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(54) Title: TREATMENT OF FRIEDREICH' S ATAXIA

(57) Abstract: Use of porphyrin compounds comprising a complexed Ca²⁺, Zn²⁺ or Mg²⁺ ion for the production of a pharmaceutical preparation for the treatment of Friedreich' s ataxia or for the treatment or prevention of a disease associated therewith.

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Treatment of Friedreich's ataxia

The present invention is concerned with a pharmaceutical preparation for the treatment of Friedreich's ataxia and for the treatment or prevention of diseases associated therewith.

Friedreich's ataxia (FRDA) is the most common of the inherited ataxias, affecting 1 in 50,000 people. FRDA is an autosomal-recessively inherited progressive neurodegenerative disease. Clinically, FRDA is characterized by multiple symptoms including progressive gait and limb ataxia, dysarthria, diabetes mellitus and hypertrophic cardiomyopathy (Sturm et al., E.J.Clin.Invest. 35 (2005) 711-717).

Friedreich's ataxia is caused by a GAA-trinucleotide expansion in the frataxin gene located on chromosome locus 9q13, resulting in a reduced expression of frataxin, a small mitochondrial protein. Due to the mitochondrial localization of frataxin, the neurological and cardiological degenerations observed in FRDA are thought to be the result of a mitochondrial defect. The exact physiological function of frataxin is unknown, but it may be involved in mitochondrial iron homeostasis and/or assembly of iron-sulfur (FeS) proteins and heme synthesis. Intramitochondrial iron accumulation has been postulated to initiate the production of hydroxyl radicals by Fenton chemistry, leading to inactivation of FeS enzymes, lipid peroxidation and damage to nucleic acids, proteins and finally resulting in cell death.

There is some debate whether mitochondrial iron accumulation within mitochondria is the result or the cause of the oxidative stress which is responsible for mitochondrial damage. Studies with conditional knockout mouse models and FRDA-patient cells indicate that deficiencies in FeS enzymes precede iron accumulation. Clinically there is an intramitochondrial iron accumulation in heart, liver, nervous system and spleen of FRDA-patients, as well as a reduction of mitochondrial DNA, the FeS cluster-containing subunits of the mitochondrial electron transport chain (complex I-III) and of the enzyme aconitase. The presence of increased levels of soluble transferrin receptor as indicator for cytosolic iron deficiency is controversial but in general FRDA-

patients have normal serum iron and ferritin concentrations. Frataxin is implicated to be necessary for normal heme biosynthesis, but there are no reports that FRDA is commonly associated with anemia.

Stimulation of frataxin in an artificial system (in recombinant BHK21 cells transfected (by CET recombinant system) with BAC-DNA containing the frataxin gene and cassettes consisting of the gene encoding EGFP linked to a kanamycin/neomycin resistance determinant) with exogenous substances was shown with hemin and butyric acid, and with substances generating reactive oxygen species (such as 3-nitropropionic acid) or those which are cytotoxic like cisplatin (Sarsero et al., J.Gene.Med. 5 (2003), 72-81; Turano et al. Neurosci. Lett. 350 (2003), 184-186). It was, however, concluded by the authors of this study that it is unlikely that normal and fused genes and proteins will behave in an identical manner under various conditions.

There is currently no effective treatment of FRDA available especially for neurological deficits. The improved understanding of the role of frataxin has led to the consideration of antioxidants such as Idebenone and iron chelators as potential therapeutic agents (EP 1 378 753 A1). The use of superoxide dismutase mimetics has been suggested to treat conditions ameliorated by reduced oxidative stress, i.a. FRDA, in US 2004/029851 A1 and WO 00/19993 A2. A cardioprotective function of Idebenone was shown in a mouse model. However, clinical studies have shown that Idebenone could be promising in the treatment of cardiomyopathies but not for FRDA; it was also assumed by the investigators of this study that antioxidant compounds, such as ascorbate or glutathione might actually be harmful because they reduce the mitochondrial iron overload from the Fe^{3+} to the Fe^{2+} oxidation state, thereby catalysing more oxygen radical formation (Rustin et al., Lancet 354 (1999), 106-107; EP 1 378 753 A1). These drugs therefore cannot cure the disease itself. Another approach to treat FRDA would be gene therapy, which will not be readily available within the near future.

