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(54) **D-SERINE TRANSPORT ANTAGONIST FOR TREATING PSYCHOSIS**

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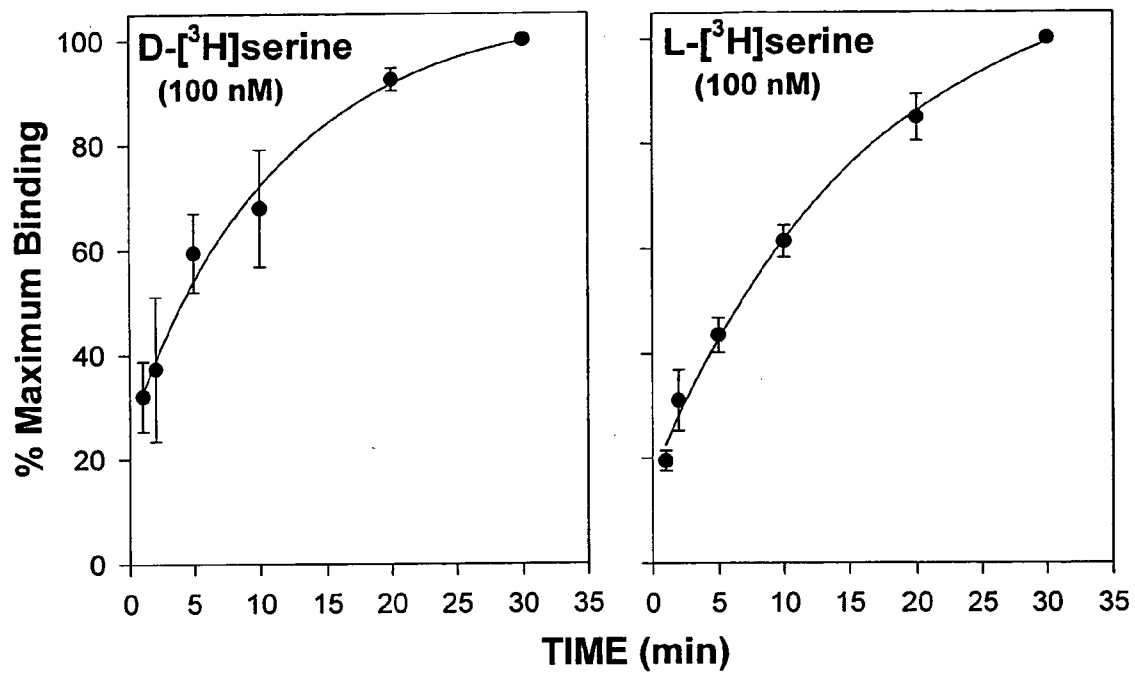
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(57) **ABSTRACT**

Method and composition for augmenting NMDA receptor mediated neurotransmission involving use of a D-serine transport inhibitor.

