medicines into water-soluble carriers such as polyethylene glycol or polyvinylpyrrolidone, Hiroshi Yuasa, et al., Application of the Solid Dispersion Method to the Controlled Release of Medicine. IV. Precise Control of the Release Rate of a Water-Soluble Medicine by Using the Solid Dispersion Method Applying the Difference in the Molecular Weight of a Polymer, Chem. Pharm. Bull. 41:933-936 (1993).

The selection of the carrier may have an influence on the dissolution characteristics of the dispersed drug because the dissolution rate of a component from a surface may be affected by other components in a multiple component mixture. For example, a water-soluble carrier may result in a fast release of the drug from the matrix, or a poorly soluble or insoluble carrier may lead to a slower release of the drug from the matrix. The solubility of poorly water soluble compounds according to the invention may also be increased owing to some interaction with the carriers.

Examples of carriers useful in solid dispersions according to the invention include, but are not limited to, water-soluble polymers such as polyethylene glycol, polyvinylpyrrolidone, or hydroxypropylmethyl-cellulose. Akihiko Hasegawa, Application of Solid Dispersions of Nifedipine with Enteric Coating Agent to Prepare a Sustained-release Dosage Form, Chem. Pharm. Bull. 33:1615-1619 (1985).

There are various methods commonly known for preparing solid dispersions. These include, but are not limited to the melting method, the solvent method and the melting-solvent method.

In the melting method, the physical mixture of a drug in a water-soluble carrier is heated directly until it melts. The melted mixture is then cooled and solidified rapidly while rigorously stirred. The final solid mass is crushed, pulverized and sieved. Us-

ing this method a super saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule may be arrested in solvent matrix by the instantaneous solidification process. A disadvantage is that many substances, either drugs or carriers, may decompose or evaporate during the fusion process at high temperatures. However, this evaporation problem may be avoided if the physical mixture is heated in a sealed container. Melting under a vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of the drug or carrier.

The solvent method has been used in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. Solvent method dispersions may be prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. The main advantage of the solvent method is that thermal decomposition of drugs or carriers may be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of its supposedly negligible amount of the solvent on the chemical stability of the drug.

Another method of producing solid dispersions is the melting-solvent method. It is possible to prepare solid dispersions by first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into a melt of polyethylene glycol, obtainable below 70 degrees, without removing the liquid solvent. The selected solvent or dissolved adenosine analogs may be selected such that the solution is not miscible with the melt of polyethylene glycol. The polymorphic form of the adenosine analogs may then be precipitated in the melt. Such a unique method possesses the advantages of both the melting and solvent methods. Win Loung Chiou, et al., Pharmaceutical Applications of Solid Dispersion Systems, J. Pharm. Sci. 60:1281-1301 (1971).

Another controlled release dosage form is a complex between an ion exchange resin and the compounds according to the invention. Ion exchange resin-drug complexes have been used to formulate sustained-release products of acidic and basic drugs. In one preferable embodiment, a polymeric film coating is provided to the ion

exchange resin-drug complex particles, making drug release from these particles diffusion controlled. See Y. Raghunathan et al., Sustained-released drug delivery system I: Coded ion-exchange resin systems for phenylpropanolamine and other drugs, J. Pharm. Sciences 70: 379-384 (1981).

5

Injectable micro spheres are another controlled release dosage form. Injectable micro spheres may be prepared by non-aqueous phase separation techniques, and spray-drying techniques. Micro spheres may be prepared using polylactic acid or copoly(lactic/glycolic acid). Shigeyuki Takada, Utilization of an Amorphous Form of a Water-Soluble GPIIb/IIIa Antagonist for Controlled Release From Biodegradable Micro spheres, Pharm. Res. 14:1146-1150 (1997), and ethyl cellulose, Yoshiyuki Koida, Studies on Dissolution Mechanism of Drugs from Ethyl Cellulose Microcapsules, Chem. Pharm. Bull. 35:1538-1545 (1987).

15 Other controlled release technologies that may be used in the practice of this invention are quite varied. They include SODAS (Spheroidal Oral Drug Absorption System), INDAS (Insoluble Drug Absorption System), IPDAS (Intestinal Protective Drug Absorption System), MODAS (Multiporous Oral Drug Absorption System), EFVAS (Effervescent Drug Absorption System), PRODAS (Programmable Oral Drug Absorption System), and DUREDAS (Dual Release Drug Absorption System) available from Elan Pharmaceutical Technologies, Dublin, Ireland. SODAS are multi particulate dosage forms utilizing controlled release beads. INDAS are a family of drug delivery technologies designed to increase the solubility of poorly soluble drugs. IPDAS are multi particulate tablet formation utilizing a combination of high density controlled release beads and an immediate release granulate. MODAS are controlled release single unit dosage forms. Each tablet consists of an inner core surrounded by a semipermeable multiparous membrane that controls the rate of drug release. EFVAS is an effervescent drug absorption system, PRODAS is a family of multi particulate formulations utilizing combinations of immediate release and controlled release mini-tablets. DUREDAS is a bilayer tablet formulation providing dual release rates within the one dosage form. Although these dosage forms are known to one of skill, certain of these dosage forms will now be discussed in more detail.

35 INDAS was developed specifically to improve the solubility and absorption characteristics of poorly water soluble drugs. Solubility and, in particular, dissolution within

the fluids of the gastrointestinal tract is a key factor in determining the overall oral bioavailability of poorly water soluble drug. By enhancing solubility, one can increase the overall bioavailability of a drug with resulting reductions in dosage. IPDAS takes the form of a high energy matrix tablet. In a preferred embodiment of the invention production involves including adenosine analogs in an amorphous form together with a combination of energy, excipients, and unique processing procedures.

Once included in the desirable physical form, the resultant high energy complex may be stabilized by an absorption process that utilizes a novel polymer cross-linked technology to prevent recrystallization. The combination of the change in the physical state of the adenosine analogs according to the invention coupled with the solubilizing characteristics of the excipients employed enhances the solubility of the adenosine analogs according to the invention. The resulting absorbed amorphous drug complex granulate may be formulated with a gel-forming erodible tablet system to promote substantially smooth and continuous absorption.

IPDAS is a multi-particulate tablet technology that may enhance the gastrointestinal tolerability of potential irritant and ulcerogenic drugs. Intestinal protection is facilitated by the multi-particulate nature of the IPDAS formulation which promotes dispersion of an irritant adenosine analog according to the invention throughout the gastrointestinal tract. Controlled release characteristics of the individual beads may avoid high concentration of drug being both released locally and absorbed systemically. The combination of both approaches serves to minimize the potential harm of the adenosine analog according to the invention with resultant benefits to patients.

