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(54) Benævnelse: **SAMMENSÆTNINGER OMFATTENDE EN KOLINESTERASE-INHIBITOR TIL BEHANDLING AF KOGNITIVE LIDELSER**

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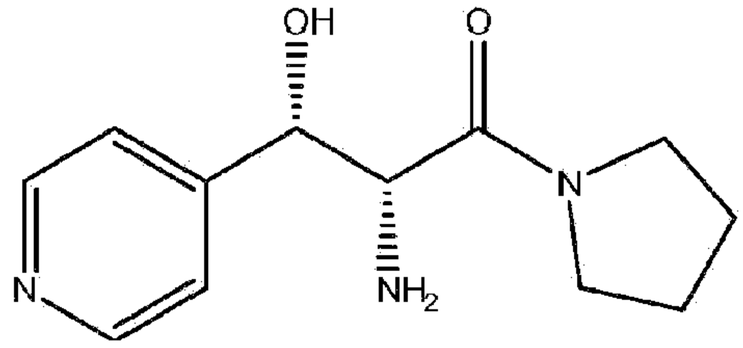
DESCRIPTION

[0001] Disclosed herein is a pharmaceutical composition for use in a method of treating a cognitive disorder selected from the group consisting of an agnosia, an amnesia, an aphasia, an apraxia, a delirium, a dementia and a learning disorder comprising:

1. (i) the cholinesterase inhibitor physostigmine, and
2. (ii) a compound represented by Formula I:



or a pharmaceutically acceptable salt thereof.

I

Cholinesterase inhibitors have many undesirable side effects, such as nausea, diarrhea, insomnia, muscle cramps, sweating, and trembling.

[0002] The inventors have discovered that administering the compound of Formula I with a cholinesterase inhibitor allows one to treat a cognitive disorder selected from the group consisting of an agnosia, an amnesia, an aphasia, an apraxia, a delirium, a dementia and a learning disorder using significantly lower doses of cholinesterase inhibitors - in some embodiments, as low as one-tenth the usual dose or even lower - thereby providing an effective treatment with fewer side effects.

BACKGROUND

[0003] WO 2008/109610, WO 2008/109285, WO 2008/109287 and WO 2009/012082 disclose the compound of Formula I and related compounds for use in the treatment of cognitive disorders, such as dementia and anxiety.

DESCRIPTION OF THE FIGURES

[0004]

Figure 1 shows the effect of Compound X (compound of Formula I) on hippocampal fEPSP amplitude recorded in the freely moving rat compared to physostigmine alone and to physostigmine combined with Compound X. Statistical results for each treatment using within group comparisons are indicated by stars (for exact values see Table 1). Comparisons between treatments involved unpaired t-tests, the results of which are illustrated next to the

respective connector lines (using unpaired t-tests across groups). BL= baseline before vehicle injection.

Figure 2 shows the effect of Compound X on cortical fEPSP amplitude recorded in the freely moving rat compared to physostigmine alone and to physostigmine combined with Compound X. Statistical results for each of the three treatments using within group comparisons are indicated by stars (for exact values see Table 2). Comparisons between treatments involved unpaired t-tests, the results of which are illustrated next to the respective connector lines (using unpaired t-tests across groups).

Figure 3 shows the effect of Compound X on cortical fEPSP amplitude recorded in the freely moving rat compared to galantamine alone and to galantamine combined with Compound X. Statistical results for each of the three treatments using within group comparisons are indicated by stars (for exact values see Table 3). Comparisons between treatments involved unpaired t-tests, the results of which are illustrated next to the respective connector lines (using unpaired t-tests across groups).

DETAILED DESCRIPTION OF THE INVENTION

Cholinesterase inhibitors

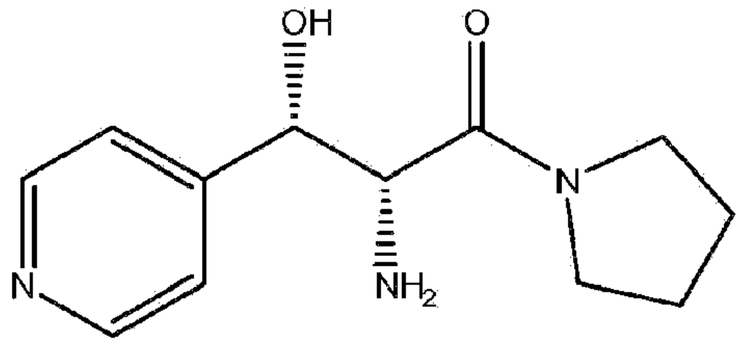
[0005] The term "cholinesterase inhibitor," as used here, means a compound that inhibits the enzymatic degredation of the neurotransmitter acetylcholine, thereby increasing the duration of action of acetylcholine and its levels in the synaptic cleft. Two enzymes are principally responsible for the degredation of acetylcholine, acetylcholinesterase and butyrylcholinesterase. "Cholinesterase inhibitor" includes a compound that inhibits or otherwise reduces the action of one or both of those enzymes. The cholinesterase inhibitor of the present invention is physostigmine or a pharmaceutically acceptable salt thereof.

