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(54) **Title**: TREATMENT OF HUNTINGTON'S DISEASE WITH CYCLOSERINE AND AN NMDA RECEPTOR ANTAGONIST

(57) **Abstract**: A method of treating or preventing Huntington's disease in a human patient in need thereof comprising co-administering D-cycloserine and an NMDA receptor antagonist or sigma receptor agonist to said patient.

TREATMENT OF HUNTINGTON'S DISEASE WITH CYCLOSERINE AND AN NMDA RECEPTOR ANTAGONIST

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application seeks priority to U.S. provisional patent application number 61/238,712 filed September 1, 2009.

FIELD

[0002] This application describes methods of using D-cycloserine and an NMDA receptor antagonist or partial agonist (at the glycine-modulatory site of the NMDA receptor) in the treatment or prevention of Huntington's disease.

BACKGROUND

[0003] Huntington's disease ("HD") is an autosomal dominant, progressive neurological disorder caused by an abnormal CAG trinucleotide repeat expansion in the huntingtin gene. This abnormal protein triggers a process that kills neurons (particularly medium-sized spiny neurons) in a brain region called the corpus striatum and leads to the symptoms of the disorder.

[0004] HD Symptomology is characterized by uncontrolled movements, emotional disturbances and mental deterioration. As the disease progresses, involuntary movements called chorea or choreiform movement (writing, squirming, jerky movements) predominate and often lead to physical disability and social isolation of these patients. Phenomenologically, the choreiform movements seen in HD patients are similar to involuntary movements (i.e., choreiform dyskinesias) seen in Parkinson's disease patients who have received long-term dopaminergic therapy and who have developed motor complications from these therapies (i.e. levodopa, dopamine agonists, and combinations thereof).

[0005] Increased levels of the excitatory neurotransmitter glutamate have been suggested to play a role in the pathogenesis of HD and altered N-methyl-D-aspartate (NMDA) receptor function has been proposed to underlie the pathogenesis of the choreiform movements. Recent

evidence suggests that there may be over-activation of the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptors as been suggested to occur in the motor complications of treated Parkinson's disease.

[0006] Presently, there are no effective palliative treatments for chorea in HD. Tranquilizers such as clonazepam (Klonopin), and antipsychotic drugs, such as haloperidol (Haldol) and clozapine (Clozaril), have been used to help control movements. Although these medications can be helpful in some cases, a common side effect is sedation, and in some cases, these medications may cause additional symptoms (akathisia, tardive dyskinesia, depression) including symptoms of parkinsonism (i.e., stiffness and rigidity). Therefore, a continuing and unmet need exists for new and improved methods of treating Huntington's disease.

SUMMARY

[0007] Disclosed herein is a method of treating Huntington's in a human patient in need thereof comprising co-administering D-cycloserine (DCS) or a DCS-like compound to a patient in need. In another embodiment, provided for is a method for treating Huntington's disease comprising D-cycloserine or DCS-like compound and an NMDA receptor antagonist to the patient. Thereby, choreiform movement in Huntington's disease can be reduced.

[0008] It is an embodiment of the invention to provide for a method of treating Huntington's disease in a human patient in need thereof comprising co-administering a glycine antagonist, wherein the glycine antagonist acts on the glycine binding site of the NMDA receptor, and an NMDA receptor antagonist. The NMDA receptor antagonist can be from the family of antagonists including a competitive antagonist, an un-competitive channel blocker or a non-competitive antagonist. Such non-competitive antagonists do not bind or target the glycine binding site on the NMDA receptor and therefore do not include glycine antagonists which specifically act on the glycine binding site of the NMDA receptor.

[0009] The glycine antagonist can include but are not limited to any antagonist or partial agonist, which under certain concentrations in vivo acts as an antagonists, those antagonists by way of example, not limitation include, D-cycloserine, 1-Aminocyclopropanecarboxylic acid (ACPC), 7-Chlorokynurenate, 5,7-dichlorokynurenic acid (DCKA), Kynurenic acid, lacosamide or others as are known in the art.

