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(71) Applicants: **PRESIDENT AND FELLOWS OF HARVARD COLLEGE** [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US). **THE GENERAL HOSPITAL CORPORATION** [US/US]; 55 Fruit Street, Boston, MA 02114 (US). **ORGANIX, INC.** [US/US]; 240 Salem Street, Woburn, MA 01801 (US).

(72) Inventors: **MADRAS, Bertha, K.**; 32 Montrose Street, Newton, MA 02458 (US). **FISCHMAN, Alan, J.**; 1 Longfellow Place, Boston, MA 02114 (US). **MELTZER, Peter, C.**; 8 Rumford Road, Lexington, MA 02173 (US).

(74) Agent: **FREEMAN, John, W.**; Fish & Richardson, P.C., 225 Franklin Street, Boston, MA 02110-2804 (US).

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(54) Title: IMAGING THE DOPAMINE TRANSPORTER TO DETERMINE AD-HD

(57) Abstract: A method of diagnosing attention deficient-hyperactivity disorder (AD-HD) in a human patient by assessing dopamine transporter in at least one region of the patient's central nervous system, where an elevated level of dopamine transporter in the patient is indicative of AD-HD. In embodiments of the invention, assessment of dopamine transporter levels includes assessing binding of a dopamine transporter ligand to dopamine transporter using PET or SPECT.

IMAGING THE DOPAMINE TRANSPORTER TO DETERMINE AD-HD

Background of the Invention

Attention deficit-hyperactivity disorder (AD-HD) is a recognized syndrome characterized by a relatively high (2-6%) incidence in children with persistence into adulthood. Some research suggests that AD-HD has a genetic component. Biederman et al., "High Risk for Attention Deficit Disorder Among Children of Parents with Childhood Onset of the Disorder: A Pilot Study," Am. J. Psychiatry, 152(3):431-35 (1995); Arnold et al., "National Institute of Health Collaborative Multimodal Treatment Study of Children with ADHD (the MTA)," Arch. Gen. Psychiatry, 54:865-70 (1997). Paradoxically, stimulant drugs such as methylphenidate, d-amphetamine and pemoline are effective medications for treating AD-HD in children and adults. Seeman and Madras, "Anti-hyperactivity Medication: Methylphenidate and amphetamine," Molecular Psychiatry, 3:385-96 (1998); Arnold et al., *supra*; Greenhill et al., "Stimulant Medications," J. Am. Acad. Child Adolesc. Psychiatry, 38(5):503-12 (1999); Wilens and Biederman, "The Stimulants," Psychiatric Clinics of N. Am., 15(1): 191-222 (1992).

Increased recognition of the disorder has led to increased prescription of stimulant medications for treating AD-HD. There is concern about the possibility of over-diagnosis of AD-HD and resulting unnecessary treatment with stimulant drugs that have inherent potential for abuse. Conversely, if AD-HD is underdiagnosed, patients who could be helped may go untreated.

Summary of the Invention

We have recognized that the dopamine transporter in the human brain is a useful protein for diagnosing and monitoring the course of AD-HD. For example, various dopamine transporter imaging agents can be used to assay the dopamine transporter as a biological marker for AD-HD. Such imaging is used to diagnose AD-HD and to monitor it, e.g. as the patient matures and/or is treated over time.

In general, in one aspect, the invention features methods of diagnosing attention deficient-hyperactivity disorder (AD-HD) in a human patient by assessing dopamine transporter in at least one region of said patient's central nervous system. An elevated level of dopamine transporter in said patient is

indicative of AD-HD. This assessment can involve an assessment of the binding of a dopamine transporter ligand to dopamine transporter. PET or SPECT imaging are particularly preferred assessment techniques. Suitable ligands include [^{11}C]CFT ([^{11}C]WIN 35,428), [^{123}I]altropane, and [^{18}F]CFT. Other suitable ligands, particularly for PET, include [^{11}C]altropane. Other suitable ligands, particularly for SPECT, include technetium-labeled phenyltropane probes, such as [99mTc]technepine, O-1505, and similar compounds. The portion of the patient's central nervous system is preferably a portion of the human brain, e.g., the striatum.