Figure 1



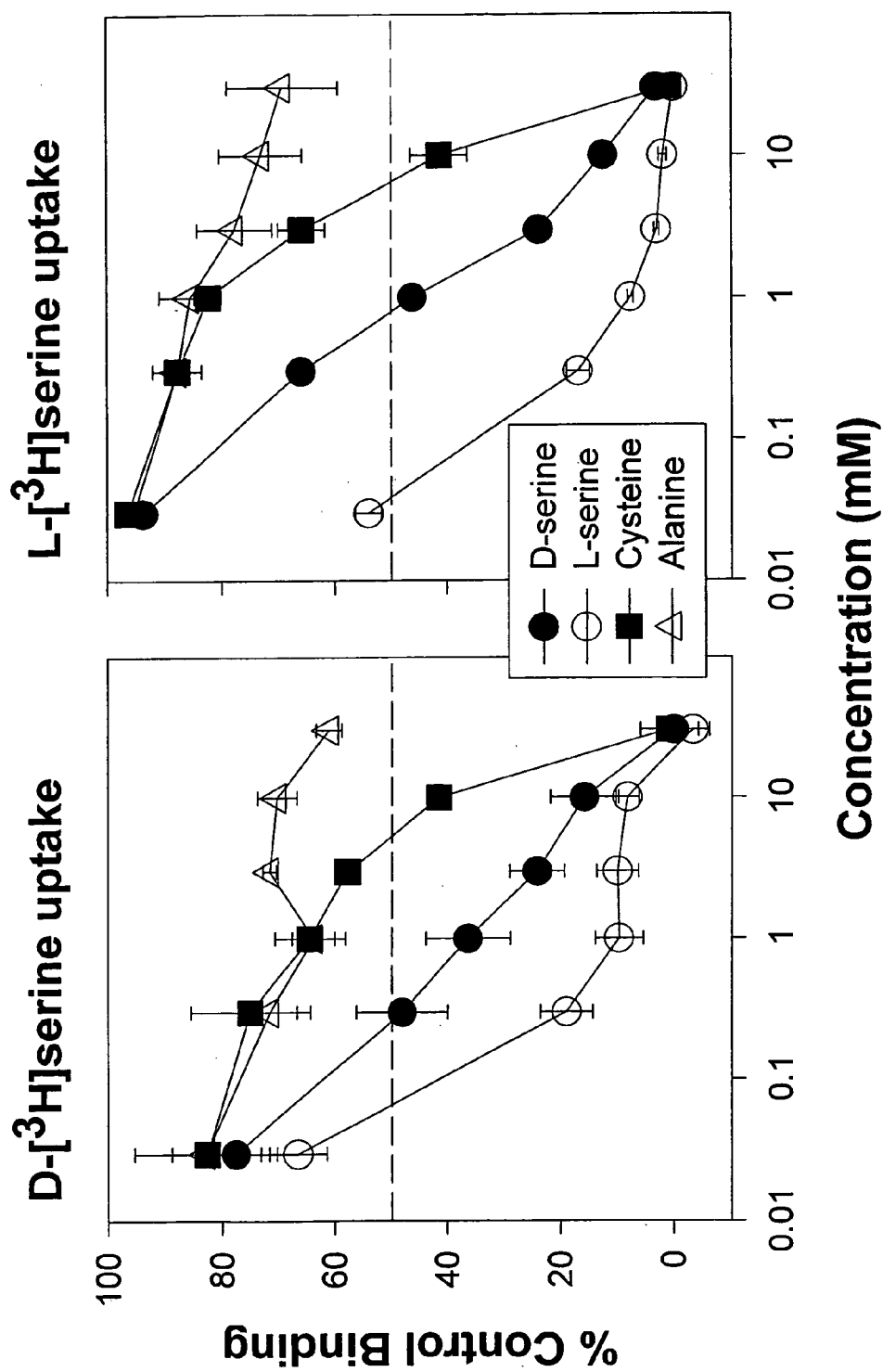
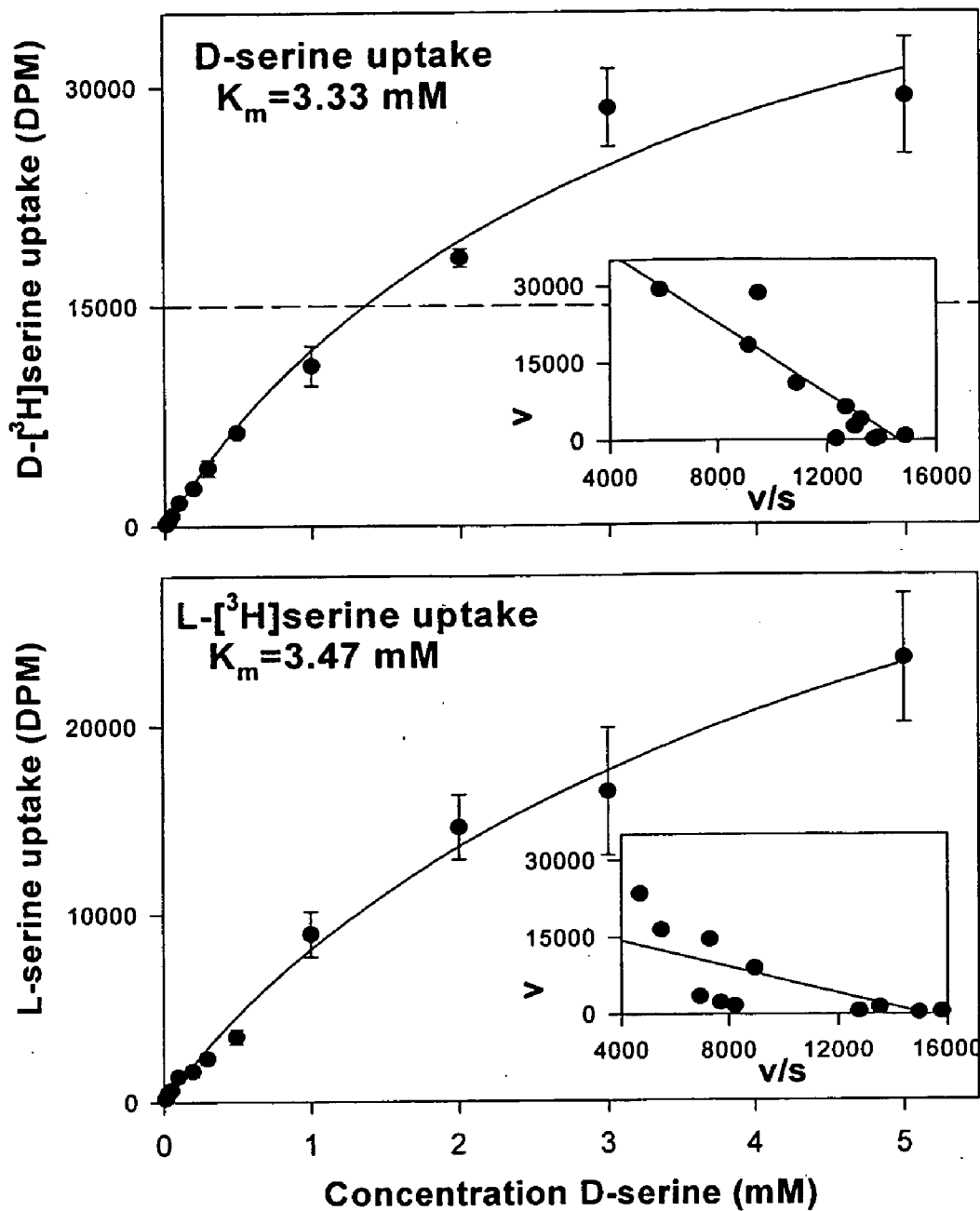