A promising therapy using recombinant erythropoietin (rEPO) was recently suggested (Sturm et al. (2005)), however, to date clin-

ical data are not available for this therapy.

It is therefore the object of the present invention to provide a pharmaceutical preparation for the treatment of Friedreich's ataxia and for the treatment or prevention of a disease associated therewith. Due to the nature of this disease, suitable drugs should be applicable for continuous administration, if necessary for the lifetime. Accordingly, such drugs should not have serious side-effects preventing such long term treatment regimes.

The present invention provides the use of porphyrin compounds comprising Ca^{2+} , Zn^{2+} or Mg^{2+} for the production of a pharmaceutical preparation for the treatment of Friedreich's ataxia or for the treatment or prevention of a disease associated therewith.

With the present invention it was surprisingly shown that porphyrin compounds comprising Ca^{2+} , Zn^{2+} or Mg^{2+} have the potential to increase the expression of frataxin. Due to their nature, these porphyrin compounds especially, the Mg^{2+} porphyrins can be administered to humans over long periods of time, if necessary over the whole life-time. By using porphyrin compounds as substances which increase the expression of frataxin itself, the disease is combatted at its root and therefore the treatment according to the present invention is suitable to treat or prevent not only FRDA itself but also all diseases which are connected or caused by FRDA (diseases associated with FRDA). Mg, Zn and Ca ions have the specific advantage that a change in charge does not occur in the course of administration (e.g. as a side reaction), in contrast to ions such as e.g. Fe, Co, Mn, etc. (from Fe^{2+} to Fe^{3+} , etc.), wherein such a change could occur in the course of redox processes. Moreover, Zn, Ca and Mg ions do not accumulate in the body of the patient and therefore long-term administration does not lead to problems with ion accumulation.

It is clear that the porphyrin compounds to be used according to the present invention must be non-toxic (in the amount and/or dose and/or time required to be administered) and provided to the patient in an efficient dosage. This dosage may be determined for each porphyrin compound in an individual manner with standard methods and the methods described herein. The exact and optimal

amount of porphyrin compounds to be administered also depends on the individual potency of increasing expression of frataxin (e.g. easily to be determined by the cellular model system provided in the example section of the present application or simply by comparison with related porphyrins), on the biological availability of the porphyrins in the patients (depending on e.g. solubility, mode of application, pharmaceutical formulation (including derivatisation by addition of targeting or solubilising molecules, such as PEGylation, etc.)). Preferably, toxicity is defined according to the appropriate international guidelines explained and referred to in Römpp's Chemielexikon, 10th ed. (1999), page 4596. In case of internationally differing limiting or maximum values or dosages, the respective values or dosages valid in Austria (or EU) should apply.

The porphyrin preparations to be used according to the present invention should preferably have a biological activity at least comparable to the activity of Cu-chlorophyllin on frataxin-expression in primary lymphocytes from patients with Friedreich's ataxia as described in the example section of the present application. Although Cu-porphyrins may be given for treatment of FRDA over a shorter period of time, long term treatment of FRDA (i.e. treatments over 3 months, especially more than 1 year) should only be performed with Mg-, Zn- or Ca-porphyrins. Accordingly, porphyrin preparations and compositions according to the present invention are preferred, which have a biological activity on frataxin-expression of at least 20%, preferably at least 50%, of the activity of Cu-chlorophyllin in this primary lymphocyte test system, i.e. that the same effect with respect to frataxin-expression is reached with maximal the 5-fold dose, preferably with maximal the double dose (of course without being toxic in these doses with the toxicity being defined as outlined above). The porphyrin compounds are therefore always administered in a suitable manner to enable the biological activity for increasing the expression of frataxin.