IPDAS is composed of numerous high density controlled release beads. Each bead may be manufactured by a two step process that involves the initial production of a micromatrix with embedded adenosine analogs according to the invention and the subsequent coating of this micromatrix with polymer solutions that form a rate limiting semipermeable membrane in vivo. Once an IPDAS tablet is ingested, it may disintegrate and liberate the beads in the stomach. These beads may subsequently pass into the duodenum and along the gastrointestinal tract, preferably in a controlled and gradual manner, independent of the feeding state. Adenosine analog release occurs by diffusion process through the micromatrix and subsequently

through the pores in the rate controlling semipermeable membrane. The release rate from the IPDAS tablet may be customized to deliver a drug-specific absorption profile associated with optimized clinical benefit. Should a fast onset of activity be necessary, immediate release granulate may be included in the tablet. The tablet
5 may be broken prior to administration, without substantially compromising drug release, if a reduced dose is required for individual titration.

MODAS is a drug delivery system that may be used to control the absorption of water soluble adenosine analogs according to the invention. Physically MODAS is a
10 non-disintegrating table formulation that manipulates drug release by a process of rate limiting diffusion by a semipermeable membrane formed in vivo. The diffusion process essentially dictates the rate of presentation of drug to the gastrointestinal fluids, such that the uptake into the body is controlled. Because of the minimal use of excipients, MODAS can readily accommodate small dosage size forms. Each
15 MODAS tablet begins as a core containing active drug plus excipients. This core is coated with a solution of insoluble polymers and soluble excipients. Once the tablet is ingested, the fluid of the gastrointestinal tract may dissolve the soluble excipients in the outer coating leaving substantially the insoluble polymer. What results is a network of tiny, narrow channels connecting fluid from the gastrointestinal tract to
20 the inner drug core of water soluble drug. This fluid passes through these channels, into the core, dissolving the drug, and the resultant solution of drug may diffuse out in a controlled manner. This may permit both controlled dissolution and absorption. An advantage of this system is that the drug releasing pores of the tablet are distributed over substantially the entire surface of the tablet. This facilitates uniform drug
25 absorption and reduces aggressive unidirectional drug delivery. MODAS represents a very flexible dosage form in that both the inner core and the outer semipermeable membrane may be altered to suit the individual delivery requirements of a drug. In particular, the addition of excipients to the inner core may help to produce a micro environment within the tablet that facilitates more predictable release and absorption
30 rates. The addition of an immediate release outer coating may allow for development of combination products.

Additionally, PRODAS may be used to deliver adenosine analogs according to the invention. PRODAS is a multi particulate drug delivery technology based on the
35 production of controlled release mini tablets in the size range of 1.5 to 4 mm in diame-

ter. The PRODAS technology is a hybrid of multi particulate and hydrophilic matrix tablet approaches, and may incorporate, in one dosage form, the benefits of both these drug delivery systems.

5 In its most basic form, PRODAS involves the direct compression of an immediate release granulate to produce individual mini tablets that contain adenosine analogs according to the invention. These mini tablets are subsequently incorporated into hard gels and capsules that represent the final dosage form. A more beneficial use of this technology is in the production of controlled release formulations. In this case,
10 the incorporation of various polymer combinations within the granulate may delay the release rate of drugs from each of the individual mini tablets. These mini tablets may subsequently be coated with controlled release polymer solutions to provide additional delayed release properties. The additional coating may be necessary in the case of highly water soluble drugs or drugs that are perhaps gastroirritants
15 where release can be delayed until the formulation reaches more distal regions of the gastrointestinal tract.

The pharmaceutical composition of the invention comprising a channel blocker may contain between 0.0001 to 90 % by volume of the compound having channel blocker
20 activity.

Examples

Example 1

25

Vasomotor responses

Young male Sprague-Dawley (Tac) rats (300 - 380 g) are exanguinated during CO₂ anaesthesia. The brains are removed and the basilar and middle cerebral arteries
30 are carefully dissected out under an operating microscope. Each vessel is cut into 1- to 2-mm long circular segments and placed in an ice-cold buffer solution gassed with 5% CO₂ in O₂. The composition of the buffer is (mM): NaCl 119, NaHCO₃ 15, KCl 4.6, CaCl₂ 1.5, NaH₂PO₄ 1.2, MgCl₂ 1.2, and glucose 5.5. The buffer is continuously aerated with oxygen enriched with 5% CO₂, resulting in a pH of 7.4. Some
35 experiments are performed in the absence of endothelium. These vessel segments

are perfused with a buffer solution containing 0.1% Triton X-100 for 15 s. The absence of endothelium is always checked by the lack of a dilator response to 10^{-5} M carbachol.

5 In order to determine vessel tension, each segment is mounted on two metal wires 40 μ m in diameter in a myograph (e.g. Model 610M, Danish Myo Technology, Denmark). The buffer solution is continuously aerated with 5% CO₂ in O₂ to maintain a stable pH of 7.4. The artery segments are allowed to equilibrate for approximately 30 min. The vessels are stretched to the internal circumference the vessel will have
10 if relaxed and exposed to a passive transmural pressure of 100 mmHg (13.3 kPa) for the basilar artery and 52 mmHg (7.0 kPa) for the middle cerebral artery. This is in order to achieve maximal active force development. Following a second 30-min equilibration period, the vessels are constricted twice with 63 mM KCl in a modified buffer solution in which NaCl is substituted for KCl on an equimolar basis.

15 Examples of contraction can be 1.9 mN in basilar and 0.7 mN in middle cerebral arteries with endothelium and to 1.5 mN in basilar and to 0.5 mN in middle cerebral arteries without endothelium.

20 In order to study the relaxant effect of K_{ATP} openers or 10^{-5} M carbachol (for control of endothelial functionality), the cerebral arteries are pre-contracted with 3×10^{-6} M prostaglandin F_{2 α} . This concentration is previously shown to induce a contraction of rat basilar and middle meningeal arteries of 60 to 70% of the maximum response.

25 Examples of stable tension can be 1.4 mN in basilar and 0.7 mN in middle cerebral arteries with endothelium and 1.5 mN in basilar and 0.4 mN in middle cerebral arteries without endothelium, to which the agonist is added in cumulative concentrations.

30 The tension may last for at least 20-30 min without a significant fall in tone. In blockade experiments, the antagonist is added to the tissue bath 15 – 20 min before the addition of K_{ATP}-channel opener in increasing concentrations. The addition of glibenclamide does not affect the tension of the vessels. Out of eight tissue segments two may serve as controls (i.e. without blocker), and the others are treated with blocker in different concentrations.

All concentration-response curves are plotted graphically. $I_{\max}$ (maximum relaxant effect obtained with a K_{ATP} -channel opener), pIC_{50} (negative logarithm of the concentration of K_{ATP} -channel opener that elicited half-maximum relaxation) are calculated arithmetically from each individual concentration-response curve.

5

The non-parametric, Mann Whitney U-test is used to determine statistical significance between the two groups of data. Kruskal-Wallis test is used to determine statistical significance between multiple groups of data with Dunn's multiple comparison test as post-test.