Figure 2

Figure 3



## D-SERINE TRANSPORT ANTAGONIST FOR TREATING PSYCHOSIS

### RELATED APPLICATION

[0001] The present application is a continuation-in-part of U.S. application Ser. No. 09/365,889 filed Aug. 3, 1999.

### BACKGROUND

[0002] Schizophrenia is a psychotic disorder associated with positive, negative and cognitive symptoms, neuropsychological deficits and poor social functioning. Traditional theories of schizophrenia have focused on abnormal dopaminergic neurotransmission. Mainstay treatments for schizophrenia including use of typical (e.g., thiorazine, haloperidol) or atypical (e.g. clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazol, sertindole) antipsychotics (also called neuroleptics or major tranquilizers). Antipsychotics may be administered orally, parenterally and in depot formulations. In addition, patients may be treated with mood stabilizers (e.g., lithium, valproic acid), antidepressants (e.g., tricyclics, SSRIs), or anti-anxiety agents (e.g., benzodiazepines, barbiturates). Recent theories postulate that schizophrenia is associated with dysfunction or dysregulation of neurotransmission mediated at brain N-methyl-D-aspartate (NMDA)-type glutamate receptors (Javitt, 1987; Javitt and Zukin, 1991). PCP and other psychotomimetic drugs mediate their effects by blocking NMDA receptor-mediated neurotransmission. NMDA agonists, including glycine and D-serine, reverse the behavioral effects of PCP in rodents (Toth et al., 1986; Javitt and Frusciant, 1997; Javitt et al., 1997; Tani et al., 1994, 1991; Nilsson et al., 1997), and induce significant improvement in negative and cognitive symptoms in remitted schizophrenics (Javitt et al., 1994; Heresco-Levy et al., 1999; Tsai et al., 1998), supporting the PCP/NMDA model of schizophrenia.

[0003] Both glycine and D-serine serve as endogenous modulators of NMDA receptors (Hashimoto et al., 1995; Hashimoto and Oka, 1997). In general, amino acid levels in brain are regulated by endogenous transporters that limit CNS levels. A potential alternate approach to increasing glycine or D-serine levels in brain, therefore, would be the use of agents that inhibit either glycine or D-serine transport in brain. This approach has been well described in the case of glycine. Glycine (GlyT1) transporters in brain are well described and have been shown to be colocalized with NMDA receptors (Smith et al., 1992; 1992; Liu et al., 1993). Further, modulation of glycine transporters has been shown to modulate NMDA receptor-mediated neurotransmission both in vitro and in vivo (Javitt and Frusciant, 1997; Javitt et al., 1997; Supplison and Bergman, 1998; Bergeron et al., 1998; Berger et al., 1998; Danyasz and Parsons, 1998), supporting the physiological relevance of amino acid transport processes.

[0004] The present invention relates to the use of D-serine transport inhibitors (also referred to as uptake antagonists) in the treatment of schizophrenia. D-Serine, like glycine, has been shown to be effective in treatment of persistent negative symptoms of schizophrenia (Tsai et al., 1998). However, as with glycine, sufficient concentrations of D-serine are already present in brain that NMDA/glycine sites (the molecular target of D-serine) would be saturated under normal circumstances (Hashimoto et al., 1995, Hashimoto

and Oka, 1997; Matsui et al., 1995). If the NMDA/glycine site were saturated by endogenous D-serine, then neither exogenous glycine or exogenous D-serine would have significant neurochemical or behavioral effects since both these agents share a common target (i.e., the NMDA/glycine site). The fact that glycine and serine do potentiate NMDA receptor-mediated neurotransmission suggests that for D-serine, as with glycine, there must be an endogenous process that "protects" NMDA receptors from extracellular D-serine. At present, D-serine transport processes in brain are poorly understood. The present application describes a novel brain D-serine transport system that is relatively selective for D-serine over other amino acids, and provides the first demonstration that agents which block D-serine transport in vitro also stimulate NMDA receptor in vivo and are effective in animal models of schizophrenia.