With the present invention it is possible to bring the expression level of frataxin to a normal level, i.e. the level of a healthy human being without being affected by FRDA. Optimisation of frataxin expression according to the present invention is usually

aiming of applying dosages of porphyrin substances sufficient and efficient to establish normal levels of frataxin expression. At least, frataxin levels should be established which reduce the risk for the patient to be affected by the diseases associated with FRDA. Preferably, such levels should be established over a sufficient term, e.g. over a whole day (so that daily dosage is sufficient), even more preferred over a duration of at least three days, of at least five days, of at least 7 days or especially over at least two weeks or at least four weeks. Suitable test systems for defining the possible range for such dosages for any porphyrin compound, including mixtures of such compounds, are readily available and workable by the skilled man in the art; preferred systems are also described in the example section of the present application.

According to the present invention any Ca-, Zn- or Mg-porphyrin (IUPAC nomenclature of tetrapyrroles: TP-0, TP-1, TP-2, TP-3, TP-4, TP-5, TP-8 and TP-9) compound can be used which shows efficient up-regulation of frataxin expression in a patient being affected by FRDA when using non-toxic dosages. Of course, also mixtures of porphyrin compounds have to be regarded as uses of a porphyrin compound according to the present invention.

Preferred porphyrin compounds to be used according to the present invention include those porphyrins which are already accepted as being well tolerated by and suitably administratable to humans. Examples of such porphyrine compounds are chlorophylls (chlorophyll a, chlorophyll b, chlorophyll c₁, chlorophyll c₂, chlorophyll d, bacteriochlorophyll a, bacteriochlorophyll b, meso-chlorophyll a or mixtures of one or more of such chlorophylls), chlorophyllins with the central ion being exchanged to Mg, Zn or Ca (Mg-, Zn- or Ca-chlorophyllins); esters thereof with 1 to 20 C-atoms preferably at the carbonyl residue attached to C¹³ or C¹⁷ or both), corrins (such as vitamin B12), corroles, phthalocyanines and metal complexes thereof.

Preferred porphyrin compounds according to the present invention

are porphyrins extracted from natural sources, especially natural plant sources or chemically synthesised versions of such porphyrins present in natural sources. On the other hand, also synthetic porphyrins not existing as such in nature or porphyrin compounds altered by biochemical or organic chemistry may be used according to the present invention if they can be administered to FRDA patients in efficient amounts to increase frataxin levels.

A preferred embodiment of the present invention is to use Ca-, Zn- or Mg-chlorophyllin compositions as porphyrin compound. Chlorophyllin compositions according to the present invention are preferably selected from Zn-, Mg- or Ca-chlorophyllins, including those chlorophyllins with attached carbohydrate moieties, preferably attached to the carboxy groups linked to C³, C¹³⁻² and/or C¹⁷; variations of the porphyrine ring, preferably: elimination or substitution of one or more of C⁵, C¹⁰, C²⁰ with C-C, C=C, N, S or O; introduction of further side chains, especially vinyl, methyl, ethyl, phytyl, CHO, CH₂COOH, CH₂CH₂COOH into the porphyrin molecule; replacement of at least one methyl group, especially at positions 2, 7, 12, 18 with H, vinyl, ethyl, phytyl, CHO, CH₂COOH, CH₂CH₂COOH; etc; di- or polymers of porphyrin compounds, modifications of porphyrin sidechains, protoporphyrin variants of chlorophyllin (although these variations also apply for the general porphyrin compounds according to the present invention).

Further examples for Zn-, Ca- or Mg-porphyrin compounds to be used according to the present invention are known and described in the art, e.g. in US 4,851,339, US 5,066,274, US 5,308,861, US 5,399,583, US 6,632,808, and especially the PEGylated porphyrins described e.g. in US 6,147,207 A and US 2004/0186285 A as well as their non-PEGylated counterparts and metal complexes of the PEGylated and non-PEGylated porphyrins. The compounds according to the present invention may additionally comprise lipophilic cation moieties (e.g. as described in US 2004/0029851 A1), preferably ammonium or phosphonium moieties, especially triphenyl phosphonium.