[0006] The compositions and methods of the invention contemplate that the cholinesterase inhibitors be pharmaceutically effective. "Pharmaceutically effective," as used here, means that the cholinesterase inhibitor is therapeutically useful in humans. The term therefore excludes those cholinesterase inhibitors used as pesticides, such as aldicarb (2-methyl-2-(methylthio)propionaldehyde O-methylcarbamoyloxime), carbofuran (2,3-dihydro-2,2-dimethyl-7-benzofuranyl methylcarbamate), and carbaryl (1-naphthyl methylcarbamate), and those cholinesterase inhibitors that are so toxic to humans that they are used as chemical weapons, such as sarin (2-(fluoro-methylphosphoryl)oxypropane), VX (S-[2-(diisopropylamino)ethyl]-O-ethyl methylphosphonothioate), and soman (3-(fluoromethyl-phosphoryl)oxy-2,2-dimethyl-butane). Most cholinesterase inhibitors that are pesticides and chemical weapons are quasi-reversible or irreversible; most cholinesterase inhibitors that are pharmaceutically effective are

reversible.

Compounds of Formula I

[0007] The pharmaceutical composition for use of the invention includes, in addition to the cholinesterase inhibitor physostigmine, a compound of Formula I:



or a pharmaceutically acceptable salt thereof.

[0008] A pharmaceutically acceptable salt is any salt of the parent compound that is suitable for administration to an animal or human. A salt comprises one or more ionic forms of the compound, such as a conjugate acid or base, associated with one or more corresponding counter-ions. Salts can form from or incorporate one or more deprotonated acidic groups (e.g. carboxylic acids), one or more protonated basic groups (e.g. amines), or both (e.g. zwitterions).

[0009] Pharmaceutically acceptable salts of acidic functional groups may be derived from organic or inorganic bases. The salt may comprise a mono or polyvalent ion. Of particular interest are the inorganic ions, lithium, sodium, potassium, calcium, and magnesium. Organic salts may be made with amines, particularly ammonium salts such as mono, di and trialkyl amines or ethanol amines. Salts may also be formed with caffeine, tromethamine and similar molecules. Hydrochloric acid or some other pharmaceutically acceptable acid may form a salt with a compound that includes a basic group, such as an amine or a pyridine ring.

[0010] Methods for producing the compound of Formula I are described in, for example, U.S. Patent Application Publication No. 2009/0036436.

[0011] Compositions useful in the method of the invention may further include an excipient. Such an excipient may be a carrier or a diluent; this is usually mixed with the active compound or permitted to dilute or enclose the active compound. If a diluent, the carrier may be solid, semi-solid, or liquid material that acts as an excipient or vehicle for the active compound. The formulations may also include wetting agents, emulsifying agents, preserving agents, sweetening agents, and/or flavoring agents.

Cognitive Disorders

[0012] The term "cognitive disorder," as used here,is selected from the group of an agnosia,

an amnesia, an aphasia, an apraxia, deliriums, dementias, and learning disorders.

[0013] In some cases, the cause of a cognitive disorder may be unknown or uncertain. In other cases, the cognitive disorder may be associated with (that is, be caused by or occur in the presence of) other conditions characterized by damage to or loss of neurons or other structures involved in the transmission of signals between neurons. Hence, cognitive disorders may be associated with neurodegenerative diseases such as Alzheimer's disease, corticobasal degeneration, Creutzfeldt-Jacob disease, frontotemporal lobar degeneration, Huntington's disease, multiple sclerosis, normal pressure hydrocephalus, organic chronic brain syndrome, Parkinson's disease, Pick disease, progressive supranuclear palsy, or senile dementia (Alzheimer type); it may be associated with trauma to the brain, such as that caused by chronic subdural hematoma, concussion, intracerebral hemorrhage, or with other injury to the brain, such as that caused by infection (e.g., encephalitis, meningitis, septicemia) or drug intoxication or abuse; and may be associated with Down syndrome and Fragile X syndrome.

[0014] Cognitive disorders may also be associated with other conditions which impair normal functioning of the central nervous system, including psychiatric disorders such as anxiety disorders, dissociative disorders, mood disorders, schizophrenia, and somatoform and factitious disorders; it may also be associated with conditions of the peripheral nervous system, such as chronic pain.

[0015] The compounds described here may be used to treat cognitive disorders selected from the group of agnosias, amnesias, agnosias, amnesias, aphasias, apraxias, deliriums, dementias and learning disorders regardless of whether their cause is known or not.
Examples of dementias which may be treated with the methods of the invention include AIDS dementia complex, Binswanger's disease, dementia with Lewy Bodies, frontotemporal dementia, multi-infarct dementia, Pick's disease, semantic dementia, senile dementia, and vascular dementia.