[0005] The next section describes state-of-the-art regarding existence of D-serine transport systems in brain. Example 1 describes the existence of multiple high affinity D-serine transport systems in synaptosomal membranes that can be differentiated based upon sensitivity to inhibition by alanine. Example 2 describes the relative ability of three amino acid derivatives, glycine dodecylamide (GDA), D-serine dodecylamide (D-Ser DA) and D-alanine dodecylamide (D-Ala DA) on amphetamine- and PCP-induced locomotor activity in rodents. These findings demonstrate likely effectiveness of D-serine transport inhibitors in treatment of persistent negative and cognitive symptoms in schizophrenia and treatment of related symptoms in other neurological and psychiatric disorders associated with reduced NMDA function including but not limited to Alzheimers disease, age associated memory impairment, autism, attention-deficit disorder, bipolar disorder, depression, Parkinsons disease, Huntingtons disease, and recovery from stroke, neurological insult or closed head injury. Example 3 demonstrates effects of the amino acid glycine and the amino acid derivative D-Ala DA on in vivo [3H] MK-801 binding, an in vivo model of NMDA receptor activation.

### DETAILED DESCRIPTION OF THE INVENTION

[0006] Brain is known to contain multiple amino acid transport systems, including system "Gly", which is specialized for uptake of glycine, system "A" which is specialized for uptake of Alanine, system "L" which is specialized for uptake of Leucine, and system "ASC" which is specialized for uptake of Alanine, Serine and Cysteine (Sershen and Lajtha, 1979; Hashimoto and Oka, 1997). Serine transport, including transport of both L- and D-isomers of serine, is generally considered to occur via system ASC (Hashimoto and Oka, 1997), although transport may also occur through system L (Sershen and Lajtha, 1979). The hallmark of this system is high affinity for alanine. Two ASC-like transporters have recently been cloned and have been termed ASCT1 (Arriza et al., 1993) and ASCT2 (Utsunomiya-Tate et al., 1996). Studies with cloned transporters have confirmed that ASC-family transporters show highest affinity for L-alanine, along with high affinity for L-cysteine and L-serine, and stereoselectivity for L- vs. D-amino acids. A related transporter, termed SATT was found to have differential affinity for serine and cysteine. However, this transporter was found not to be sensitive to D-serine (Shafiqat et al., 1993). Based on the relatively low affinity of these transporters for

D-amino acids, Hashimoto et al. (1997) concluded that "further study is needed to clarify a specific transport system for D-serine in mammals." D-Serine transport has also been studied in glioma cells (Hayashi et al., 1997) and astrocyte cultures (Schell et al., 1995). Glia have also been shown to accumulate exogenously administered D-serine in vivo (Wako et al., 1995; Schell et al., 1995). Transport in these cells, like transport through cloned receptors, was found to be inhibited most strongly by L-cysteine, L-alanine, and L-serine. D-Serine was transported, but affinity for D-serine was approximately 20-fold lower than affinity for L-serine. This finding is consistent with glial D-serine uptake being mediated by system ASC transporters. The relative insensitivity of these transporters to D-serine makes it unlikely that they regulate synaptic D-serine levels in vivo.

[0007] Further suggestion that additional D-serine transporters are present in brain comes from a study by Tanii et al. (1994). In that study, they observed that intracerebroventricularly administered D-alanine was significantly more potent in reversing PCP-induced hyperactivity than was intracerebroventricularly administered D-serine, even though D-serine is more potent in binding to the NMDA/glycine site. This finding suggests the existence of a brain transporter with higher affinity for serine and alanine. Such a pattern would be opposite to the known selectivity pattern of system ASC. In discussing relative potency of D-serine to other amino acids, Tanii et al. (1994) postulated the existence of "specific metabolizing systems" for D-serine, but did not specifically postulate the existence of a selective transporter. Moreover, despite the recognition that D-serine serves as an endogenous agonist of NMDA receptors, use of selective D-serine transport antagonists in the treatment of schizophrenia has not been previously suggested.

[0008] For this study, two novel amino acid derivatives were synthesized—D-serine dodecylamide (D-Ser-DA) and D-alanine dodecylamide (D-Alanine-DA). Synthesis was performed by addition of an alkyl group to the C-terminus (COOH or equivalent) of the amino acid by amide linkage. Variations of this approach, wherein other hydrophobic groups are linked to either the C- or N-terminus (NH<sub>2</sub> or equivalent) of glycine, D-serine, D-alanine, L-serine or L-alanine, are obvious extensions of this invention. Such groups would include but not be limited to alkyls (C1-C13) such as methyl, phenyls or phenylalkyls (C1-C13), cyano, halogen such as fluoro or halalkyl (C1-C13) such as fluoromethyl groups.