[0010] Another embodiment disclosed herein, is a composition for treating Huntington's disease in a human patient in need thereof comprising a glycine antagonist, such as D-cycloserine or others disclosed herein, and an NMDA receptor antagonist and a pharmaceutically acceptable excipient.

[0011] Additional features may be understood by referring to the following detailed description and examples.

DETAILED DESCRIPTION

[0012] Disclosed herein is a method of treating Huntington's in a human patient in need thereof comprising co-administering D-cycloserine (DCS) or a DCS-like agent to a patient in need. In another embodiment, provided for is a method for treating Huntington's disease comprising D-cycloserine or DCS-like compound and an NMDA receptor antagonist to the patient. Thereby, also reduced are choreiform movements in Huntington's disease patients. As used herein, "DCS-like compounds" means compounds which are partial glycine agonists, which when given at an appropriate doses, act as a functional antagonist to the glycine modulatory site of the NMDA receptor (also referred to herein as glycine binding site) and antagonists to the glycine modulatory site of the NMDA receptor.

[0013] It is an embodiment of the invention to provide for a method of treating Huntington's disease in a human patient in need thereof comprising co-administering a glycine antagonist, wherein the glycine antagonist acts on the glycine binding site of the NMDA receptor, and an NMDA receptor antagonist. The NMDA receptor antagonist can be from the family of antagonists including a competitive antagonist, an un-competitive channel blocker or a non-competitive antagonist. Such non-competitive antagonists do not bind or target the glycine binding site on the NMDA receptor and therefore do not include glycine antagonists which specifically act on the glycine binding site of the NMDA receptor.

[0014] The glycine antagonist can include but are not limited to any antagonist or partial agonist, which under certain concentrations in vivo acts as an antagonists, those antagonists by way of example, not limitation include, D-cycloserine, 1-Aminocyclopropanecarboxylic acid (ACPC), 7-Chlorokynurenate, 5,7-dichlorokynurenic acid (DCKA), Kynurenic acid, and lacosamide. In the instance of D-cycloserine, D-cycloserine in low concentraionts acts as an agonist of the NMDA receptor while at higher concentrations, as used in the methods herein

described, is a NMDA receptor antagonist.

[0015] A competitive antagonist of the NMDA receptor for use in the present method may also include, but is not limited to, R-2-amino-5-phosphonopentanoate, 2-amino-7-phosphonoheptanoic acid, and 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid. Uncompetetive channel blockers, NMDA antagonists, used in concert with the glycine antagonists, e.g. D-cycloserine, can be Amantadine, Dextromethorphan, Dextrorphan, Memantine, or other NMDA antagonists as are known in the art. Also, non-competitive antagonist can be selected from dexanabinol, aptiganel and remacemide. It would be clear to one of skill in the art that one or more of the described NMDA receptor antagonists may be used, and in any combination, as a co-therapy with a glycine receptor antagonist such as D-cycloserine. In specific embodiments, the method the NMDA antagonist can be Amantadine or Dextromethorphan and the glycine antagonist is D-cycloserine.

[0016] Another embodiment disclosed herein, is a composition for treating Huntington's disease in a human patient in need thereof comprising a glycine antagonist, such as D-cycloserine or others disclosed herein, and an NMDA receptor antagonist and a pharmaceutically acceptable excipient. As described for use in the methods of treating Huntington's disease, the NMDA receptor antagonist comprises a competitive antagonist, a un-competitive channel blocker or a non-competitive antagonist; wherein the competitive antagonist can be R-2-amino-5-phosphonopentanoate, 2-amino-7-phosphonoheptanoic acid, or 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid, the uncompetitive channel blocker can be Amantadine, Dextromethorphan, Dextrorphan, or wherein the non-competitive antagonists can be dexanabinol, aptiganel or remacemide, among others as are known in the art.

[0017] In a specific embodiment of the composition, the NMDA antagonist is Amantadine or Dextromethorphan and the glycine antagonist is D-cycloserine.