[0016] Examples of learning disorders which may be treated with the methods of the invention include Asperger's syndrome, attention deficit disorder, attention deficit hyperactivity disorder, autism, childhood disintegrative disorder, and Rett syndrome.

[0017] Examples of aphasia which may be treated with the methods of the invention include progressive non-fluent aphasia.

[0018] The compounds described here may also be used to treat patient having deficits in mental activities that are mild or that otherwise do not significantly interfere with daily life. Mild cognitive impairment is an example of such a condition: a patient with mild cognitive impairment displays symptoms of dementia (e.g., difficulties with language or memory) but the severity of these symptoms is such that a diagnosis of dementia may not be appropriate. The compounds described here may be used to treat mild cognitive impairment and other, similarly less severe forms of cognitive disorders.

Pharmaceutical compositions

[0019] Pharmaceutical compositions of the invention comprise the pharmaceutically effective cholinesterase inhibitor physostigmine and a compound of Formula I.

Dose

[0020] The pharmaceutical compositions for use according to the invention may be formulated such that a patient receives a dose of a cholinesterase inhibitor physostigmine that is usually effective, when administered separately, to treat the cognitive disorder for which the cholinesterase inhibitor is indicated, and a dose of a compound of Formula I that is usually effective, when administered separately, to treat the cognitive disorder. But the pharmaceutical compositions of the invention may also be formulated such that doses of each compound may be those that are ineffective or minimally effective when the compounds are administered alone. This allows one to administer to a patient a formulation of the invention that is as effective as larger doses of the cholinesterase inhibitor physostigmine and a compound of Formula I administered alone, but that is less likely to lead to side effects. This does not mean, however, that formulations of the invention comprise cholinesterase inhibitors and compounds of Formula I in only such doses which are, when administered alone, minimally effective: a patient administered a composition comprising the usual dose of such compounds is likely to experience an improvement that is greater than the improvement the patient would experience when administered the compounds alone.

[0021] The precise dose and frequency of administration depends on the severity and nature of the patient's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound employed, and on the judgment of the prescribing physician. Determining dose is a routine matter that is well within the capability of someone of ordinary skill in the art. Doses of pain-relieving anticonvulsants for treating convulsions, discussed in previous sections, may moreover be used as a guide.

[0022] It may be desirable to administer a dose of the cholinesterase inhibitor physostigmine and the compound of Formula I that is ineffective or minimally effective when the compounds are administered alone. Determining such a dose is a routine matter. Typical such doses are set forth below:

Table 2 - Doses of cholinesterase inhibitors not falling within the scope of the present invention that are generally ineffective or minimally effective, when administered alone, to treat dementia in adult patients

COMPOSITION	INEFFECTIVE DOSES
Donepezil	< 5 to 10 mg once per day
Galantamine	< 8 to 12 mg twice per day

COMPOSITION	INEFFECTIVE DOSES
Rivastigmine	< 3 to 6 mg twice per day

[0023] Should one desire to administer a dose of the cholinesterase inhibitor that is effective when administered alone, one can generally use in excess of the doses stated above.

Excipients and dosage forms

[0024] Those skilled in the art will readily understand that for administering pharmaceutical compositions of the invention the cholinesterase inhibitor physostigmine and a compound of Formula I can be admixed with pharmaceutically acceptable excipient which are well known in the art.

[0025] A pharmaceutical composition to be administered systemically may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

[0026] For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in U.S. Patent No. 4,256,108, No. 4,166,452, and No. 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

[0027] Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as

liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

Pharmaceutical Compositions for Use of Treating A Cognitive Disorder According to the Claims

[0028] The compositions of the invention are useful for treating cognitive disorders selected from the group consisting of an agnosia, an amnesia, an aphasia, an apraxia, a delirium, a dementia and a learning disorder. To "treat," as used here, means to deal with medically. It includes, for example, administering a compound of the invention to prevent the onset of a cognitive disorder as well as to alleviate its severity.

[0029] One can administer to a patient having a cognitive disorder a pharmaceutical composition comprising a cholinesterase inhibitor and a compound of Formula I. But one can also administer these compounds separately, administering one immediately after the other, or administering one within a short interval after the other (e.g., 5-15 minutes, or 15-30 minutes, or 30 minutes - 1 hour), or administering one within a longer interval after the other (e.g., 1-2 hours, 2-4 hours, 4-6 hours, 6-12 hours, or 12-24 hours). One can also administer one compound more frequently than another, administering, for example, a cholinesterase inhibitor one or more times daily and a compound of Formula I two or more times daily (or vice versa).

EXAMPLES

[0030] The invention is illustrated further by the following examples.