#### EXAMPLE 1

[0009] Based upon the observation that glycine is effective in the treatment of schizophrenia (Javitt and Zukin, U.S. Pat. No. 5,854,286), it can be concluded that glycine sites are not saturated under normal physiological conditions in schizophrenia. Extracellular concentrations of D-serine in brain are known to be above those necessary to saturate NMDA/glycine sites. These findings raise the possibility that brain may contain a D-serine transporter that protects NMDA receptors from extracellular D-serine concentrations. Actions of such a transporter would be analogous to the role played by glycine transporters in protecting NMDA receptors from extracellular glycine levels. Use of glycine transport inhibitors in treatment of schizophrenia were described in a separate application (Javitt, U.S. Pat. No. 5,837,730). The present application demonstrates the existence of a

novel D-serine transporter, supporting the feasibility of use of D-serine transport inhibitors in treatment of schizophrenia.

[0010] In order to investigate the existence of a synaptosomal D-serine transporter, synaptosomal (P2) preparations were prepared from rodent brain. This preparation permits identification of transport mechanisms on pre- and post-synaptic terminals and so is crucial for identifying systems that may be co-localized with NMDA receptors which are located on synaptic terminals. In contrast, the majority of transport studies are performed using either cloned transporters or brain slices, which provide less specificity for identifying perisynaptic transport mechanisms. An obvious extension of the present invention, however, is use of an assay system in which the D-serine transporter is cloned and expressed in a suitable expression system. Methods for cloning would include but not be limited to derivation of mRNA from rodent or human brain, including postmortem human brain tissue, or from other suitable brain tissue or from other tissues expressing D-serine transporters, and progressive fractionation of such mRNA until relevant sequences are obtained, or from expression libraries derived from rodent, primate or other appropriate sources, or from cell lines expressing D-serine transporters. Cloned transporters would be expressed in a suitable expression system including, but not limited to, *Xenopus* oocytes, or immortalized cells derived from mammalian, reptilian or avian sources. Obvious extensions would also be use of brain slices, use of cell culture lines which express D-serine transporters or primary culture of neurons.

[0011] Synaptosomal (P2) preparations were prepared from brains of Sprague-Dawley rats (200-250 g) using the method of Debler and Lajtha (1987). Rodents were decapitated and brains (cortex+hippocampus) were homogenized in 0.32 M sucrose buffered to pH 7.4 with Tris-HCl. Homogenate was centrifuged at 1000 g for 12 min at 4° C. The supernatant was centrifuged at 14,000 g 12 min and the P2 pellet was resuspended in Krebs solution (pH 7.4) containing 124 mM NaCl, 26 mM NaHCO<sub>3</sub>, 10.5 mM glucose, 5 mM KCl, 1.3 mM MgSO<sub>4</sub>, 1.2 mM KH<sub>2</sub>PO<sub>4</sub>, and 2.4 mM CaCl<sub>2</sub>. For uptake studies, membranes were incubated at 37° C. in the presence of L- or D-[<sup>3</sup>H]serine, as appropriate. L- and D-[<sup>3</sup>H]Serine were obtained from DuPont-NEN (Natick, Mass.) and had specific activities of 25.4 and 19.7 Ci/mM, respectively. Incubation was terminated by filtration under reduced pressure through Whatman GF/B filters, rinsing twice with 5 ml ice-cold buffer.

[0012] For initial kinetic studies, incubations were conducted at 6 time points between 1 and 30 min. Non-specific binding was determined in the presence of 30 mM L- or D-serine. For inhibition studies, L-alanine, L-cysteine, L-serine, and D-serine were tested at 6 concentrations between 0.03 and 10 mM. Control uptake levels were defined as uptake levels in the absence of added L-alanine, L-cysteine, L-serine, or D-serine. % control binding was defined as level of uptake in the presence of specified concentrations of antagonist divided by uptake under control conditions, expressed as a percent. 1 mM concentrations of HA-966, L-trans-pyrrolidine-2,4-dicarboxylic acid (L-PDC), nipecotic acid, 2-aminobicyclo (2,2,1)heptane-2 carboxylic acid (BCH) and methylaminoisobutyric acid (MeAIB) and 10 mM sarcosine were added to the homogenate to prevent binding to NMDA-associated glycine bind-

ing sites, and potential uptake via glutamate, GABA, system L, system A and system GLY transporters, respectively. Incubations were terminated following 30 min. For both kinetic and inhibition studies, non-specific binding was determined in the presence of 30 mM D- or L-serine, as appropriate.

**[0013]** For saturation studies, L- and D-serine were added at 12 concentrations between 0.01 and 5 mM. Assays were conducted at 37° C. Non-specific binding was determined at 0° C. Incubations were terminated following 5 min. Assays were conducted in the presence of 30 mM L-alanine to prevent uptake through system ASC, along with 1 mM concentrations of HA-966, L-PDC, nipecotic acid, BCH and MeAIB. Km values were determined by non-linear regression to a single rectangular, 3 parameter hyperbolic function using Sigmaplot 2000 (SPSS Inc., Chicago, Ill.). Data in text represent mean  $\pm$ sem. Statistical comparisons were performed using two-tailed Student's t statistic.