[0018] The glycine site on the NMDA receptor is critical for the functioning of the NMDA receptor since glycine is a co-agonist with glutamate for activation of the receptor. Recent studies suggest that the glycine site on the NMDA receptor may not be saturated in vivo under normal conditions but is likely saturated under conditions of excessive glutamate release, as suspected to occur in HD. Therefore, the modulation of this site may be physiologically significant. It is therefore an object of the invention to provide form therapy aimed at antagonizing the glycine site having therapeutic implications. Therefore, inhibiting NMDA

receptor activation in way that blocks the physiological functioning of the receptor could decrease involuntary movements associated with excess NMDA-mediated neurotransmission in the striatum and may also extend some neuroprotection by decreasing NMDA-mediated excitotoxicity.

[0019] Accordingly, it is an embodiment of the invention to use combinations of available drugs with complementary antagonistic actions at different targets on the NMDA receptor to effectively reduce involuntary movements associated with HD. Also, the method minimizes side effects that would arise from simply antagonizing the NMDA receptor by use of a competitive or non-competitive antagonists alone. This is because it is anticipated that lower doses of these complementary antagonists could be used to achieve beneficial effect when used in combination with a DCS-like compound, which functions as a partial glycine binding site agonist or glycine binding site antagonist. The invention utilizes the properties of D-cycloserine at doses compatible with antagonism of the glycine modulatory site of the NMDA receptor together with, for example, the NMDA antagonist amantadine. The combination of these two drugs with complementary actions at the NMDA receptor provides superior effects than can be expected with either drug alone.

[0020] When amantadine is bound in the channel of NMDA receptors, it increases the rate of channel closure As a result, the predominant inhibitory mechanism of amantadine is not blockade of current flow through open channels but rather increasing occupancy of channel closed states. The unusual properties of amantadine may play an important role in its clinical safety. After blocking the open channel, amantadine encourages NMDA receptor channels to occupy closed conformations. This unusual ability of amantadine increases its affinity, despite its fast unbinding from receptors with an open channel. Thus, the principal mode of action of amantadine is that of a gating antagonist rather than channel blocker. This activity of amantadine is complementary to the modulation of the NMDA receptor through antagonism of the glycine modulatory site of the NMDA recepetor by D-cycloserine.

[0021] An attractive feature of D-cycloserine, and amantadine, is the fact that they been used clinically for many years and their side-effect profiles are well-known. For D-cycloserine, at high doses used for tuberculostatic treatment (e.g., 500-2,000 mg/day), D-cycloserine can produce a number of side-effects, involving the CNS, confirming both its entry into the CNS and its antagonistic effects on NMDA receptors. These side-effects appear to be dose-related

and are mainly associated with doses of greater than 250 mg at one time and mainly occur at plasma levels above 30 mcg/mL.

[0022] In another embodiment, this invention provides a formulation of D-cycloserine that can rapidly achieve therapeutic NMDA receptor antagonistic blood levels and maintain them over the typical waking period (10-12 hours) for an HD patient without exceeding, at any point in time, safe blood levels above 30 mcg/mL, together with a safe and effective dose of amantadine (e.g., 200-400 mg/day). Various types of formulation (bi-layer tablets, controlled release capsules etc.) that may be suitable to achieve the desired pharmacokinetic profiles include formulations that provide immediate release amantadine (e.g., half-life of approximately 16 hrs, range 9-31 hrs) and immediate release D-cycloserine, followed by controlled release of D-cycloserine and extended release of amantadine.

[0023] In yet another embodiment, this invention also includes a formulation of D-cycloserine that can rapidly achieve therapeutic (NMDA receptor antagonistic) blood levels and maintain them over the typical waking period (e.g., 10-12 hours) for an HD patient without exceeding, at any point in time, safe blood levels above 30 mcg/mL together with a safe and effective dose of memantine HCl (e.g., 5-20 mg/day). Various types of formulation, e.g. bi-layer tablets, controlled release capsules etc. and others as are known arts that may be suitable to achieve the desired pharmacokinetic profiles include formulations providing immediate release amantadine (terminal elimination half-life approximately 60-80 hrs) and immediate release D-cycloserine, followed by controlled (e.g., extended or pulsed) release of D-cycloserine and memantine.