The porphyrin preparation comprising Zn²⁺-, Ca²⁺- or Mg²⁺-porphyrins to be used for the treatment of FRDA according to the present invention may contain also mixtures of different porphyrins. Also

other ingredients, such as further active ingredients, pharmaceutically acceptable carriers, etc. can be included in such porphyrin preparations

The pharmaceutical preparation according to the present invention comprising Ca^{2+} -, Zn^{2+} - or Mg^{2+} -porphyrins can be administered in any pharmaceutically acceptable form to increase frataxin expression in FRDA patients. Suitable forms are unit dosage forms, such as tablets, effervescent tablets, powder dragees, capsules, sachets, etc., as solution for injection (e.g. intravenous or intramuscular) or infusion, as an orally applicable solution, suppositories, nasal spray, nanoparticles or implant; or as lyophilized product, e.g. by the intravenous, intramuscular, intracranial or intranasal route (as nose spray). The invention is further directed to a new medical application of a pharmaceutical preparation containing porphyrin compounds comprising a complexed Ca^{2+} , Zn^{2+} or Mg^{2+} ion to increase the expression of the protein frataxin.

When administered as a therapeutic treatment, the porphyrin compound according to the present invention may be administered at a dose between 1 nanogram and 0.5 to 1 gram per kg body weight (for example 1 microgram to 100 micrograms per kg), without appreciable toxicity, such as cytotoxicity. Although the porphyrin compounds may be administered by a wide variety of routes (direct administration into the CNS, intracranial ventricular, intrathecal, aural, transdermal, intravenous, intramuscular, subcutaneous, oral, olfactory, ocular and rectal), the porphyrin compounds of the present invention are particularly advantageous because many of them are believed to readily pass the blood brain barrier. Compounds having increased lipophilicity, or in pharmaceutical carriers such as liposomes, will have enhanced penetration of the CNS.

Preferably a porphyrin compound is used for which sufficient frataxin increase is reached with a maximal dose of 1 g/day, preferably of 500 mg/day, especially a maximum dose of 300 mg/day (well tolerated with no side effects). Preferred doses are - referred to chlorophyllin - 1 to 1000 mg per day, preferably 5 to

500 mg per day, especially 10 to 300 mg per day.

According to a preferred embodiment of the present invention, administration of the porphyrin compound should be established to enable a concentration of the porphyrin compound in the blood of the patient of above 200 nanoM, preferably above 1 microM, especially above 5 microM.

The present invention is based on the finding that porphyrin compounds can significantly increase the expression of frataxin in various cell types, e.g. in primary lymphocytes from FRDA patients in a dose-dependent manner. Therefore porphyrin compounds described above can be used for the production of a pharmaceutical preparation for the treatment of Friedreich's ataxia or for the treatment or prevention of a disease associated therewith.

Using mouse embryonic carcinoma P19 cells (neuronal type) significant increases in frataxin expression after incubation with the porphyrin compounds according to the present invention was found.

Further preferred embodiments are the use of porphyrin compounds comprising a complexed Ca^{2+} , Zn^{2+} or Mg^{2+} for the production of a pharmaceutical preparation for the treatment or prevention of a disease associated with Friedreich's ataxia, in particular

- a heart disease of a patient showing decreased expression of frataxin,
- diabetes of a patient showing decreased expression of frataxin,
- a neurodegenerative disease of a patient showing decreased expression of frataxin,
- a bone deformation, in particular scoliosis and pes cavus, of a patient showing decreased expression of frataxin,
- nystagmus of a patient showing decreased expression of frataxin,
- impaired hearing of a patient showing decreased expression of frataxin,
- an eye disease, in particular optic atrophy, of a patient showing decreased expression of frataxin,
- cancer of a patient showing decreased expression of frataxin.

According to another aspect, the present invention relates to the treatment of a disease which is characterized by a decreased expression of frataxin: Such diseases may be treated by administration of an effective amount of porphyrin to a patient as described herein. All preferred embodiments e.g. with respect to Zn^{2+} -, Ca^{2+} - and Mg^{2+} -porphyrins, (pharmaceutical) preparations of porphyrin, etc., as described above for FRDA also apply to this aspect of the present invention. Preferably, the diseases associated with a decreased frataxin expression are selected from the group consisting of heart diseases, especially cardiomyopathies, diabetes, especially diabetes mellitus, neurodegenerative diseases, especially any form of ataxia, bone deformations, especially scoliosis and pes cavus, nystagmus, impaired hearing, eye diseases, especially optic atrophy, and cancer.