10

Example 2

Binding studies in arteries

15

Membrane preparation

20

Male Sprague-Dawley rats (200-350g) are killed by stunning and decapitation, the hearts are quickly removed and placed in ice-cold buffer containing (in mM): NaCl 139, KCl 5, $MgCl_2$ 1.2, HEPES (4-(2-hydroxyethyl)-1-piperazine-ethanesulphonic acid) 5 and EGTA (ethylene glycol-bis-(2-aminoethylether)-N,N,N',N'-tetra-acetic acid) 1 at pH 7.4. The atria are removed and the ventricles minced in 3 vol g^{-1} wet weight of hypotonic buffer containing HEPES (10 mM), EGTA (1mM), phenylmethylsulphonyl fluoride (PMSF; 0.2 mM), pepstatin A (0.2 μM), leupeptin (10 μM) and soybean trypsin inhibitor (10 $\mu g\ ml^{-1}$). The material is homogenized by three 10 s burst at 12,000 rpm with a polytron homogenizer (e.g. probe PT-DA 3007/2) and the resulting homogenate is passed through a stainless steel sieve of mesh 320 μm , to remove connective tissue and larger coronary vessels. The homogenate is then centrifuged for 45 min at $10^5 \times g$ and the resulting pellet is suspended in 15-20 volumes of ice-cold HEPES-buffer (in mM: NaCl 139, KCl 5, $MgCl_2$ 2 and HEPES 20 (pH 7.4)) to a protein concentration of $\approx 50\ mg\ ml^{-1}$ and is frozen at $-80^\circ C$. The protein concentration is determined with bovine serum albumin as the standard.

30

Equilibrium binding experiments with [^3H]-P1075

For saturation experiments, the membrane preparation (0.8-0.9 mg ml⁻¹) is incubated with [³H]-P1075 (0.7-23 nM) in a total volume of 1.1 ml at 37°C and pH 7.4 for 30 min in an incubation buffer containing (in mM): NaCl 139, KCl 5, MgCl₂ 25, CaCl₂ 1.25 and HEPES 20; the buffer is supplemented with creatine phosphokinase (50 u

5

ml⁻¹), creatine phosphate (20 mM) and Na₂ATP (3 mM). The high concentration of Mg²⁺ is necessary to account for Mg²⁺ binding of creatine phosphate (equilibrium dissociation constant ≈ 25 mM). Incubation is stopped by dilution 0.3 ml aliquots (in triplicate) in 8 ml of ice-cold quench solution (50 mM Tris, 154 mM NaCl, pH 7.4).

10

Bound and free ligand are separated by rapid filtration under vacuum over Whatman GF/C filters. Filters are washed twice with 8 ml of ice-cold quench solution and counted for ³H in the presence of 3 ml of scintillant (e.g. Ulitma Gold; Packard). In the concentration range from 0.5 to 5 μM, [³H]-P1075 is used in undiluted form; for higher concentrations it is diluted 1:10 with unlabelled P1075. Nonspecific binding (B_{NS}) is determined in the presence of 10 μM unlabelled P1075.

15

B_{NS} is proportional to free label concentration, L, and is fitted to the equation, B_{NS} = a × L, where a denotes the proportionality constant. Total binding (B_{tot}) is then analysed as the sum of specific and non-specific binding and is fitted to the equation,

$$B_{\text{tot}} = B_{\text{max}} \times L \times (L + K_D)^{-1} + a \times L$$

20

to estimate the values of the equilibrium dissociation constant (K_D) and the maximum concentration of binding sites (B_{max}, fmol mg⁻¹ protein) by the method of least squares.

Inhibition of [³H]-P1075 binding is studied in the presence of [³H]-P1075 (1 nM) and the inhibitor (I) of interest as described above.

25

Example of B_{tot} is 7.5 fmol mg⁻¹ protein and B_{NS} may amount to 35% of B_{tot}. B_S in the presence of inhibitor I is normalized to % of B_S in the absence of I and fitted to the Law of Mass Action, taking into account two binding components:

$$B_S = 100 - A_1 \times I \times (IC_{50,1} + I^{-1} - A_2 \times I \times (IC_{50,2} + I)^{-1}$$

30

Here, A₁ and A₂ denote the extents of inhibition at saturation (amplitudes) of the two components and IC_{50,1} and IC_{50,2} represent the midpoints. Since the label concentration, L = 1 nM, is of the same order of magnitude as the K_D value of P1075 (= 6 nM), the IC₅₀ values for the inhibitors may deviate from the respective inhibition constant K_i by e.g. 17% according to the Cheng-Prusoff equation. Alternatively, data are fitted to the Hill equation,

35

$$B_S = 100 - A_H^n \times I_H^n \times (IC_{50,H}^n + I_H^n)^{-1}$$

where n_H is the Hill coefficient.

Kinetic experiments

- 5 To measure the association kinetics, membranes ($0.5\text{--}0.6\text{ mg ml}^{-1}$ final concentration) are added to the incubation buffer supplemented with [^3H]-P1075 ($1\text{--}6\text{ nM}$), ATP (3mM) and the ATP-regenerating system at 37°C . Aliquots ($500\text{ }\mu\text{l}$) are withdrawn at different time points for separation of bound and free ligand as described above. In some cases, pH is measured in the absence of radiolabel with a KCl/AgCl
- 10 electrode connected to a pH-metre. Nonspecific binding, determined in the presence of P1075 ($10\text{ }\mu\text{M}$), usually will not change with time. Since the label concentration (L) is in large excess over the concentrations of binding sites the data are fitted to a single exponential as function of time (t),
- $$B_S = B_{eq} \times [1 - \exp(-k_{app} \times t)] \text{ with } k_{app} = k_{on} \times L + k_{of}$$
- 15 where B_{eq} denotes the concentration of the receptor-label complex at equilibrium and k_{app} the apparent rate constant of association which depends on the rate constants of association and dissociation (k_{on} , k_{off}) and on the concentration of L as indicated above.
- 20 Dissociation is initiated by addition of P1075 ($10\text{ }\mu\text{M}$) to the receptor-label complex at equilibrium, after incubation of the microsomal preparation with [^3H]-P1075 (1 nM) at 37°C for 30 min . Aliquots are then withdrawn to follow the dissociation kinetics which are fitted to the equation of exponential decay,
- $$B_S = B_{eq} \times \exp(-k_{off} \times t)$$
- 25 with B_{eq} and k_{off} defined as above.

Example 3

Vasomotor responses in vitro

- 30 Young male Sprague-Dawley (Tac) rats ($300\text{--}380\text{ g}$, Taconic M&B, Denmark) were exsanguinated during CO_2 anaesthesia. The brains were removed and the basilar and middle cerebral arteries were carefully dissected out under an operating microscope. Each vessel was cut into $1\text{--}2\text{-mm}$ long circular segments and placed in an ice-cold buffer solution gassed with $5\%\text{ CO}_2$ in O_2 . The composition of the buffer
- 35 was (mM): NaCl 119 , NaHCO_3 15 , KCl 4.6 , CaCl_2 1.5 , NaH_2PO_4 1.2 , MgCl_2 1.2 , and

glucose 5.5. The buffer was continuously aerated with oxygen enriched with 5% CO₂, resulting in a pH of 7.4.