**[0014]** For initial studies, uptake was measured over a 30 min. period (**FIG. 1**). Uptake of L- and D-[<sup>3</sup>H]serine was linear over the first 10 min. with a tendency for plateau by 30 min. Uptake was unaffected by incubation with the selective system L antagonist BCH (10 mM). Effects of the system ASC substrates alanine, cysteine and serine were evaluated at concentrations between 0.03 and 30 mM (**FIG. 2**). Complete inhibition of serine uptake was obtained with either L- or D-serine. In both cases, L-serine showed greater potency than D-serine in inducing inhibition. Inhibition was also obtained with cysteine, although potency of cysteine was significantly less than that of either L- or D-serine. In contrast, only partial inhibition was observed with alanine, even at doses as high as 30 mM. This pattern of inhibition is opposite to that of system ASC, indicating that the observed L- and D-serine uptake is mediated primarily by a system other than system ASC. This system has not been previously described.

**[0015]** Finally, in order to characterize kinetics of uptake, saturation studies were conducted following 5 min. incubation with concentrations of L- and D-serine between 0.01 and 5 mM (**FIG. 3**). Studies were conducted in the presence of 30 mM L-alanine to prevent uptake through system ASC. Even in the presence of alanine, significant uptake of L- and D-serine was observed. Saturation of D-serine binding was observed between 3 and 5 mM, with half-maximal binding occurring between 1-2 mM. A Michaelis-Menton constant (Km) of 3.33 mM was obtained by non-linear regression. An Eadie-Hofstee plot demonstrated linear uptake, supporting the concept that this uptake occurs via a discrete, alanine-insensitive D-serine transport system with approximately equal affinity for D- and L-serine. The presence of such a system in synaptosomal tissue from rodent forebrain indicates that it may play a crucial role in regulation of D-serine concentrations in the vicinity of NMDA receptors. Inhibition of this system would be expected to increase local D-serine concentrations in brain, leading to augmentation of NMDA receptor-mediated neurotransmission. Inhibition of selective serine uptake would thus constitute a novel mechanism for stimulation of NMDA receptor-mediated neurotransmission in vivo.

**[0016]** In summary, the present example demonstrates the existence of multiple transport systems for D-serine in P2 synaptosomal membranes which can be distinguished based upon sensitivity to inhibition by alanine.

## EXAMPLE 2

**[0017]** We have previously reported ability of the glycine derivative glycyldodecylamide (GDA) to inhibit synaptosomal glycine transport. This study evaluated the ability of two novel amino acid derivatives D-serine dodecylamide (D-Ser-DA) and D-alanine dodecylamide (D-Ala-DA) to inhibit glycine and D-serine uptake in vitro and to affect rodent activity in vivo. Effects of these agents on synaptosomal glycine and D-serine transport were determined using assay methods described previously in Javitt and Frusciant, 1997 and in Example 1, above. The amino acid derivatives were then evaluated in a rodent behavioral model that assesses locomotor hyperactivity following administration of either the dopamine releasing agent amphetamine or the NMDA antagonist PCP. Atypical antipsychotics and agents that potentiate NMDA receptor mediated neurotransmission are more effective in modulating effects of PCP than of amphetamine. The relationship between ability to antagonize D-serine transport in vitro and to modulate PCP-induced hyperactivity in vivo was then assessed.

**[0018]** Effects of amino acid derivatives on glycine and D-serine uptake are shown in Table 1. As shown previously (Javitt and Frusciant, 1997), GDA significantly inhibited glycine uptake into synaptosomes. Similar effects were shared by dSDA whereas dADA was ineffective. GDA also significantly inhibited D-serine uptake into synaptosomes at concentrations similar to those used to inhibit glycine transport. Similar effects were shared by dADA but not dSDA.

**[0019]** To assess effectiveness of these agents in modulating NMDA receptor-mediated neurotransmission, amphetamine and PCP-induced was evaluated in absence and presence of these agents. Assays were conducted using methods of Javitt et al. (1997). Mice (C57) were acclimated to automatic test chambers. As opposed to BALB/c mice which were used in prior studies, C57 mice were used for the present study because they are known to have relatively little spontaneous hyperactivity in response to PCP. Such mice are thus more similar to primates that have a predominant reduction in activity in response to PCP. Therefore, in C57 mice, as in primates, it is predicted that the prominent behavioral response to NMDA agonists would be a decrease in activity following amphetamine administration and an increase in activity following PCP administration.

**[0020]** Baseline activity was monitored for 30 min. Animals were then pretreated with saline, GDA, D-Ser-DA or D-Ala-DA and activity was monitored for an additional 15 min. All drugs were administered at a dose of 1.6 mg/kg. Finally, animals were challenged with amphetamine (1 mg/kg) or PCP (3 mg/kg). Distance traveled (cm) per min (DT) was used as the primary dependent measure.