Example 1

Basal Excitatory Synaptic Transmission in the Hippocampus and Cortex of the Freely Moving Rat

[0031] Experiments were carried out in freely moving male Sprague-Dawley rats implanted with depth stimulating and recording electrodes in the hippocampus and olfactory cortex to (1) characterize the effect of a compound of Formula 1 ((2R,3S)-2-amino-3-hydroxy-3-(pyridin-4-yl)-1-(pyrrolidin-1-yl)propan-1-one) ("Compound X") on basal excitatory synaptic transmission, a measure positively associated with behavioral performance and encoding of information; and (2) determine a possible interaction on synaptic transmission when Compound X is coapplied

with physostigmine - a member of the cholinesterase inhibitor family which has pro-cognitive efficacy in Alzheimer's Disease patients.

[0032] Compound X by itself significantly enhanced hippocampal excitatory synaptic transmission, and was similarly effective at enhancing transmission in the olfactory cortex. Physostigmine had marginal effects on synaptic transmission in hippocampus and cortex at the doses tested. Physostigmine, when co-applied with Compound X, facilitated synaptic transmission to a degree that was significantly larger than the increase obtained with Compound X alone for both hippocampus and cortex. This synergism between two structurally and functionally very different classes of compounds suggests that the pro-cognitive effects of Compound X can be magnified with cholinergic compounds already approved for Alzheimer's disease.

Methods

[0033] Field excitatory post-synaptic responses (fEPSPs) evoked by electrical stimulation were recorded in freely moving animals with depth electrodes permanently implanted in the hippocampus and olfactory cortex. Experiment 1 compared the effect of one dose level (6 mg/kg ip) of Compound X on hippocampal and cortical fEPSPs with vehicle control data.

Subjects

[0034] Male Sprague Dawley rats, 3 months of age at the time of surgery, were used. The animals were housed individually and kept in a 12:12 light/dark cycle with food and water available ad libitum.

Preparation for Chronic Hippocampal and Cortical Electrophysiology

[0035] Preparation of animals with chronically implanted electrodes followed procedures essentially as described in earlier published work (U. Staubli and J. Scafidi, J. J. Neurosci. 17: 4820-4828 (1997)). For recordings from the hippocampus, the stimulating electrode was placed in the perforant path within the entorhinal cortex, and the recording electrode in the hilus of the hippocampal dentate gyrus. For recording from the olfactory cortex, the stimulating electrode was placed in the olfactory tract and the recording electrode in the layer I of the piriform cortex.

Recording From Freely Moving Rats

[0036] Ten days following recovery from surgery, the animals were acclimated to the recording

cage as well as to the attachment of a recording lead to the head stage. Recording sessions began by adjusting current intensities (25-1 00μA) and pulse width of the monophasic stimulation pulse (100-250μsec) to produce a field excitatory postsynaptic potential (fEPSP) that was 50-60% of the maximum amplitude of the population-spike free response which typically ranged between 4 and 8 mV. Recording signals were amplified and filtered with a band pass of 1 Hz to 5 kHz and fed into a PC running specialized software (NacGather) that digitizes measures and stores the evoked responses. Baseline recording sessions where fEPSPs were evoked every 20 sec were conducted daily for 20-45 min for at least 3 days, and only animals exhibiting and maintaining adequate and stable evoked monosynaptic fEPSPs were selected for further study.

Drug Testing

[0037] Hippocampal animals (subjects with electrodes implanted into hippocampus) were randomly assigned to one of 3 groups, i.e., Compound X alone, Compound X plus physostigmine, physostigmine alone. Cortical animals (subjects with electrodes implanted into olfactory cortex) were randomly assigned to 3 groups, i.e., Compound X alone, Compound X plus physostigmine, or physostigmine aloneFor each test, baseline responses were recorded for at least 15 minutes to establish stability, followed by injection of vehicle solution (ddw) and recording for another 20 min to verify that the injection procedure or the vehicle did not affect baseline responses. If changes in baseline greater than + 5 % were observed, the experiment was terminated for that day. All other animals were injected with test compound 20 min after vehicle, and fEPSP recording was continued for at least 2 hours, but 4 hrs if the drug effect was still present at 2 hrs. In cases where animals were used repeatedly, a minimum of three washout days followed each test session. Responses were sampled once every 20 sec throughout the experiment.

Test Compounds

[0038] Compound X was kept frozen at approximately -20°C in a freezer as a powder. Immediately prior the powder was dissolved in double distilled water (ddw) to make a 12mg/ml stock and then diluted by 50% for injection at 6mg/kg at a final volume of 1 ml/kg.

[0039] Physostigmine (eserine hemisulfate) was purchased from Sigma Aldrich and dissolved in ddw to make a 1 mg/ml stock solution. For injection the stock was diluted 10x and administered at 0.1 mg/kg at a final volume of 1 ml/kg.