- In order to determine vessel tension, each segment was mounted on two metal wires 40 µm in diameter in a myograph (Model 610M, Danish Myo Technology, Denmark). The buffer solution was continuously aerated with 5% CO₂ in O₂ to maintain a stable pH of 7.4. The artery segments were allowed to equilibrate for approximately 30 min. The vessels were stretched to the internal circumference the vessel would have if relaxed and exposed to a passive transmural pressure of 100 mmHg (13.3 kPa). This was in order to achieve maximal active force development. Following a second 30-min equilibration period, the vessels were constricted twice with 63 mM KCl in a modified buffer solution in which NaCl was substituted for KCl on an equimolar basis. In order to study the relaxant effect of P-1075 the arteries were pre-contracted with 3×10^{-6} M prostaglandin F_{2α}. This concentration was previously shown to induce a contraction of rat basilar and middle cerebral arteries of 60 to 70% of the maximum response to which the P-1075 was added in cumulative concentrations. The tension lasted for at least 20-30 min without a significant fall in tone. In blockade experiments, PNU37883A was added to the tissue bath 15 – 20 min before the addition P-1075 in increasing concentrations. Out of eight tissue segments two served as controls (i.e. without PNU37883A), and the others were treated with PNU37883A in different concentrations. Values are given as means $\pm$ S.E.M
- In rat middle cerebral and basilar arteries the Kir6.1/SUR2B selective K_{ATP} channel blocker PNU37883A is a very potent antagonist of P-1075 induced relaxation. P-1075 is a potent K_{ATP} channel opener in rat middle cerebral and basilar arteries (Figure 1).
- Figure 1 show the concentration-response curves for P-1075 in rat basilar and middle cerebral arteries in absence and in presence of PNU37883A 10^{-8} , 3×10^{-8} M and 10^{-7} M. Values are given as means $\pm$ S.E.M.

As P-1075 is binding to the SUR2 subunit and PNU37783A is binding to the Kir6.1 subunit the effect is not competitive (The curves do not reach the same maximum response).

Claims

1. Use of a K_{ATP} -channel blocker for the manufacture of a medicament for treatment or alleviation of migraine and/or other headaches.
2. The use according to claim 1, wherein said K_{ATP} -channel blocker blocks K_{ATP} -channels comprising at least one of the subunits SUR2B, kir6.1 and kir6.2.
3. The use according to any of the preceding claims, wherein said K_{ATP} channels are located in or in connection to vascular tissue.
4. The use according to any of claims 1 to 2, wherein said K_{ATP} channels are located in or in connection to smooth muscle.
5. The use according to any of claims 1 to 3, wherein said K_{ATP} channels are located in or in connection to arteries, arterioles, capillary system, and/or veins within the head of an individual.
6. The use according to claim 5, wherein said arteries are selected from cerebral and/or dural arteries.
7. The use according to claim 5, wherein said arteries are selected from the group of vertebral arteries, common carotid arteries, external carotid arteries, internal carotid arteries, anterior communicating arteries, anterior cerebral arteries, middle cerebral arteries, posterior communicating arteries, posterior cerebral arteries, superior cerebellar arteries, anterior inferior cerebellar arteries, basilar arteries, precuneal arteries, paracentral artery, pericallosal arteries, callosomarginal arteries, frontopolar arteries, medial orbitofrontal arteries, posterior temporal arteries, angular arteries, posterior parietal arteries, anterior parietal arteries, central arteries, precentral arteries, ascending frontal arteries, lateral orbitofrontal arteries, anterior temporal arteries, middle temporal arteries, anterior inferior cerebellar arteries, posterior temporal arteries, calcarine arteries, parietooccipital arteries,

posterior pericallosal arteries, medial lenticulostriate arteries, lateral lenticulostriate arteries.

- 5 8. The use according to any of claims 3 to 7, wherein said K_{ATP} -channels are located to the smooth muscle cells of the vessels and/or to the endothelial cells and/or to perivascular nerve endings.
- 10 9. The use according to any of the preceding claims, wherein said treatment is prophylactic and/or acute.
- 10 10. The use according to any of the preceding claims, wherein said treatment is systemic.
- 15 11. The use according to any of the preceding claims, wherein said K_{ATP} -channel blocker blocks K_{ATP} -channels with SUR subunits and/or subunits of the Kir6.0 subfamily.
- 20 12. The use according to claim 11, wherein said SUR subunit is a SUR2B subunit, and said Kir subunit is Kir6.1 and/or Kir6.2.
- 25 13. The use according to any of the preceding claims, wherein said K_{ATP} -channel blocker specific binds to the K_{ATP} -channel with a SUR2B subunit and where said K_{ATP} -channel binds at least 3 times more specific than a non-specific K_{ATP} -channel blocker.
- 30 14. The use according to any of the preceding claims, wherein said K_{ATP} -channel blocker inhibits K_{ATP} -channel openers to act with the K_{ATP} -channels.
15. The use according to any of the claims 5 to 14, wherein said K_{ATP} -channel blocker reduces or inhibits dilatation of arteries.
16. The use according to any of the preceding claims, wherein said K_{ATP} -channel blocker is a specific K_{ATP} -channel blocker.

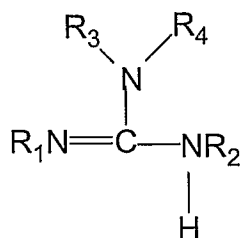
17. The use according to claim 16, wherein said K_{ATP} -channel blocker has a tissue selectivity characterised by a higher selectivity to K_{ATP} -channels within the intracranial blood vessels than to K_{ATP} -channel in the peripheral vascular tissue, pancreatic tissue and cardiac tissue.
- 5
18. The use according to any of the preceding claims, wherein said K_{ATP} -channel blocker binds with a significantly higher affinity equal or above 1.5 to K_{ATP} channels consisting of the SUR2B subunit in combination with Kir6.1 and/or Kir6.2 subunits than K_{ATP} -channels consisting of SUR 1 and SUR2A subunits
- 10 in combination with Kir6.1 and/or Kir6.2.
19. The use according to claim 17, wherein said affinity is equal or above 3, such as equal or above 5, such as equal or above 10, such as equal or above 15, such as equal or above 20, such as equal or above 25, such as
- 15 equal or above 30, such as equal or above 35, such as equal or above 40, such as equal or above 45, such as equal or above 50, such as equal or above 55, such as equal or above 60, such as equal or above 65, such as equal or above 70, such as equal or above 75, such as equal or above 80, such as equal or above 85, such as equal or above 90, such as equal or
- 20 above 95, such as equal or above 100, such as equal or above 105, such as equal or above 110, such as equal or above 115, such as equal or above 120, such as equal or above 125, such as equal or above 150, such as equal or above 175, such as equal or above 200, such as equal or above 225, such as equal or above 250, such as equal or above 275, such as equal or
- 25 above 300, such as equal or above 325, such as equal or above 350, such as equal or above 375, such as equal or above 400, such as equal or above 425, such as equal or above 450, such as equal or above 475, such as equal or above 500.
- 30
20. The use according to any of the preceding claims, wherein said medicament is formulated as powder, pills or as a solution.
21. The use according to claim 20, wherein an administration form of said medicament is selected from pills for oral ingestion, suppository, solution for
- 35 subcutan injection and nasal vaporiser.