**[0021]** All agents produced a numerical reduction in amphetamine-induced activity and increase in PCP-induced activity, suggesting similar effects by both glycine and D-serine transport inhibitors. For statistical analysis, data were collapsed across treatments associated with D-serine transport inhibition (GDA, dADA) vs. those not associated with inhibition (saline, D-Ser-DA). A 2x2 ANOVA evaluated alteration in amphetamine vs. PCP induced hyperactivity by agents associated with D-serine transport inhibition vs. those not associated with serine transport inhibition. A significant amphetamine/PCP X serine transport inhibitor interaction effects was observed (F=4.82, df=1/60, p=0.03), reflecting ability of D-serine transport inhibitors to both decrease amphetamine-induced hyperactivity and reverse PCP-induced hypoactivity. The ability of D-serine transport

inhibitors to modulate amphetamine and PCP induced effects suggests effectiveness of these agents in treatment of neuropsychiatric illness.

### EXAMPLE 3

[0022] An additional assay system that has been shown to be sensitive to effects of NMDA agonists is in vivo [<sup>3</sup>H]MK-801 binding (Murray et al., 2000). Consequently, the in vivo [<sup>3</sup>H]MK-801 binding system, therefore, was used to evaluate effects of glycine site agonists and antagonists on NMDA activation in vivo. To implement this protocol, mice (C57) were pretreated with either saline, glycine (1.6 g/kg) or D-Ala-DA (16 mg/kg) administered i.p. Animals used for “nonspecific” in vivo binding were then administered unlabelled MK-801 (3 mg/kg) by retroorbital injection whereas animals used for “total binding” were administered saline. Both “nonspecific” and “total binding” animals then

1133±1455 DPM/500  $\mu$ l homogenate. Under these circumstances, the difference between nonspecific and total binding was specific at trend level (p=0.1, one tail). However, the level of specific binding following glycine treatment was not significantly greater than control levels. Treatment with D-Ala-DA led to a 250% increase in specific binding to 3888±1734 DPM/500  $\mu$ l homogenate. In the presence of D-Ala-DA, total binding was significantly higher than nonspecific indicating substantial NMDA activation (p=0.015, one tail). Further, there was a significant trend toward increased specific binding following D-Ala-DA than under control conditions (p=0.1, one tail). These findings support the concept that agents that activate the glycine site either directly (e.g., glycine, D-serine) or by inhibition of glycine or D-serine transport (e.g., D-Ala-DA) potentiate NMDA receptor-mediated neurotransmission in vivo.

TABLE 1

Inhibition of glycine and D-serine uptake by glycyldodecylamide (GDA), D-serine dodecylamide (D-Ser-DA) and D-alanine dodecylamide (D-Ala-DA). Values represent percent control uptake in the presence of specified concentration of antagonist. Data are mean of 3 separate experiments each performed in triplicate

Compound	Concentration ( $\mu$ M)	Glycine uptake		D-serine uptake		T Value			
		Average:	Std. Dev.	T Value	P value	Average:	Std. Dev.	(df = 2)	P value
GDA	1	99.2	6.1	0.24	0.8	95.1	9.46	0.89	0.5
	10	99.7	6.3	0.07	0.9	102.4	5.33	-0.78	0.5
	25	88.1	3.2	6.41	0.02	104.0	1.44	-4.83	0.04
	50	70.7	9.2	5.52	0.03	97.4	6.62	0.69	0.6
	100	41.5	2.6	38.36	0.0007	77.6	3.08	12.6	0.006
	200	31.6	1.9	61.95	0.0003	60.9	6.82	9.91	0.01
D-SER-DA	500	24.4	4.4	29.90	0.001	47.6	1.98	45.9	0.0005
	1	90.9	4.7	3.33	0.08	95.2	8.0	4.09	0.4
	10	83.5	4.8	5.94	0.03	100.6	7.5	0.07	0.9
	25	60.2	12.1	5.70	0.03	97.0	8.5	3.64	0.6
	50	42.0	17.5	5.73	0.03	96.7	9.5	13.3	0.6
	100	24.1	15.4	8.57	0.02	96.4	19.2	7.65	0.8
D-ALA-DA	200	13.7	16.4	9.12	0.02	105.9	44.7	5.30	0.8
	500	10.2	12.9	12.09	0.007	83.5	21.7	3.85	0.3
	1	101.9	11.0	-0.30	0.8	94.9	4.0	0.41	0.2
	10	98.9	11.7	0.16	0.9	101.4	5.9	-0.89	0.7
	25	92.5	16.4	0.79	0.5	93.3	8.1	-0.85	0.3
	50	83.4	32.3	0.89	0.5	86.2	4.0	0.47	0.03
	100	79.3	51.1	0.70	0.6	67.1	5.5	0.43	0.009
	200	70.7	51.5	0.99	0.4	51.3	17.2	-0.26	0.04
	500	67.8	53.4	1.04	0.4	44.1	2.8	1.51	0.0009

received [<sup>3</sup>H]MK-801 (200  $\mu$ Ci/kg, 28.9 Ci/mmol) by retroorbital injection. “Specific” binding to NMDA receptors was defined as the difference between “total binding” and “nonspecific.” Following 10 min, animals were sacrificed. Brains were removed and homogenized in 40 vol/w buffer. 500  $\mu$ l aliquots were then filtered in triplicate under reduced pressure through Whatman GF/B filters. [<sup>3</sup>H]MK-801 levels were determined by liquid scintillation. It has previously been demonstrated by others that treatment with NMDA agonists increases including D-serine increases specific binding to NMDA receptors in vivo whereas treatment with glycine site antagonists decreases specific binding (Murray et al., 2000).