[0040] For combination treatment of Compound X and physostigmine the 12 mg/ml stock solution of Compound X and the 1 mg/ml stock of physostigmine were diluted by 50% and 10%, respectively, and injected at a final volume of 1 ml/kg.

[0041] All compounds were injected intraperitoneally (ip).

Calculations

[0042] All electrophysiological data were collected and digitized by NacGather 2.0.7.2 Neurodata Acquisition Systems, and then analyzed using NacShow and graphed using GraphPad Prism. All results were expressed relative to fEPSP amplitude values across the 15 min baseline period preceding vehicle injection and are presented as means ± SEM. For drug effects on excitatory synaptic transmission (fEPSP amplitude), statistical comparisons were done for each compound separately, using paired two-tailed t-tests between averaged data for the entire 15 min pre-drug vehicle period vs. averaged data over a 15 min post-drug period identified as showing the largest increase. Statistical comparisons between facilitatory effects of combination treatments (Compound X with physostigmine) vs Compound X alone or cholinesterase inhibitors alone, respectively, were done using unpaired one-tailed t-tests between post-drug peak values averaged over 15 min. The significance value was set at $p< 0.05$ (indicated by *), $p<0.01$ (indicated by **) and $p<0.001$ (indicated by ***).

Results

[0043] Table 1 shows the effect physostigmine, Compound X, and Compound X combined with physostigmine on hippocampal excitatory synaptic transmission in the freely moving rat. Drug effects were assessed by measuring changes in amplitude of the fEPSP in presence of drug relative to changes occurring following vehicle injection that immediately preceded drug administration. Both Compound X by itself, and co-applied with physostigmine, significantly enhanced hippocampal fEPSPs, in contrast to physostigmine which caused no significant alterations in basal transmission. Moreover, the facilitation produced by coapplication of Compound X with physostigmine was significantly larger than that observed with Compound X alone or physostigmine alone (see Figure 1).

Table 1

TREATMENT	DOSE (MG/KG)	VEHICLE FEPSP AMPLITUDE [% OF PRE-VEHICLE BASELINE ± S.E.M.]	DRUG FEPSP AMPLITUDE [% OF PRE-VEHICLE BASELINE ± S.E.M.]	P-VALUE (DRUG vs. VEHICLE)
Physostigmine	0.1	0.86 + 0.49	2.33 + 2.91	0.62
Compound X	6.0	-1.24 + 0.43	7.86 + 2.98	0.05*
Compound X plus Physostigmine	6.0 plus 0.1	-1.0 + 0.44	18.1 + 2.04	0.02*

[0044] Table 1 shows Compound X at 6 mg/kg ip alone (n=5) and combined with physostigmine at 0.1 mg/kg ip (n=3) had significant facilitatory activity on basal excitatory synaptic transmission in the hippocampus of freely moving Sprague-Dawley rats. Physostigmine by itself (n=3) was inactive, demonstrating no significant enhancement of basal synaptic transmission. Individual t-test (two-tailed, paired) comparison values are shown.

[0045] Table 2 shows the effect physostigmine, Compound X, and Compound X combined with physostigmine on excitatory synaptic transmission in the olfactory cortex. Drug effects were assessed by measuring changes in amplitude of the fEPSP in presence of drug relative to changes occurring following vehicle injection that immediately preceded drug administration. Both Compound X by itself, and co-applied with physostigmine, significantly enhanced hippocampal fEPSPs. Physostigmine also caused a significant increase in basal transmission, but this effect was significantly smaller than that observed with Compound X alone or Compound X co-applied with physostigmine (see Figure 2). In addition, the facilitation produced by co-application of Compound X plus physostigmine was significantly larger than that observed with Compound X alone (see Figure 2).

Table 2

TREATMENT	DOSE (MG/KG)	VEHICLE FEPSP AMPLITUDE [% OF PRE-VEHICLE BASELINE ± S.E.M.]	DRUG FEPSP AMPLITUDE [% OF PRE-VEHICLE BASELINE ± S.E.M.]	P-VALUE (DRUG vs. VEHICLE)
Physostigmine	0.1	0.54 + 0.23	5.30 + 0.69	0.004**
Compound X	6.0	0.17 + 0.60	10.67 + 1.67	0.00002***
Compound X plus Physostigmine	6.0 plus 0.1	0.64 + 1.00	17.51 + 3.06	0.0004**

[0046] Table 2 shows that Compound X at 6 mg/kg ip alone (n=11) and combined with physostigmine at 0.1 mg/kg ip (n=7) had significant facilitatory activity on basal excitatory synaptic transmission in the olfactory cortex of freely moving Sprague-Dawley rats. Physostigmine by itself (n=5) also produced a significant enhancement of basal synaptic transmission. Individual t-test comparison values (two-tailed, paired) are shown. The facilitation produced by physostigmine alone was significantly smaller than that obtained both with Compound X alone or Compound X plus physostigmine combined. These experiments show that Compound X, at a dose which enhances memory in rodents, produced a significant increase in basal hippocampal and cortical excitatory synaptic transmission, a measure positively associated with behavioral performance and learning. This response of Compound X in the freely moving rat was significantly enhanced by co-administration of subthreshold doses of physostigmine in both hippocampus and olfactory cortex, and to a similar degree. Physostigmine by itself at the same dose did not affect basal transmission. These results demonstrate that Compound X can magnify or synergize with physostigmine.