22. The use according to any of the preceding claims, wherein said K_{ATP} -channel blocker is selected from the group of 2,3-Butanedione monoxime; 4-aminopyridine (4-AP); 5-Hydroxydecanoate; 7-nitroindazole; 8-oxo-berberine; A-184209; Acecainide; Adenosine (ATP); Aflatrem; Agatoxin, ω -type (ω -Agatoxin); Agitoxin-1; Agitoxin-2; Agitoxin-3; AL 275; Alinidine ST 567; Almokalant H 234/09; Alpha-dendrotoxin; AM 92016; Ambasilide; Ambasilide LU 47110; AN 132; Antioxidants; Apamin; ARH 050642; ATI 2042; ATP; AWD 12-260; AWD 160275; AWD 23-111; AZD 7009; AZDF 265; Azimilide; Barium chloride; Bay K8644 (R)-(+)-form; BDS-I; BDS-II; Bepridil; Berlambine; Bertosamil; Beta-bungarotoxin (β -BuTX); Beta-dendrotoxin; BIIA 0388; BMS 208782; BMS 208783; BRBI 28; Bretylium; BRL 32872; Bromide dendrotoxin; BTS 67582; Bupivacaine; Carsatrin Succinate RWJ 24517; Caryachine; CGX 1007; Changrolin pyrozone; Charybdotoxin; Charylotoxin; CHF 1522 Cyclo-dextrin complex of glibenclamide; Chlorpropamide; Chromanol 293 isomer; Chromanol 293B; Cibenzoline; Ciclazindol; Clamikalant HMR 1098; Clamikalant HMR 1883; Clausenamide (- form); Clausenamide (racemic); Clofilium LY 150378; Clofilium tosylate; Clotrimazole; CNS 1237; CP 308408; CP 339818; CP 366660; CP 92713; CPU 86017; Cyanoguanidine; Dendrotoxin (DTX); Dendrotoxin I (DTX-I); Dendrotoxin K (DTX-K); Dequalinium chloride; Dexsotalol BMY; 057631D d-sotalol; Dicentrine; Dimethyl sulfoxide; DKAH 269; DMP 543; Dofetilide; DPC 543; DPI 201106; Dronedarone SR 33589; DTX, α -type (α -DTX); DTX, β -type (β -DTX); DTX, γ -type (γ -DTX); DTX, δ -type (δ -DTX); E-4031; Efaroxan; EGIS 7229; Englitazone; Ersentilide (+/- form); Ersentilide (S-form); Ethanol; Evodiamine (S); Fampridine 4-aminopyridine EL 970; Fosinoprilat; Gamma-dendrotoxin; GEA 857; Glemanserin MDL 11939; GLG V 13; Glibenclamide; Glimepiride; Glipizide (GLP); Glipizide K 4024; Glipizide TK 1320; Glucagons antagonists; Glybenclamide; Glyburide; Guanethidine; Guanidinium moieties; GYKI 16638; HA 7; HMR 1372; HMR 1402; HMR 1556; HMR 1883; Hydroxy; Iberiotoxin; Ibutilide; Ibutilide U 70226; ICA 17043; ICI 181037; IK Channel Blocker; IMID-1M; IMID-26F; IMID-4F; IMID-4F hydrochloride; Imidazoline moieties; Ipazilide WIN 54177; Ipidacrine NIK 247; Ivabradine; JKL 1073A oxy-berberine; JTV 519; Kaliotoxin; KCB 328; KMC IV 84; KW 3407; L 691121; L 702958; L 706000; L 735821; L 742084;

L 768673; L755860 and related compounds; Levosemotiadil SA 3212;
 Levosemotiadil SD 3212; Limbatoxin; Limbatustoxin; Liriodenine; Lq2; LQE
 908 Pinokalan; LY 190147; LY 97241; Margatoxin; Mitiglinide KAD 1229 S-
 21403; MK 499; N 3601; N-allyl secoboldine; Nateglinide; Nateglinide AY
 5 4166; Neuropeptide Y; Nibentan; Nifekalan MS 551; Niguldipine hydrochlo-
 ride S(+)-form; NIP 142; NOS inhibitors; Noxiustoxin; NS 004; NS 1546;
 OPC 88117; ORG 20781; Pandinotoxin-K α ; Paspalitrem; Paxilline; PD
 157667; Penitrem A; PGE 844384; Phencyclidine; Phentolamine; Phentola-
 mine; Pirmenol CI 845; Pirocixan; PNU 18177A; PNU 37883A; PNU 89692;
 10 PNU 94126; PNU 94158; PNU 94563; PNU 94750; PNU 96179; PNU 96293;
 PNU 97025E; PNU 99963; Pyrdo triazoles; Quinidine; Quinine; Quinine
 hemisulfate salt; Repaglinide AGEE 623; Repaglinide NN 623; Repaglinide;
 Rimonabant SR 141716; Risotilide; Ro-034563; Ropivacaine AL 281;
 Ropivacaine LEA 103; RP 58866; RP 66784 RSD 1000; RSD 1019; Rutae-
 15 carpine; RWJ 28810; RX 871024; S 16260; S 9947; Salicylaloxime; Saxi-
 toxin; SB 237376; Scyllatoxin; SDZ DNJ 608; Sematilide; Sematilide CK
 1752; Sematilide ZK 110516; Sinominine; Sodium 5-hydroxydecanoate; So-
 talol; SPM 928; Spriadoiline; SSR 149744B; Stichodactyla toxin; Sulfony-
 lureas; TEA (tetraethylammonium); Tedisamil; Tedisamil KC 8857; Terikalant
 20 RP 62719; Tertipin; Tertipin-Q; Tetraethylammonium chloride; Tetraethyl-
 ammonium ions; Tetrodotoxin; TH 9121; TH 9122; Tityustoxin K; Tityustoxin-
 K α ; TMB-8; TN 871; Tolazamide; Tolbutamide; Toxin based therapeutics BRI
 6906; TRAM 30; Troglitazone; U 37883A; U 50488H; U-37883A; U-45194A;
 UCL 1439; UCL 1530; UCL 1559; UCL 1608; UCL 1684; UK 66914; UK
 25 78282; WAY 123223; WAY 123398; WIN 17317-3; WIN 61773; XE 991; Y
 39677; YM 026; YM 19348 Racemate; YM 193489-R; YM 193489-S; YT 1;
 Zatebradine; ZM 181037; ZM 181037; ZM 244085.

23. The use according to any of the preceding claims, wherein said K_{ATP}-channel
 30 blocker is a morpholinoguanidine.

24. The use according to any of the preceding claims, wherein said K_{ATP}-channel
 blocker is a compound of the formula



wherein R₁, R₂, R₃ and R₄ are individually selected from the group of adamantyl, hydrogen, alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, phenyl, phenalkyl where alkyl is one to three carbon atoms, inclusive, and mono- or di-substituted phenyl or phenyl moiety of the phenalkyl wherein the substituents are the same or different and are selected from the group consisting of alkyl of one to three carbon atoms, inclusive, halogen, trifluoromethyl and alkoxy of from one to three carbon atoms, inclusive, halo, and trifluoromethyl; hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur. When the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms. When the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof.