The invention is further described in the example section and the drawing figures, yet without being restricted thereto.

Fig.1 shows increase of frataxin expression in human primary lymphocytes of FRDA patients upon exposure to Cu-chlorophyllin;

Figs.2 and 3 show increase of frataxin expression mouse embryo carcinoma cells (P 19), differentiated to neurons using retinol upon exposure to Cu-chlorophyllin (Fig.2) and Mg-chlorophyllin (Fig.3).

Figs.4 and 5 show increase of frataxin protein levels in mice (heart (Fig.4) and brain (Fig.5)).

EXAMPLES

In the following examples, the effect of porphyrin compounds on frataxin expression in various cell types and in mice is demonstrated (also by using the general techniques according to Sturm et al. (2005)). Using mouse embryonic carcinoma P19 cells (neuronal type) significant increases in frataxin expression after incubation with Mg-chlorophyllin, Ca-chlorophyllin, Zn-chlorophyllin and Cu-chlorophyllin can be found.

Reagents and antibodies

All chemicals were purchased from Sigma (Vienna, Austria) if not cited otherwise. The primary rabbit polyclonal antibody against mature human and mouse frataxin was prepared as described previously (Cavadini et al., Hum Mol Genet. 11 (2002), 217-277); the secondary goat-anti-rabbit horse radish peroxidase conjugated antibody was purchased from DakoCytomation (Vienna, Austria).

Cell Cultures

Lymphocytes - Lymphocytes from 7 FRDA patients (GAA repeats in the range from 240 to 800) were collected from fresh blood samples and isolated with Biocoll Separating Solution, density 1.077g/ml (Biochrom AG, Berlin, Germany) according to the manufacturer's procedure. Finally, cells were diluted to a density of 1×10^6 cells and cultured in RPMI media supplemented with 10% fetal calf serum, 2 mM L-glutamine and antibiotics and were used for experiments.

Neuronal cells - The P19 clone was obtained from the European Cell Culture Collection (ECACC Cat. Nr. 95102707, Salisbury, UK). Cells were cultured in α -modified Eagle's medium (α -MEM) supplemented with 7.5% calf serum (Euroclone, Vienna, Austria) and 2.5% fetal bovine serum (Gibco, Vienna, Austria), 2 mM L-glutamine, 10ml/l essential amino acids and antibiotics in a 5% CO₂ humidified chamber. Cellular differentiation was carried out as described by Santos et al. (Santos et al., Hum.Mol.Genet.10 (2001), 1935-1944).

Immunoblotting of frataxin

Expression of frataxin was detected by Western blot. After treatment with porphyrins for the indicated periods and after extensive washings the cells were lysed with cell culture lysis reagent (Promega, Vienna, Austria) and transferred to a microcentrifuge tube. Fifty micrograms of proteins were separated on 12% SDS (sodium dodecyl sulfate) - polyacrylamide gel electrophoresis under non-reducing conditions using Prosieve 50 Gel solution (BMA, BioWhittaker from Biozym, Vienna, Austria) and Tris/Tricine-electrode buffer (0.1 M Tris, 0.1 M Tricine, 0.1% SDS, pH 8.3) and electroblotted onto nitrocellulose membranes. Primary antibody was directed against mature frataxin (Cavadini et al., 2002) and

as a secondary antibody a goat-anti rabbit HRP antibody (1:10000) (DAKO) was used.

Statistical analysis

Statistical analysis was performed with GraphPad Prism software. Differences were examined for statistical significance using the t-test. Significant differences are marked in the figures with * ($p < 0.05$), ** ($p < 0.01$) and *** ($p < 0.001$). Differences with $p < 0.05$ were assumed to be significant.

Example 1:

Effects of Cu-chlorophyllin on frataxin-expression in primary lymphocytes from patients with Friedreich's ataxia.