REFERENCES CITED IN THE DESCRIPTION

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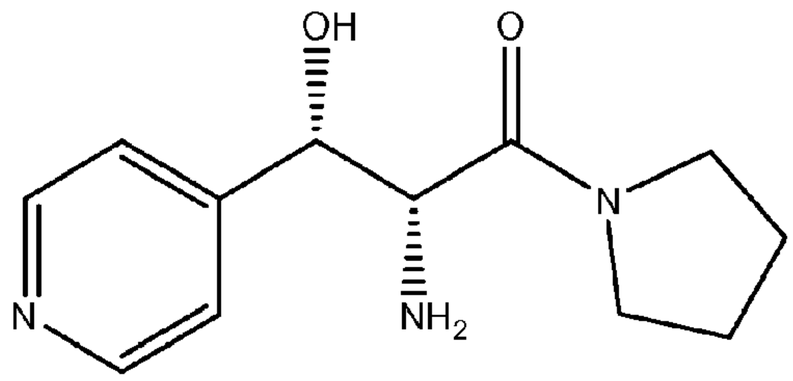
Patentkrav

1. Farmaceutisk sammensætning til anvendelse i en fremgangsmåde til behandling af en kognitiv lidelse valgt fra gruppen bestående af en agnosi, en amnesi, en afasi, en apraxi, en delirium, en demens og en indlæringsforstyrrelse omfattende:

(i) kolinesterase-inhibitor-physostigmin, og

(ii) en forbindelse af formel I

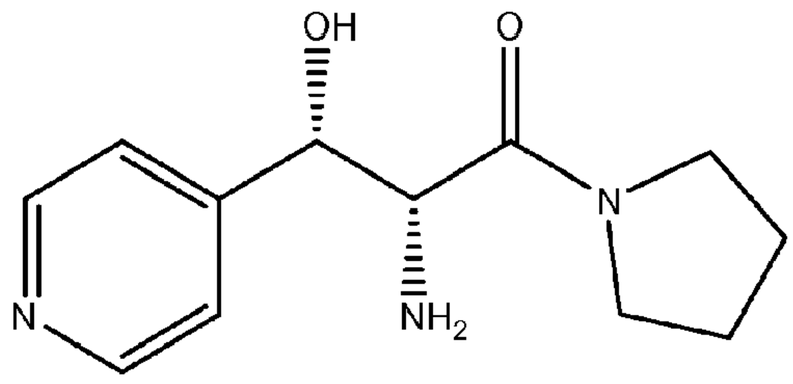


eller et farmaceutisk acceptabelt salt deraf.

2. Farmaceutisk sammensætning til anvendelse ifølge krav 1 omfattende:

(i) kolinesterase-inhibitor-physostigmin; og

(ii) en forbindelse af formel I:



eller et farmaceutisk acceptabelt salt deraf, hvor kolinesterase-inhibitoren er administreret ved en dosis der er ineffektiv eller har minimal effekt til at behandle nævnte kognitive lidelser når administreret alene.

3. Farmaceutisk sammensætning til anvendelse ifølge krav 2, hvor kolinesterase-inhibitoren forstærker den pro-kognitive effekt af forbindelsen af formel I eller det farmaceutisk acceptable salt deraf.

4. Kombination af første og anden farmaceutiske sammensætninger til anvendelse i en fremgangsmåde til behandling af en kognitiv lidelse valgt fra gruppen bestående af en agnosi, en amnesi, en afasi, en apraxi, en delirium, en demens

og en indlæringsforstyrrelse, hvor den første farmaceutiske sammensætning omfatter kolinesterase-inhibitor-physostigminen, og den anden farmaceutiske sammensætning omfatter en forbindelse af formel I som defineret i krav 1 eller et farmaceutisk acceptabelt salt deraf