25. The use according to claim 23, wherein

R₁ is adamantyl,

R₂ is selected from the group consisting of hydrogen, alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, phenyl, phenalkyl where alkyl is one to three carbon atoms, inclusive, and monosubstituted phenyl wherein the substituent is selected from the group consisting of alkyl of one to three carbon atoms, inclusive, alkoxy of one to three carbon atoms, inclusive, halo, and trifluoromethyl,

5 R₃ is selected from the group consisting of hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur, and

10 when the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms and,

when the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof,

15 R₄ is selected from the group consisting of hydrogen and alkyl of one to eight carbon atoms, inclusive, cycloalkyl of five to eight carbon atoms, inclusive, and when taken together with the nitrogen atom to which they are attached form a saturated heterocyclic ring with methylene, or nitrogen coupled with hydrogen or alkyl of one to three carbon atoms, inclusive, oxygen; or sulphur, and

20 when the heterocyclic ring is with methylene, the heterocyclic ring has from four to six carbon atoms, and

25 when the heterocyclic ring is with oxygen or sulfur, the heterocyclic ring is piperazino, N-alkylpiperazino, morpholino or thiomorpholino, and pharmaceutically acceptable acid addition salts thereof.

26. The use according to any of claims 24 to 25, wherein said compound is selected from a mixture of the (R)-enantiomer and the (S)-enantiomer or substantially pure (R)-enantiomer or substantially pure (S)-enantiomer.

27. A pharmaceutical composition comprising an effective amount of at least one K_{ATP}-channel blocker as defined in any of the claims 1 to 26 or a salt thereof, optionally further comprising a pharmaceutically acceptable carrier substance.

28. A method for treating or alleviating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to blockade of the K_{ATP} channel, which method comprises administering to such a living animal body a therapeutically-effective amount of a K_{ATP} -channel blocker as defined in any of the claims 1 to 26.

29. A method for identifying a K_{ATP} -blocker that blocks a K_{ATP} -channel comprising at least one of the subunits SUR2B, kir6.1 and kir6.2, said method comprises:

- a. obtaining a compound being a possible K_{ATP} -blocker,
- b. obtaining isolated cerebral and/or dural arteries of an animal,
- c. dividing said arteries into pre-determined segments,
- d. placing said divided arteries into a buffer composition in a tissue bath,
- e. affecting said cerebral and/or dural arteries with a K_{ATP} -channel opener by addition of said K_{ATP} -channel opener to the buffer composition, whereby said K_{ATP} -channel opener induce increased diameter/relaxation of the arteries,
- f. affecting said K_{ATP} -channel opener induced cerebral and/or dural arteries with said possible K_{ATP} -blocker by addition of said possible K_{ATP} -channel blocker to the buffer composition,
- g. determining the effect of said possible K_{ATP} -blocker on the diameter of said K_{ATP} -channel opener induced arteries, and
- h. wherein said possible K_{ATP} -blocker is determined to be a K_{ATP} -blocker when the diameter of said K_{ATP} -channel opener induced response in the isolated arteries is reduced by said possible K_{ATP} -blocker.

30. A method for identifying a K_{ATP} -blocker that blocks the K_{ATP} -channel comprising at least one of the subunits SUR2B, kir6.1 and kir6.2, said method comprises

- a. obtaining pancreas, heart and/or cerebral tissue of an animal,
- 5 b. homogenising said tissue,
- c. sieving said homogenised tissue to obtain a filtrate,
- d. ultra-centrifugating said filtrate to obtain a pellet,
- e. resuspending said pellet, to obtain a membrane preparation including membranes from said tissue,
- 10 f. incubating said membrane preparation with a ^3H -labelled K_{ATP} -channel agent, whereby said ^3H -labelled K_{ATP} -channel agent binds to said membranes,
- g. filtrating under vacuum over a filter said membrane preparation incubated with said ^3H -labelled K_{ATP} -channel agent, whereby said
15 membranes in said membrane preparation is deposited on said filter,
- h. washing said filter,
- i. counting the amount of ^3H -labelled K_{ATP} -channel agent on said filter, hereby obtaining a standard signal,
- 20 j. incubating a second membrane obtained from step f with possible K_{ATP} -blocker, performing step g-i with said second membrane to obtain an inhibition signal,
- k. comparing said inhibition signal with said standard signal and hereby determining the displacing properties of said possible K_{ATP} -blocker,
- 25 l. wherein said possible K_{ATP} -blocker is determined to be a K_{ATP} -blocker when said inhibition signal is less than said standard signal.

31. The method according to claim 30, wherein said K_{ATP} -channel agent is a K_{ATP} -channel opener.
32. The method according to claim 31, wherein said K_{ATP} -channel opener is
5 selected from the group of P1075, levcromakalim, cromakalim, pinacidil, nicorandil, ZM226600, diazoxide, ZD6169, celikalim, bimakalim, WAY-133537, Y26763, Y27152, BMS-180448, JTV-506, KR-30450, SDZ PCO 400, YM 934, KC-399, BRL 55834, rilmakalim and SDZ 217-744.
33. Use of a BK_{Ca} -channel blocker for the manufacture of a medicament for
10 treatment or alleviation of migraine and/or headache.
34. The use according to claim 33, wherein said BK_{Ca} -channel blocker blocks
15 BK_{Ca} -channels comprising at least one of the subunits KCNMA1, KCNMB1, KCNMB2, KCNMB3, KCNMB4.
35. The use according to any of claims 33 to 34, wherein said BK_{Ca} -channels are located in connection to vascular tissue.
36. The use according to any of claims 33 to 34, wherein said BK_{Ca} -channels are
20 located in or in connection to smooth muscle and/or to the endothelial cells and/or perivascular nerve endings.
37. The use according to any of claims 33 to 36, wherein said perivascular nerve
25 endings are of sympathetic, parasympathetic or sensory origin.
38. The use according to any of claims 33 to 37, wherein said BK_{Ca} -channels are
30 located in or in connection to arteries, arterioles, capillary system, and/or veins within the head of an individual.
39. The use according to any of claims 37, wherein said BK_{Ca} -channels are located in connection to basilar arteries, cerebral arteries, pial arteries and/or dural arteries.