Assessing dopamine transporter to determine dopamine transporter levels may include assessing dopamine transporter availability or binding potential.

In general, in another aspect, the invention features a method of determining the effectiveness of an AD-HD treatment for a human patient. The method includes assessing an initial dopamine transporter level in at least one region of the patient's central nervous system, applying the treatment, and then assessing a subsequent dopamine transporter level in the region, e.g., more than two weeks later. The initial and subsequent dopamine transporter levels are then compared.

In this aspect of the invention, the treatment can include administration of a pharmaceutical, such as methylphenidate, pemoline, or an amphetamine, and the assessing step can include PET or SPECT.

In general, in another aspect, the invention features a method of determining whether an individual has a heightened probability of having AD-HD. The method includes assessing dopamine transporter in at least one region of the patient's central nervous system and comparing the patient's dopamine transporter level to a normal dopamine transporter level. A higher than normal level is indicative of a heightened probability of having AD-HD.

In general, in another aspect, the invention features a method of monitoring the progress of a treatment for AD-HD in a human patient. The method includes assessing dopamine transporter in at least one region of the patient's central nervous system a plurality of times during the treatment.

The invention may include one or more of the following advantages. Assessing dopamine transporter levels allows an objective, biologically based diagnosis of AD-HD. Diagnosis based on dopamine transporter levels can be used for patients of all ages and both sexes.

The imaging agents used to assess dopamine transporter levels, such as [^{123}I]altropane, are safe and well tolerated by patients.

Other features and advantages of the invention will be apparent to those skilled in the arts from the following description of the preferred embodiments and from the claims.

Description of the Preferred Embodiments

We have discovered that abnormal levels of the dopamine transporter in human brain is indicative of AD-HD. Assessing dopamine levels in the brain, therefore, can confirm a diagnosis of AD-HD, or can assist in monitoring treatment of AD-HD.

Dopamine Transporter Assessment Techniques

Assessing dopamine transporter levels can be performed by assessing dopamine transporter availability using, e.g., PET (positron emission tomography) or SPECT (single photon emission computed tomography). To measure dopamine transporter availability, a labeled probe that targets the transporter is introduced into the brain, e.g., intravenously, and PET or SPECT is performed. From the PET or SPECT images, the density of the dopamine transporter is quantified by measuring the binding potential, where binding potential is defined as the maximum number of binding cites, B_{max}, divided by a dissociation constant, K_d, where K_d is related to affinity.

Imaging agents that target the dopamine transporter include [^{11}C]altropane, [^{11}C or ^{18}F]WIN 35,428 ([^{11}C]CFT), [^{123}I]altropane, [99^{m}Tc]O-1505, [99^{m}Tc]technepine, and similar compounds. These agents bind the dopamine transporter with varying affinities, allowing multiple, dissimilar assessments to be performed. Structures, synthesis, and/or sources of some of the above agents are described in, e.g., Fischman et al., "Rapid Detection of Parkinson's Disease by SPECT with Altropane: A Selective Ligand For

Dopamine Transporters," Synapse, 29:125-41 (1998) ([^{123}I]altropane); Madras et al., "Technipine: A High Affinity ^{99m}Technetium Probe to Label the Dopamine Transporter in Brain by SPECT Imaging," Synapse, 22:239-46 (1996); Meltzer et al., "Substituted 3-Phenyltropane Analogs of Cocaine: Synthesis, Inhibition of Binding of Cocaine Recognition Sites, and Positron Emission Tomography Imaging," J. Med. Chem., 36:855-62 (1993); and Milius et al., "Synthesis and Receptor Binding of N-Substituted Tropine Derivatives, High Affinity Ligands for the Cocaine Receptor," J. Medicinal Chem., 34:1728-31 (1990), each of which is incorporated by reference herein in its entirety.

Other techniques to identify anomalies in brains of AD-HD patients include SPECT imaging to measure blood flow and functional MRI to measure regional metabolic function. Both techniques demonstrate abnormal function of the frontal cortex.