5

DRAWINGS

Figure 1

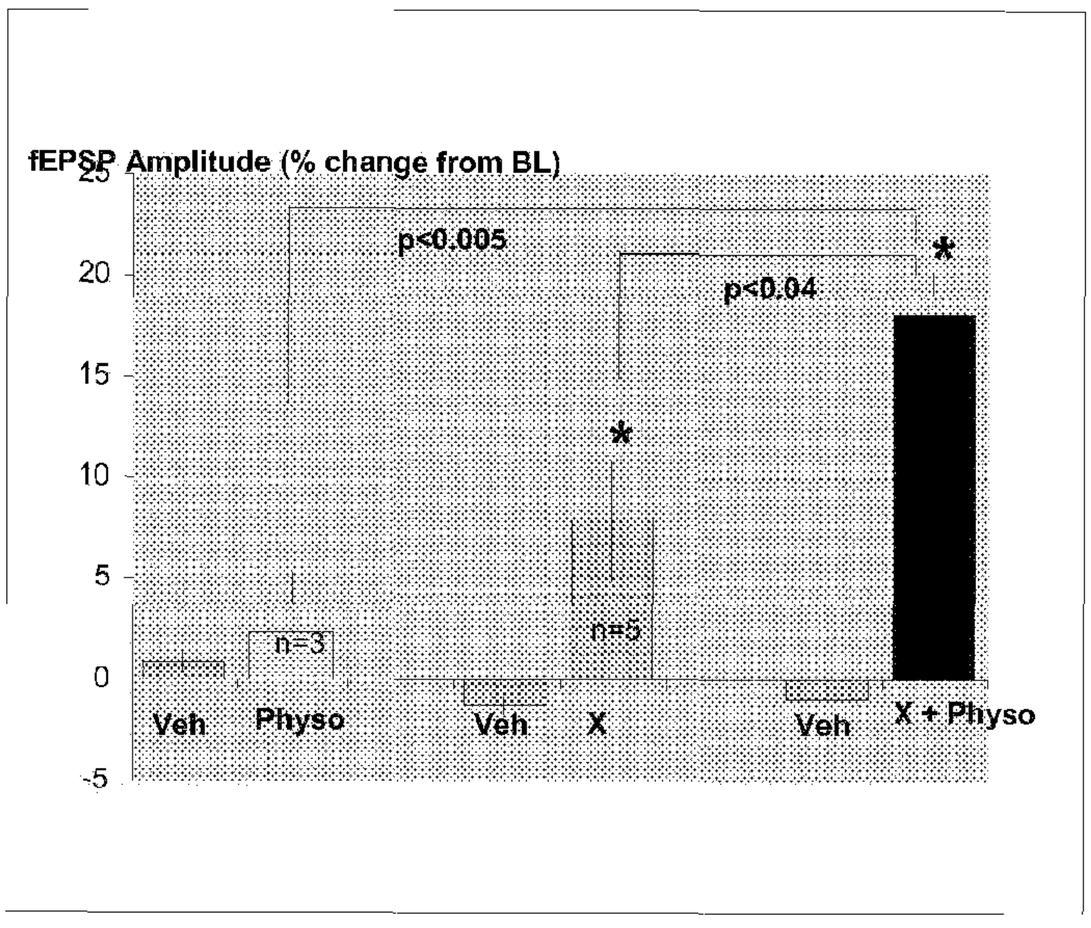


Figure 2

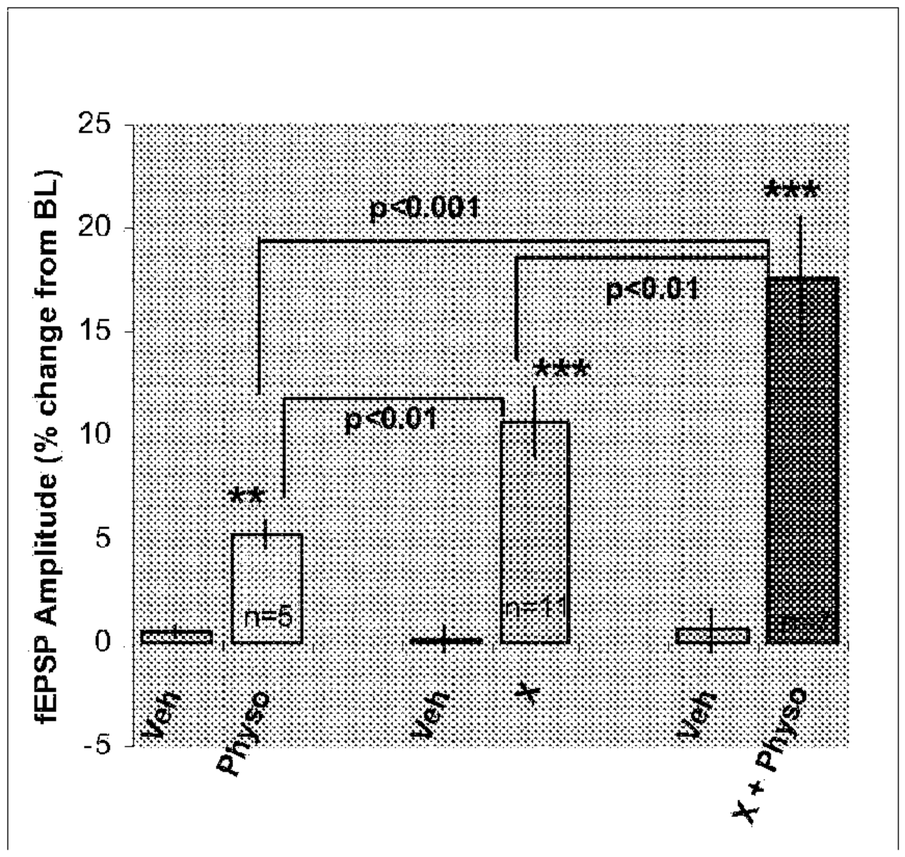
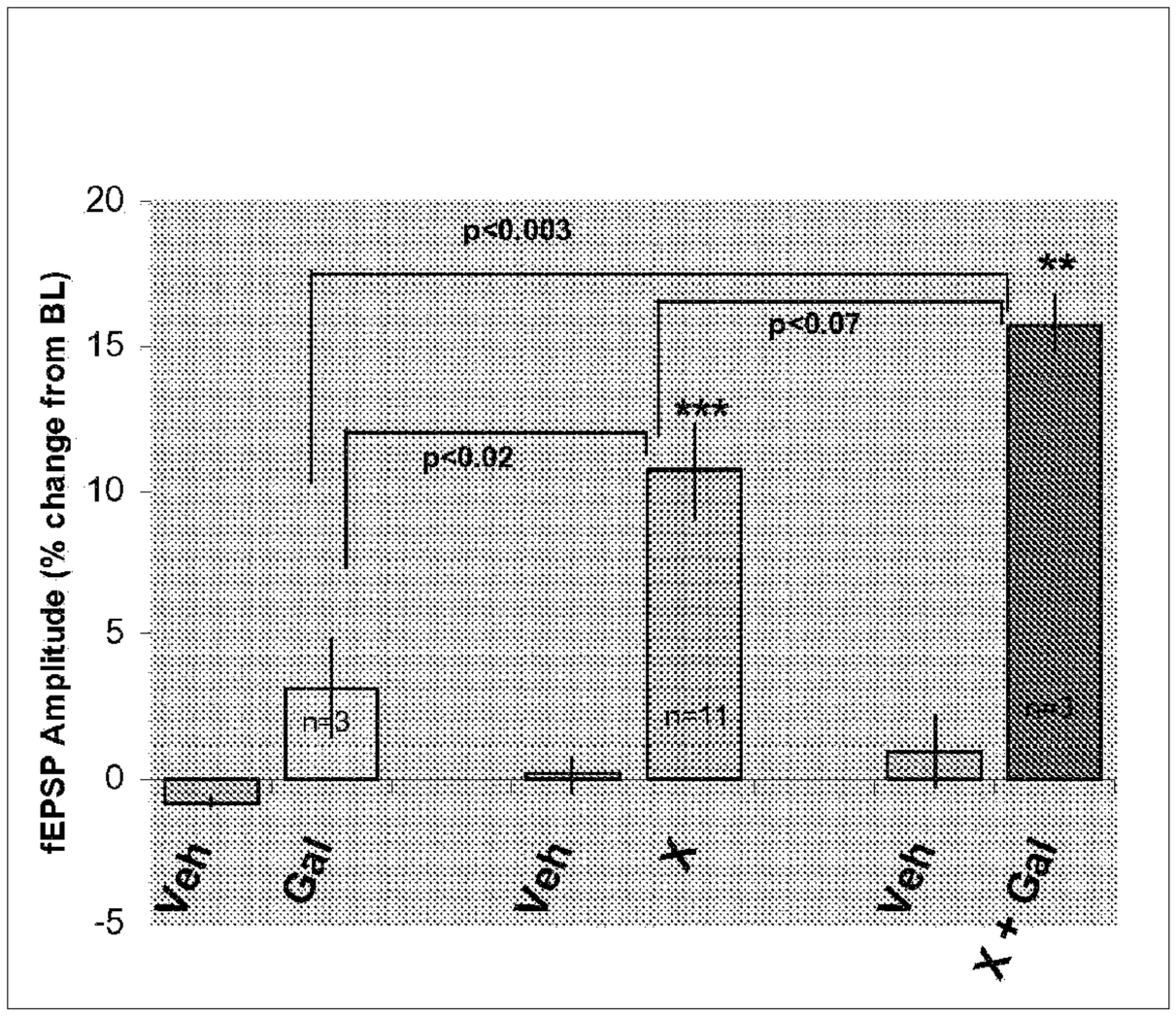

fEPSP Amplitude (% change from BL)
25
20
15
10
5
0
-5
p<0.001
p<0.01
p<0.01
**
***
***
n=5
n=11
n=7
Veh
Physo
Veh
X
Veh
X + Physo

Figure 3


fEPSP Amplitude (% change from BL)
20
15
10
5
0
-5
p<0.003
p<0.07
p<0.02
***
**
n=3
n=11
n=3
Veh
Gal
Veh
X
Veh
X + Gal