40. The use according to claim 37, wherein said arteries are selected from the group of vertebral arteries, common carotid arteries, external carotid arteries, internal carotid arteries, anterior communicating arteries, anterior cerebral arteries, middle cerebral arteries, posterior communicating arteries, posterior cerebral arteries, superior cerebellar arteries, anterior inferior cerebellar arteries, basilar arteries, precuneal arteries, paracentral artery, pericallosal arteries, callosomarginal arteries, frontopolar arteries, medial orbitofrontal arteries, posterior temporal arteries, angular arteries, posterior parietal arteries, anterior parietal arteries, central arteries, precentral arteries, ascending frontal arteries, lateral orbitofrontal arteries, anterior temporal arteries, middle temporal arteries, anterior inferior cerebellar arteries, posterior temporal arteries, calcarine arteries, parietooccipital arteries, posterior pericallosal arteries, midial lenticulostriate arteries, lateral lenticulostriate arteries.
41. The use according to any of claims 33 to 40, wherein said BK_{Ca}-channels are located to the smooth muscle cells of the vessels and/or to the endothelial cells and/or to perivascular nerve endings.
42. The use according to any of the claims 33 to 41, wherein said treatment is prophylactic and/or acute.
43. The use according to any of the claims 33 to 42, wherein said treatment is systemic.
44. The use according to any of the claims 33 to 43, wherein said BK_{Ca}-channel blocker blocks an α -subunit of the BK_{Ca}-channel.
45. The use according to any of the claims 33 to 44, wherein said BK_{Ca}-channel blocker is a specific BK_{Ca}-channel blocker which binds to the BK_{Ca}-channel at least 3 times more specific than a non-specific BK_{Ca}-channel blocker.
46. The use according to any of the claims 33 to 45, wherein said BK_{Ca}-channel blocker inhibits BK_{Ca}-channel openers to act with the BK_{Ca}-channels.

47. The use according to any of the claims 33 to 46, wherein said BK_{Ca}-channel blocker reduces or inhibits dilatation of arteries.
48. The use according to any of the claims 33 to 47 , wherein said BK_{Ca}-channel blocker is a specific BK_{Ca}-channel blocker.
49. The use according to any of the claims 33 to 48, wherein said BK_{Ca}-channel blocker has a tissue selectivity characterised by a higher selectivity to BK_{Ca}-channels within the cranial circulation than to BK_{Ca}-channel in the CNS and peripheral tissues
50. The use according to any of the claims 33 to 49, wherein said affinity is equal or above 3, such as equal or above 5, such as equal or above 10, such as equal or above 15, such as equal or above 20, such as equal or above 25, such as equal or above 30, such as equal or above 35, such as equal or above 40, such as equal or above 45, such as equal or above 50, such as equal or above 55, such as equal or above 60, such as equal or above 65, such as equal or above 70, such as equal or above 75, such as equal or above 80, such as equal or above 85, such as equal or above 90, such as equal or above 95, such as equal or above 100, such as equal or above 105, such as equal or above 110, such as equal or above 115, such as equal or above 120, such as equal or above 125, such as equal or above 150, such as equal or above 175, such as equal or above 200, such as equal or above 225, such as equal or above 250, such as equal or above 275, such as equal or above 300, such as equal or above 325, such as equal or above 350, such as equal or above 375, such as equal or above 400, such as equal or above 425, such as equal or above 450, such as equal or above 475, such as equal or above 500.
51. The use according to any of the claims 33 to 50, wherein said medicament is formulated as powder, pills or as a solution.
52. The use according to any of the claims 33 to 51, wherein an administration form of said medicament is selected from pills for oral ingestion, suppository, solution for subcutan injection and nasal vaporiser.

53. The use according to any of the preceding claims, wherein said BK_{Ca}-channel blocker is selected from the group of 2,3-Butanedione monoxime; 4-aminopyridine (4-AP); 5-Hydroxydecanoate; 7-nitroindazole; 8-oxo-berberine; A-184209; Acecainide; Adenosine (ATP); Aflatrem; Agatoxin, ω -type (ω -Agatoxin); Agitoxin-1; Agitoxin-2; Agitoxin-3; AL 275; Alinidine ST 567; Almokalant H 234/09; Alpha-dendrotoxin; AM 92016; Ambasilide; Ambasilide LU 47110; AN 132; Antioxidants; Apamin; ARH 050642; ATI 2042; ATP; AWD 12-260; AWD 160275; AWD 23-111; AZD 7009; AZDF 265; Azimilide; Barium chloride; Bay K8644 (R)-(+)-form; BDS-I; BDS-II; Bepridil; Berlambine; Bertosamil; Beta-bungarotoxin (beta-BuTX); Beta-dendrotoxin; BIIA 0388; BMS 208782; BMS 208783; BRBI 28; Bretylium; BRL 32872; Bromide dendrotoxin; BTS 67582; Bupivacaine; Carsatrin Succinate RWJ 24517; Caryachine; CGX 1007; Changrolin pyrozone; Charybdotoxin; Charylotoxin; CHF 1522 Cyclo-dextrin complex of glibenclamide; Chlorpropamide; Chromanol 293 isomer; Chromanol 293B; Cibenzoline; Ciclazindol; Clamikalant HMR 1098; Clamikalant HMR 1883; Clausenamide (- form); Clausenamide (racemic); Clofilium LY 150378; Clofilium tosylate; Clotrimazole; CNS 1237; CP 308408; CP 339818; CP 366660; CP 92713; CPU 86017; Cyanoguanidine; Dendrotoxin (DTX); Dendrotoxin I (DTX-I); Dendrotoxin K (DTX-K); Dequalinium chloride; Dexsotalol BMY; 057631D d-sotalol; Dicentrine; Dimethyl sulfoxide; DKAH 269; DMP 543; Dofetilide; DPC 543; DPI 201106; Dronedarone SR 33589; DTX, α -type (α -DTX); DTX, β -type (β -DTX); DTX, γ -type (γ -DTX); DTX, δ -type (δ -DTX); E-4031; Efaroxan; EGIS 7229; Englitazone; Ersentilide (+/- form); Ersentilide (S-form); Ethanol; Evodiamine (S); Fampridine 4-aminopyridine EL 970; Fosinoprilat; Gamma-dendrotoxin; GEA 857; Glemanserin MDL 11939; GLG V 13; Glibenclamide; Glimepiride; Glipizide (GLP); Glipizide K 4024; Glipizide TK 1320; Glucagons antagonists; Glybenclamide; Glyburide; Guanethidine; Guanidinium moieties; GYKI 16638; HA 7; HMR 1372; HMR 1402; HMR 1556; HMR 1883; Hydroxy; Iberiotoxin; Ibutilide; Ibutilide U 70226; ICA 17043; ICI 181037; IK Channel Blocker; IMID-1M; IMID-26F; IMID-4F; IMID-4F hydrochloride; Imidazoline moieties; Ipazilide WIN 54177; Ipidacrine NIK 247; Ivabradine; JKL 1073A oxy-berberine; JTV 519; Kaliotoxin; KCB 328; KMC IV 84; KW 3407; L 691121; L 702958; L 706000; L 735821; L 742084;