Applications of Dopamine Transporter Assessments

Traditionally, AD-HD is diagnosed by assessing a patient's cognitive and attentional skills. For example, according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), evidence of either inattention or hyperactivity and impulsivity are required to support a diagnosis of AD-HD. Under the DSM-IV standard, a finding of inattention must be supported by six or more of the following symptoms, persisting for at least six months to a degree that is maladaptive and inconsistent with the patient's level of development: (1) fails to give close attention to details; (2) has difficulty sustaining attention to activities; (3) does not listen when spoken to directly; (4) does not follow through on instructions; (5) has difficulty organizing tasks; (6) avoids engaging in tasks that require sustained mental effort; (7) loses things necessary for activities; (8) is easily distracted by extraneous stimuli; (9) is forgetful in daily activities. Similarly, under the DSM-IV standard, a finding of hyperactivity and impulsivity must be supported by six or more of the following symptoms, persisting for at least six months to a degree that is maladaptive and inconsistent with the patient's level of development: (1) is fidgety; (2) leaves seat when expected to remain seated; (3) runs about in situations in which it is inappropriate; (4) has difficulty playing quietly; (5) acts as if "driven by a motor"; (6) talks excessively; (7) blurts out answers before questions have been completed; (8) has difficulty taking turns; (9) interrupts or intrudes on others. When used to diagnose AD-HD in adults, the above criteria are modified slightly to apply to adult environments.

Diagnosis of AD-HD using the DSM-IV standard is inherently somewhat subjective, leading to inconsistent diagnosis.

Assessment of dopamine transporter levels can complement, and in some cases, supplant, traditional AD-HD diagnostic techniques. The dopamine transporter level assessments using PET or SPECT provide objective, biological criteria for diagnosing AD-HD, and can be used, e.g., to confirm an AD-HD diagnosis under the DSM-IV standard, to resolve conflicting diagnoses, or to call into question a diagnosis or non-diagnosis of AD-HD. Dopamine transport assessments can also be used to refine subjective testing criteria for AD-HD.

In addition, PET and SPECT imaging of the dopamine transporter can be used to monitor and adjust treatment of AD-HD. For example, methylphenidate, a drug commonly used to treat AD-HD, may occupy the dopamine transporter. Volkow et al., "Dopamine Transporter Occupancies in the Human Brain Induced by Therapeutic Doses of Oral Methylphenidate," Am J. Psychiatry, 155:1325-31 (1998). The effectiveness of methylphenidate treatment for a particular patient could be monitored by assessing dopamine transporter levels both before and after administration of methylphenidate. For example, dopamine transporter levels can be assessed immediately before a treatment, and then, e.g., two weeks, months, or longer after administration of treatment. If the methylphenidate successfully occupies dopamine transporters, it will displace the radio-labeled probe, decreasing the availability of dopamine transporter. The decreased availability of dopamine transporter will manifest as decreased binding potential in the PET or SPECT images. Such objective data can assist a physician in determining the most effective drug and the most effective dosage for a particular patient.

Dopamine transporter level assessments can also be used to monitor treatment over the long term, and to help a physician and patient determine whether treatment affects transporter levels and whether treatment can be stopped.

Finally, dopamine transporter level assessments can identify individuals at risk for AD-HD. Patients found to have elevated dopamine transporter levels can, e.g., be referred for conventional AD-HD testing.

Experimental Studies

Experimental data confirm the efficacy of diagnosing AD-HD by detecting elevated dopamine transporter levels.

SPECT imaging of the dopamine transporter with [^{123}I]altropane was conducted on six subjects previously diagnosed with AD-HD, and on control individuals without a diagnosis of AD-HD. For each individual tested, greater than 1 mCi of [^{123}I]altropane was administered by intravenous injection at the onset of imaging. Images of the striatum were collected and analyzed by a radiologist to determine striatal binding potentials. In general, the methodology

used for the SPECT imaging was the same as the methods described in Fischman et al., "Rapid Detection of Parkinson's Disease by SPECT with Altropane: A Selective Ligand For Dopamine Transporters," Synapse, 29:125-41 (1998), which is incorporated herein by reference in its entirety.