Freshly isolated lymphocytes obtained from 7 patients with Friedreich's ataxia were incubated with 3 μ M Cu-Chlorophyllin for 24 hours. Cell lysates (50 μ g protein) were separated on 12% SDS-polyacrylamide gel electrophoresis under non-reducing conditions using Tris/Tricine-electrode buffer (0.1 M Tris, 0.1 M Tricine, 0.1% SDS) and electroblotted onto nitrocellulose membranes. Western blot analysis was performed with a polyclonal antibody against human frataxin. Western blot densitometric analysis of frataxin expression from two independent experiments is shown. Density of the frataxin band of the control (untreated lymphocytes in the absence of Cu-Chlorophyllin from the same patients) was set as 1 a.u. (arbitrary units). Values represent means $\pm$ SEM of 3 different experiments. Differences were examined for statistical significance using the paired t-test. Significant differences vs. control are marked in the figures with *** ($p < 0.001$).

Example 2:

Frataxin expression in neuronal cells increases after treatment with Cu-chlorophyllin.

P19 mouse cells (neuronal-type) were incubated with various concentrations of Cu-chlorophyllin (3.125 to 50 μ M) for 24h. Cell lysates (50 μ g protein) were separated on 12% SDS-polyacrylamide gel electrophoresis under non-reducing conditions using Tris/Tricine-electrode buffer (0.1 M Tris, 0.1 M Tricine, 0.1% SDS) and electroblotted onto nitrocellulose membranes. Western blot analysis

was performed with a polyclonal antibody against human frataxin, which also detects mouse frataxin due to 94% sequence homology. Western blot densitometric analysis of frataxin expression from three experiments is shown. Density of the frataxin band of the control (in the absence of Cu-chlorophyllin) was set as 1a.u. (arbitrary units). Values represent means $\pm$ SEM of 3 different experiments. Differences were examined for statistical significance using the paired t-test. Significant differences vs. control are marked in the figures with * ($p < 0.05$), ** ($p < 0.01$) and *** ($p < 0.001$).

Example 3:

Frataxin expression in neuronal cells increases after treatment with Mg-chlorophyllin.

P19 mouse cells (neuronal-type) were incubated with various concentrations of Mg-chlorophyllin (3.125 to 50 μ M) for 24h. Cell lysates (50 μ g protein) were separated on 12% SDS-polyacrylamide gel electrophoresis under non-reducing conditions using Tris/Tricine-electrode buffer (0.1 M Tris, 0.1 M Tricine, 0.1% SDS) and electroblotted onto nitrocellulose membranes. Western blot analysis was performed with a polyclonal antibody against human frataxin, which also detects mouse frataxin due to 94% sequence homology. Western blot densitometric analysis of frataxin expression from three experiments is shown. Density of the frataxin band of the control (in the absence of Mg-chlorophyllin) was set as 1a.u. (arbitrary units). Values represent means $\pm$ SEM of 3 different experiments. Differences were examined for statistical significance using the paired t-test. Significant differences vs. control are marked in the figures with * ($p < 0.05$), ** ($p < 0.01$) and *** ($p < 0.001$).

Example 4:

One group of mice (n=3) received 250 μ g Mg-Chlorophyllin per gramm bodyweight per day i.p. for three days, the other group of mice (control, n=3) received the solvent only. After sacrifice of the mice heart and brain tissues were homogenized and treated with solubilisation buffer. Proteins were separated by 12% SDS-PAGE. After blotting on nitrocellulose the protein frataxin was

detected by westernblotting, using a rabbit polyclonal antibody against whole human frataxin, which also recognizes mice frataxin due to the high homology to human frataxin. Density of the frataxin band of the control was set as 100%. Values represent means $\pm$ SEM (n=3). Differences were examined for statistical significance using the paired t-test. Significant differences vs control are marked in the figures with ** (p<0,01) and *** (p<0,001).