[0024] Another potential embodiment of this invention consists of the combination of D-cycloserine and dextromethorphan. Dextromethorphan is a non-competitive NMDA receptor agonist with affinity for the phencyclidine binding site on the NMDA receptor. It also has low affinity for sigma-2 receptors. These compositions are a therapeutically effective dosage of dextromethorphan ("DM"), or a pharmaceutically acceptable salt or analog thereof, in combination with a therapeutically effective dosage of D-cycloserine. Dextromethorphan is widely available over-the-counter in cough syrups, at dosages up to about 120 mg/day for an adult. In the present invention, DM dosages in the range of about 20 mg/day to about 200 mg/day, preferably in the range of 20 to 150 mg/day, depending on factors such as the weight of the patient, the severity of the disorder, and the potency and dosage of the D-cycloserine used in conjunction with DM. DM may also be administered with quinidine, a specific inhibitor of

cytochrome P450 2D6 enzyme (responsible for first-pass metabolism of DM to its primary metabolite dextrorphan in the liver). By administering DM with quinidine (25-30 mg to provide maximal suppression of DM metabolism), the amount of systemically available DM is significantly increased.

[0025] Sustained release formulations of dextromethorphan are known. Peak levels for sustained release products generally occur about six hours after ingestion. Onset of action is rapid and serum levels peak 2.5 hours after oral administration. Peak concentration of the major metabolite (dextrorphan) is 1.6 to 1.7 hours. The biological half-life of dextromethorphan is approximately two to four hours in people with normal metabolism. A formulation including a controlled release dosage of D-cycloserine and sustained release DM, and quinine, is preferred.

[0026] Another embodiment of this invention includes with D-cycloserine a combination of a therapeutically effective dose of amantadine and a therapeutically effective dose of dextromethorphan in a sustained release formulation.

[0027] The invention may also be used as rational combination therapy for treating levodopa - induced dyskinesias in Parkinson's disease patients.

[0028] In summary, there currently is no cure for HD and palliative therapies are minimally effective if at all and are mostly associated with undesirable side effects. This new approach, using rational combination therapies, will promote deceased activity at over-active NMDA receptors, thus reducing unwanted movements in HD patients. By inhibiting NMDA receptor over-activity, these therapies may also exert neuroprotective effects by reducing excitotoxicity and may slow the progression of functional decline in HD patients.

[0029] While this description is made with reference to exemplary embodiments, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope. In addition, many modifications may be made to adapt a particular situation or material to the teachings hereof without departing from the essential scope. Also, in the drawings and the description, there have been disclosed exemplary embodiments and, although specific terms may have been employed, they are unless otherwise stated used in a generic and descriptive sense only and not for purposes of limitation, the scope of the claims therefore not being so limited. Moreover, one skilled in the art will appreciate that certain steps of the methods discussed herein may be sequenced in alternative order or steps may be combined. Therefore, it is intended that the

appended claims not be limited to the particular embodiment disclosed herein.

[0030] Each of the applications and patents cited in this text, as well as each document or reference cited in each of the applications and patents (including during the prosecution of each issued patent; "application cited documents"), and each of the PCT and foreign applications or patents corresponding to and/or claiming priority from any of these applications and patents, and each of the documents cited or referenced in each of the application cited documents, are hereby expressly incorporated herein by reference in their entirety. More generally, documents or references are cited in this text, either in a Reference List before the claims; or in the text itself; and, each of these documents or references ("herein-cited references"), as well as each document or reference cited in each of the herein-cited references (including any manufacturer's specifications, instructions, etc.), is hereby expressly incorporated herein by reference.