The results of the imaging of AD-HD patients are summarized below in Table 1:

Table 1: AD-HD Patients

INDIVIDUAL	AGE	BINDING POTENTIAL
ADHD-1	34	2.98
ADHD-2	45	2.34
ADHD-3	24	2.71
ADHD-4	53	2.33
ADHD-5	51	2.16
ADHD-6	41	3.51
MEAN	41	2.67

These six AD-HD individuals show elevated binding potential, and, therefore, elevated dopamine transporter levels compared to expected levels for aged matched normal individuals, which may range, generally, between about 1.0 and 2.2.

What is claimed is:

CLAIMS:

1. A method of diagnosing attention deficient-hyperactivity disorder (AD-HD) in a human patient comprising assessing dopamine transporter in at least one region of said patient's central nervous system, wherein an elevated level of dopamine transporter in said patient is indicative of AD-HD.

2. The method of claim 1 in which said assessment is by PET or SPECT imaging.

3. The method of claim 1 in which said assessment comprises assessing binding of a dopamine transporter ligand to dopamine transporter.

4. The method of claim 3 in which said dopamine transporter ligand comprises [^{11}C]CFT ([^{11}C]WIN 35,428).

5. The method of claim 4 in which said assessment comprises imaging by PET.

6. The method of claim 3 in which said dopamine transporter ligand comprises [^{11}C]altropane.

7. The method of claim 6 in which said assessment comprises imaging by PET.

8. The method of claim 3 in which said ligand comprises [^{123}I]altropane and said assessment comprises imaging by SPECT.

9. The method of claim 3 in which said ligand comprises a technetium-labeled phenyltropane probe.

10. The method of claim 9 in which said ligand comprises [^{99}mTc]technepine, O-1505.

11. The method of claim 9 in which said assessment comprises imaging by SPECT.

12. The method of claim 1 in which said at least one region of said patient's central nervous system comprises a portion of the brain.

13. The method of claim 12 in which said portion of the brain comprises the striatum.

14. The method of claim 1 in which the assessing step includes assessing dopamine transporter availability.

15. The method of claim 1 in which the assessing step includes assessing dopamine transporter binding potential.

16. A method of determining the effectiveness of an AD-HD treatment for a human patient, the method comprising:

assessing an initial dopamine transporter level in at least one region of said patient's central nervous system;

applying the treatment;

assessing a subsequent dopamine transporter level in said at least one region of said patient's central nervous system; and

comparing the initial and subsequent dopamine transporter levels.

17. The method of claim 16 in which the second assessing step occurs greater than two weeks after the applying step.

18. The method of claim 16 in which the treatment comprises a pharmaceutical treatment.

19. The method of claim 18 in which the pharmaceutical treatment comprises administration of a pharmaceutical selected from the group consisting of methylphenidate, pemoline, and an amphetamine.

20. The method of claim 16 in which the assessing step includes PET or SPECT.

21. A method of determining whether an individual has a heightened probability of having AD-HD, the method comprising:

assessing dopamine transporter in at least one region of said patient's central nervous system;

comparing said patient's dopamine transporter level to a normal dopamine transporter level, wherein a higher than normal level indicates a heightened probability of having AD-HD.

22. A method of monitoring the progress of a treatment for AD-HD in a human patient, the method comprising assessing dopamine transporter in at least one region of said patient's central nervous system a plurality of times during said treatment.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61B 5/00
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 600/300,407,425,431,436

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 practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 6,011,070 A (FROIMOWITZ et al) 04 January 2000, see entire document	1-22
X	US 5,770,180 A (MADRAS et al) 23 June 1998, see entire document	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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当前申请(专利权)人(译)	主席和哈佛学院院士 总医院CORPORATION ORGANIX INC.		
[标]发明人	MADRAS BERTHA K FISCHMAN ALAN J MELTZER PETER C		
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摘要(译)

一种通过评估患者中枢神经系统的至少一个区域中的多巴胺转运蛋白来诊断人类患者注意力缺陷多动障碍（AD-HD）的方法，其中患者中多巴胺转运蛋白水平升高指示AD-HD。在本发明的实施方案中，多巴胺转运蛋白水平的评估包括使用PET或SPECT评估多巴胺转运蛋白配体与多巴胺转运蛋白的结合。