Claims:

1. Use of porphyrin compounds comprising a complexed Ca^{2+} , Zn^{2+} or Mg^{2+} ion for the production of a pharmaceutical preparation for the treatment of Friedreich's ataxia or for the treatment or prevention of a disease associated therewith.
2. Use according to claim 1, characterized in that said porphyrin compounds comprise a complexed Mg^{2+} ion.
3. Use according to claims 1 or 2, characterized in that Friedreich's ataxia is diagnosed by means of gene analysis and/or ELISA and/or realtime-PCR and that expression of frataxin is decreased due to GAA-repeat-expansion or mutations on one or on both alleles in the frataxin gene.
4. Use according to claims 1 or 2, characterized in that said disease associated with Friedreich's ataxia is selected from one or more of the group consisting of a heart disease of a patient showing decreased expression of frataxin,
 - diabetes of a patient showing decreased expression of frataxin,
 - a neurodegenerative disease of a patient showing decreased expression of frataxin,
 - a bone deformation, in particular scoliosis and pes cavus, of a patient showing decreased expression of frataxin
 - nystagmus of a patient showing decreased expression of frataxin,
 - impaired hearing of a patient showing decreased expression of frataxin,
 - an eye disease, in particular optic atrophy, of a patient showing decreased expression of frataxin, and

- cancer of a patient showing decreased expression of frataxin.

5. Use according to any one of claims 1 to 4, characterized in that said porphyrin compounds are Mg^{2+} -chlorophyllin, Zn^{2+} -chlorophyllin, Ca^{2+} -chlorophyllin, or mixtures thereof.

6. Use of porphyrin compounds comprising a complexed Ca^{2+} , Zn^{2+} or Mg^{2+} ion for the production of a pharmaceutical preparation for the treatment of a disease which is characterized by a decreased expression of frataxin, preferably heart diseases, especially cardiomyopathies, diabetes, especially diabetes mellitus, neurodegenerative diseases, especially any form of ataxia, bone deformations, especially scoliosis and pes cavus, nystagmus, impaired hearing, eye diseases, especially optic atrophy, and cancer.

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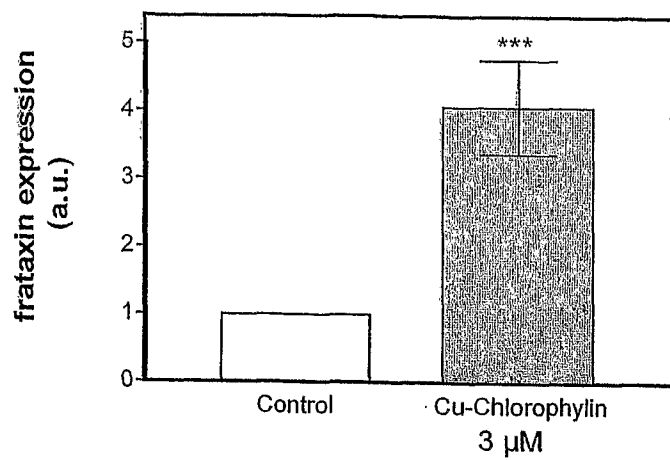