L 768673; L755860 and related compounds; Levosemotiadil SA 3212;
 Levosemotiadil SD 3212; Limbatoxin; Limbatustoxin; Liriodenine; Lq2; LQE
 908 Pinokalan; LY 190147; LY 97241; Margatoxin; Mitiglinide KAD 1229 S-
 21403; MK 499; N 3601; N-allyl secoboldine; Nateglinide; Nateglinide AY
 5 4166; Neuropeptide Y; Nibentan; Nifekalan MS 551; Niguldipine hydrochlo-
 ride S(+)-form; NIP 142; NOS inhibitors; Noxiustoxin; NS 004; NS 1546;
 OPC 88117; ORG 20781; Pandinotoxin-K α ; Paspalitrem; Paxilline; PD
 157667; Penitrem A; PGE 844384; Phencyclidine; Phentolamine; Phentola-
 mine; Pirmenol CI 845; Pirocixan; PNU 18177A; PNU 37883A; PNU 89692;
 10 PNU 94126; PNU 94158; PNU 94563; PNU 94750; PNU 96179; PNU 96293;
 PNU 97025E; PNU 99963; Pyrdo triazoles; Quinidine; Quinine; Quinine
 hemisulfate salt; Repaglinide AGEE 623; Repaglinide NN 623; Repaglinide;
 Rimonabant SR 141716; Risotilide; Ro-034563; Ropivacaine AL 281;
 Ropivacaine LEA 103; RP 58866; RP 66784 RSD 1000; RSD 1019; Rutaec-
 15 carpine; RWJ 28810; RX 871024; S 16260; S 9947; Salicylaldehyde; Saxi-
 toxin; SB 237376; Scyllatoxin; SDZ DNJ 608; Sematilide; Sematilide CK
 1752; Sematilide ZK 110516; Sinominine; Sodium 5-hydroxydecanoate; So-
 talol; SPM 928; Spriadoiline; SSR 149744B; Stichodactyla toxin; Sulfonyl-
 ureas; TEA (tetraethylammonium); Tedisamil; Tedisamil KC 8857; Terikalant
 20 RP 62719; Tertiapin; Tertiapin-Q; Tetraethylammonium chloride; Tetraethyl-
 ammonium ions; Tetrodotoxin; TH 9121; TH 9122; Tityustoxin K; Tityustoxin-
 K α ; TMB-8; TN 871; Tolazamide; Tolbutamide; Toxin based therapeutics BRI
 6906; TRAM 30; Troglitazone; U 37883A; U 50488H; U-37883A; U-45194A;
 UCL 1439; UCL 1530; UCL 1559; UCL 1608; UCL 1684; UK 66914; UK
 25 78282; WAY 123223; WAY 123398; WIN 17317-3; WIN 61773; XE 991; Y
 39677; YM 026; YM 19348 Racemate; YM 193489-R; YM 193489-S; YT 1;
 Zatebradine; ZM 181037; ZM 181037; ZM 244085.

54. The use according to any of the preceding claims, wherein said BK_{Ca}-
 30 channel blocker is a protein comprising at least a sequence of amino acids
 characterised as Pyr-Phe-Thr-Asp-Val-Asp-Cys-Ser-Val-Ser-Lys-Glu-Cys-
 Trp-Ser-Val-Cys-Lys-Asp-Leu-Phe-Gly-Val-Asp-Arg-Gly-Lys-Cys⁸-Met-Gly-
 Lys-Lys-Cys-Arg-Cys-Tyr-Gln.

55. The use according to claim 54, wherein said protein has a configuration characterised by Pyr-Phe-Thr-Asp-Val-Asp-Cys⁷-Ser-Val-Ser-Lys-Glu-Cys¹³-Trp-Ser-Val-Cys¹⁷-Lys-Asp-Leu-Phe-Gly-Val-Asp-Arg-Gly-Lys-Cys²⁸-Met-Gly-Lys-Lys-Cys³³-Arg-Cys³⁵-Tyr-Gln-OH and wherein there are disulfide bonds between amino acids 7 → 28; 13 → 35; and 17 → 33.
56. The use according to any of claim 33 to 55, wherein said BK_{Ca}-channel blocker is a protein comprising a homology of at least 50% of the protein of claim 54 to 55, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 87%, such as at least 90%, such as at least 92%, such as at least 94%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as at least 99.5% in respect of the corresponding amino acid sequences.
57. The use according to any of claim 33 to 56, wherein said BK_{Ca}-channel blocker is selected from the group of Iberitoxin, Aflatrem, Charybdotoxin, Kaliotoxin, Limbatoxin, Paspalitrem, Paxilline, Penitrem A.
58. A pharmaceutical composition comprising an effective amount of at least one BK_{Ca}-channel blocker as defined in any of the claims 33 to 57 or a salt thereof, optionally further comprising a pharmaceutically acceptable carrier substance.
59. A method for treating or alleviating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to blockade of the BK_{Ca}-channel, which method comprises administering to such a living animal body a therapeutically-effective amount of a BK_{Ca}-channel blocker as defined in any of the claims claims 33 to 57.
60. A method for identifying a compound that blocks the BK_{Ca}-channel, the method comprises, said method comprises:
- obtaining a compound being a possible BK_{Ca}-channel blocker,
 - obtaining isolated cerebral and/or dural arteries of an animal,

- 5
- c. dividing said arteries into pre-determined segments,
- d. placing said divided arteries into a buffer composition in a tissue bath,
- 10
- e. affecting said cerebral and/or dural arteries with a BK_{Ca} -channel opener by addition of said BK_{Ca} -channel opener to the buffer composition, whereby said BK_{Ca} -channel opener induce increased diameter/relaxation of the arteries,
- f. affecting said BK_{Ca} -channel opener induced cerebral and/or dural arteries with said possible BK_{Ca} -channel blocker by addition of said possible BK_{Ca} -channel blocker to the buffer composition,
- 15
- g. determining the effect of said possible BK_{Ca} -channel blocker on the diameter of said BK_{Ca} -channel opener induced arteries, and
- 20
- h. wherein said possible BK_{Ca} -channel blocker is determined to be a BK_{Ca} -channel blocker when the diameter of said BK_{Ca} -channel opener induced response of the isolated arteries is reduced by said possible BK_{Ca} -channel blocker.
61. A method for identifying a BK_{Ca} -channel blocker that blocks the BK_{Ca} -channel, said method comprises
- 25
- a. obtaining peripheral arteries or veins, intestine, kidney, pancreas, heart and/or cerebral arteries of an animal,
- b. homogenising said tissue,
- c. sieving said homogenised tissue to obtain a filtrate,
- d. ultra-centrifugating said filtrate to obtain a pellet,
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- e. resuspending said pellet, to obtain a membrane preparation including membranes from said tissue,

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- f. incubating said membrane preparation with a ^{125}I -labelled BK_{Ca} -channel agent, whereby said ^{125}I -labelled BK_{Ca} -channel agent binds to said membranes,
- g. filtrating under vacuum over a filter said membrane preparation incubated with said ^{125}I -labelled BK_{Ca} -channel agent, whereby said membranes in said membrane preparation is deposited on said filter,
- h. washing said filter,
- i. counting the amount of ^{125}I -labelled BK_{Ca} -channel agent on said filter, hereby obtaining a standard signal,
- 10 j. incubating a second membrane obtained from step f with a possible BK_{Ca} -channel blocker, performing step g-i with said second membrane to obtain an inhibition signal,
- 15 k. comparing said inhibition signal with said standard signal and hereby determining the displacing properties of said possible BK_{Ca} -channel blocker,
- l. wherein said possible BK_{Ca} -channel blocker is determined to be a BK_{Ca} -channel blocker when said inhibition signal is less than said standard signal.

20 62. The method according to claim 61, wherein said tissue is arteries.

63. The method according to claim 61 and 62, wherein said BK_{Ca} -channel agent is a fusion protein of any of the proteins mentioned in claim 57.