CLAIMS

1. A method of treating Huntington's disease in a human patient in need thereof comprising administering wherein said glycine antagonist acts on the glycine binding site of the NMDA receptor.

2. The method of claim 1 further comprising co-administering, with said glycine antagonist, an NMDA receptor antagonist.

3. The method of claim 1, wherein said glycine antagonist is selected from the group of said glycine antagonists consisting of D-cycloserine, 1-Aminocyclopropanecarboxylic acid (ACPC), 7-Chlorokynurenate, 5,7-dichlorokynurenic acid (DCKA), Kynurenic acid, and lacosamide.

4. The method according to claim 2, wherein said NMDA receptor antagonist comprises a competitive antagonist, a un-competitive channel blocker or a non-competitive antagonist.

5. The method according to claim 4, wherein said competitive antagonist is selected from the group consisting of R-2-amino-5-phosphonopentanoate, 2-amino-7-phosphonoheptanoic acid, and 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid.

6. The method according the claim 4, wherein said uncompetitive channel blocker is selected from the group consisting of Amantadine, Dextromethorphan, Dextrorphan and Memantine.

7. The method according to claim 4, wherein said non-competitive antagonist is selected from the group consisting of dexanabinol, aptiganel and remacemide.

8. The method according to claim 1, wherein said glycine antagonist is D-cycloserine or a DCS-like compound.

9. The method according the claim 2, wherein said NMDA antagonist is Amantadine or Dextromethorphan.

10. A method of treating Huntington's disease in a human patient in need thereof comprising administering D-cycloserine or a DCS-like compound wherein said D-

cycloserine or DCS-like compound targets the glycine binding site of the NMDA receptor.

11. The method of claim 10, further comprising co-administering, with said D-cycloserine or a DCS-like compound, an NMDA receptor antagonist.

12. The method according to claim 11, wherein said NMDA receptor antagonist comprises a competitive antagonist, a un-competitive channel blocker or a non-competitive antagonist.

13. The method according to claim 12, wherein said competitive antagonist is selected from the group consisting of R-2-amino-5-phosphonopentanoate, 2-amino-7-phosphonoheptanoic acid, and 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid.

14. The method according the claim 12, wherein said uncompetitive channel blocker is selected from the group consisting of Amantadine, Dextromethorphan, Dextrorphan and Memantine

15. The method according to claim 12, wherein said non-competitive antagonist is selected from the group consisting of dexanabinol, aptiganel and remacemide.

16. The method according the claim 10 wherein said NMDA antagonist is Amantadine or Dextromethorphan.

17. The method according to claims 2 or 11, wherein said NMDA receptor antagonist is sigma receptor agonist.

18. A composition for treating Huntington's disease in a human patient in need thereof comprising D-cycloserine or a DCS-like compound and a pharmaceutically acceptable excipient.

19. The composition of claim 18, further comprising an NMDA receptor antagonist.

20. The composition according to claim 19, wherein said NMDA receptor antagonist comprises a competitive antagonist, a un-competitive channel blocker or a non-competitive antagonist.

21. The composition according to claim 20, wherein said competitive antagonist is selected

from the group consisting of R-2-amino-5-phosphonopentanoate, 2-amino-7-phosphonoheptanoic acid, and 3-[(R)-2-carboxypiperazin-4-yl]-prop-2-enyl-1-phosphonic acid.

22. The composition according to claim 20, wherein said uncompetitive channel blocker is selected from the group consisting of Amantadine, Dextromethorphan, Dextrorphan and Memantine.

23. The composition according to claim 20, wherein said non-competitive antagonist is selected from the group consisting of dexanabinol, aptiganel and remacemide.

24. The composition according to claim 19, wherein said NMDA antagonist is Amantadine or Dextromethorphan.

25. The composition of claim 18, wherein said DCS-like compound is selected from the group consisting of -Aminocyclopropanecarboxylic acid (ACPC), 7-Chlorokynurenate, 5,7-dichlorokynurenic acid (DCKA), Kynurenic acid, and lacosamide.