[0023] In this experiment, specific binding under control conditions was 990±2766 DPM/500  $\mu$ l homogenate (n=3). Under control conditions, difference between total and nonspecific was not significant given the small n, indicating low levels of NMDA activation under control conditions. Pretreatment with glycine increased specific binding by 15% to

[0024]

TABLE 2

Effect of amino acid derivatives on rodent activity levels following amphetamine (1 mg/kg) or PCP (3 mg/kg) challenge. DT = distance traveled. n = 8 per group

Condition	Baseline		Amph/			
	DT (cm)	Std dev	Pretreatment		PCP challenge	
			DT (cm)	Std dev	DT (cm)	Std dev
			Amphetamine treatment			
Saline	69.0	46.4	69.0	49.7	211.3	141.4
GDA	52.5	31.1	53.4	52.5	207.9	97.8
D-Ser-DA	60.6	44.6	103.2	91.8	196.2	100.1
D-Ala-DA	48.3	36.6	48.0	35.3	100.3	77.9



TABLE 2-continued

Effect of amino acid derivatives on rodent activity levels following amphetamine (1 mg/kg) or PCP (3 mg/kg) challenge. DT = distance traveled. n = 8 per group						
Condition	Baseline		Amph/			
	DT		Pretreatment		PCP challenge	
	(cm)	Std dev	DT (cm)	Std dev	DT (cm)	Std dev
	PCP treatment					
Saline	41.4	27.6	85.6	58.9	91.5	51.0
GDA	51.3	64.2	77.2	72.5	132.6	69.0
D-Ser-DA	59.2	63.0	59.2	27.6	108.2	48.3
D-Ala-DA	64.5	41.1	83.2	47.3	149.2	66.2

Variations of the invention will be apparent to the skilled artisan.

### 1-26. (canceled)

**27.** A D-serine transport inhibitor compound comprising a serine or alanine compound having a hydrophobic group linked to either the C-or N-terminus, wherein the hydrophobic group is selected from the group consisting of a C1-13 alkyl group optionally substituted with a halogen atom, a phenyl group optionally substituted with a C1-13 alkyl group, a cyano group and a halogen atom.

**28.** The D-serine transport inhibitor compound according to claim 27, wherein the serine or alanine compound is selected from D-serine, L-serine, D-alanine and L-alanine.

**29.** The D-serine transport inhibitor compound according to claim 27, wherein the compound is a selective D-serine transport inhibitor.

**30.** The D-serine transport inhibitor compound according to claim 27, which is selective for glycine uptake inhibition.

**31.** The D-serine transport inhibitor compound according to claim 30, wherein the inhibitor compound is D-serine dodecylamide.

**32.** The D-serine transport inhibitor compound according to claim 29, which is selective for D-serine uptake inhibition.

**33.** The D-serine transport inhibitor compound according to claim 32, wherein the inhibitor compound is D-alanine dodecylamide.

**34.** A process for augmentation of N-methyl-D-aspartate receptor-mediated neurotransmission in vivo which comprises administration of an effective amount of a selective D-serine transport inhibitor.

**35.** The process of claim 34, wherein a psychotic disorder associated with decreased N-methyl-D-aspartate receptor-mediated neurotransmission is treated.

**36.** The process of claim 34, wherein schizophrenia is treated.

**37.** The process of claim 34, wherein a neuropsychiatric disorder selected from the group consisting of Alzheimer's disease, bipolar illness, depression and an anxiety disorder is treated.

**38.** The process of claim 34, wherein the inhibitor compound is a serine or alanine compound having a hydrophobic group linked to either the C-or N-terminus, wherein the hydrophobic group is selected from the group consisting of a C1-13 alkyl group optionally substituted with a halogen atom, a phenyl group optionally substituted with a C1-13 alkyl group, a cyano group and a halogen atom.

**39.** The process according to claim 38, wherein the serine or alanine compound is selected from D-serine, L-serine, D-alanine and L-alanine.

**40.** The process according to claim 38, wherein the inhibitor is selective for D-serine uptake inhibition.

**41.** The process according to claim 40, wherein the inhibitor is D-alanine dodecylamide.

**42.** The process according to claim 38, wherein the inhibitor is selective for glycine uptake inhibition.

**43.** The process according to claim 42, wherein the inhibitor is D-serine dodecylamide.

**44.** A composition for treating schizophrenia comprising an effective amount of a D-serine transport inhibitor according to claim 27 and a pharmaceutically acceptable carrier.

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