Fig. 1

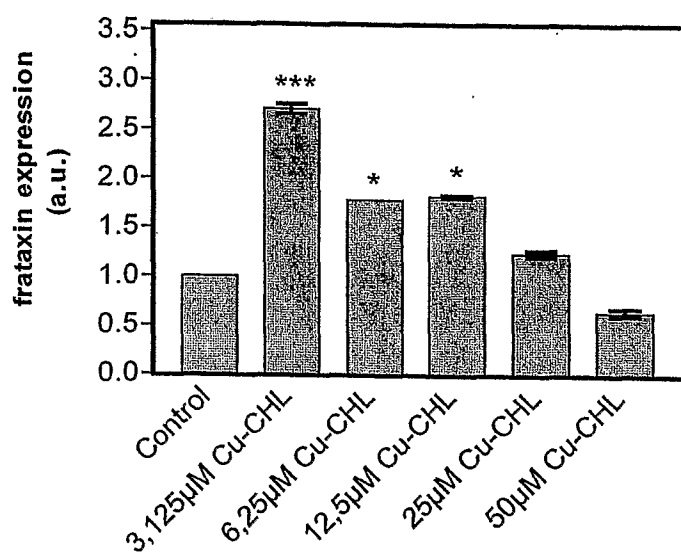


Fig. 2

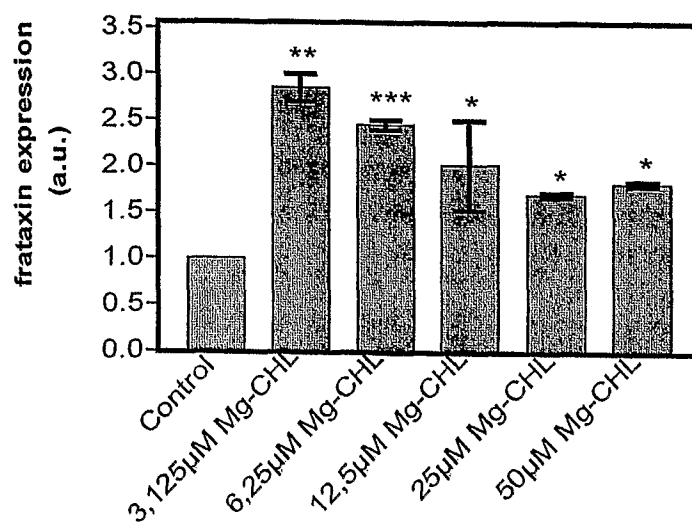


Fig. 3

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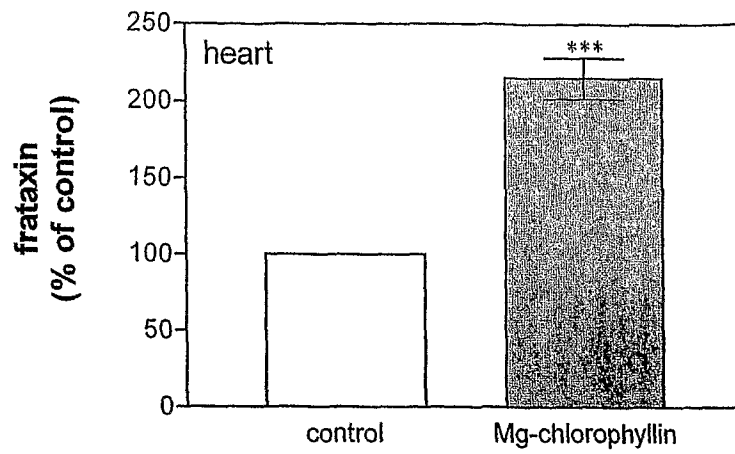


Fig. 4

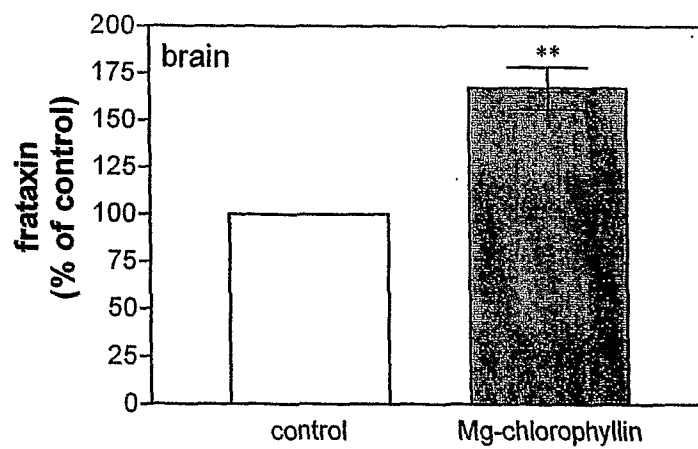


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/AT2007/000035

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/409 A61K33/06 A61P25/28 C07F3/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 2006/050819 A (MEDIZINISCHE UNI WIEN [AT]; SCHEIBER-MOJDEHKAR BARBARA [AT]; STURM BRI) 18 May 2006 (2006-05-18) the whole document	1-6
Y	STURM B ET AL: "Recombinant human erythropoietin: effects on frataxin expression in vitro" EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 35, no. 11, November 2005 (2005-11), pages 711-717, XP002431406 ISSN: 0014-2972 cited in the application abstract	1-6
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

27 April 2007

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

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