

Behavioral and Neuroendocrine Effects of the Partial NMDA Agonist D-cycloserine in Healthy Subjects

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The effects of D-cycloserine, a partial agonist of the N-Methyl-D-Aspartate (NMDA) receptor, were assessed in a (neuroendocrine) challenge paradigm to examine NMDA systems in male healthy volunteers, using a double-blind, placebo-controlled crossover design. Oral D-cycloserine (15, 50, and 150 mg) was readily absorbed and its plasma concentration increased dose-dependently. Behavioral and hormonal responses were measured for 240 minutes after administration of the drug. D-cycloserine was well tolerated and did not induce side-effects according to the Visual Analog Scales (VAS), the Brief Psychiatric Rating Scale

(BPRS) and the Adverse Events Checklist (AEC) & codes. D-cycloserine failed to elicit a neuroendocrine response as evaluated by cortisol, prolactin, and luteinizing hormone (LH) plasma levels. The present result suggests that D-cycloserine can readily be administered to healthy volunteers but that, in the dosages used, neuroendocrine secretion fails to serve as a model for testing NMDA receptor function in humans. [Neuropsychopharmacology 16, 317-324] © 1997 American College of Neuropsychopharmacology

KEY WORDS: *D-cycloserine; NMDA; schizophrenia; LH; cortisol*

In schizophrenia research, interest in the role of glutamate, one of the excitatory amino acids, is increasing (Henn 1995; Olney and Farber 1995). A possible role for excitatory amino acids and their receptors in the pathophysiology of schizophrenia was suggested after the observation that antagonists to one of the receptors of glutamate, the N-Methyl-D-Aspartate (NMDA) receptor, like phencyclidine (PCP) and ketamine, were able to induce schizophrenia-like symptoms in healthy subjects and to cause exacerbation of schizophrenic

symptoms in patients with schizophrenia (Luby et al. 1962, for review see Javitt and Zukin 1991; Krystal et al. 1994; Lahti et al. 1995). These observations suggest that a hypofunction of the glutamatergic system might play a role in the pathophysiology of schizophrenia. This hypothesis is supported by postmortem studies: an increase in glutamatergic receptors in the prefrontal (Nishikawa et al. 1983; Toru et al. 1988), parietal, and occipital cortex (Ishimaru et al. 1994) of the brain of patients with schizophrenia was found. This increase in glutamatergic receptors has been explained as a compensatory mechanism for decreased function of glutamatergic neurons. Indeed, by measuring presynaptic markers of glutamatergic neurons (N-acetylaspartylglutamate and N-acetyl- α -linked acidic dipeptidase), a hypofunction of glutamatergic neurotransmission in the prefrontal cortex and hippocampus in schizophrenic patients has recently been supported (Tsai et al. 1995). Finally, diminished function of glutamatergic neurons in schizophrenia is suggested by the observation that treatment of patients

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Received March 15, 1996; revised August 23, 1996; accepted August 23, 1996.

with agonists of the glycine recognition site of the NMDA receptor, like D-cycloserine and glycine, ameliorated some (mainly negative) symptoms of schizophrenia (Javitt et al. 1994; Goff et al. 1995; van Berckel et al. 1996). Limited *in vivo* information is available about the glutamatergic system and NMDA receptor function in patients with schizophrenia. As in animals glutamate is one of the major regulatory neurotransmitters in the secretion of pituitary hormones, acting mainly through non-NMDA (van den Pol et al. 1990), but also through NMDA, receptors (Carbone et al. 1996), neuroendocrine secretion in response to NMDA receptor ligands may serve as a probe to test NMDA receptor function. This neuroendocrine challenge paradigm has already been used to examine serotonin (5-HT; Kahn and Wetzler 1991) and noradrenalin (NA; Glazer et al. 1987) systems in healthy subjects and various patient groups, including schizophrenic patients. That this approach may be useful in examining the NMDA system as well is suggested by animal studies, as NMDA receptors appear to be involved in regulating secretion of luteinizing hormone (LH) (Schainker and Cicero 1980; Arslan et al. 1988; Petersen et al. 1991), ACTH (Jezova et al. 1991) and prolactin (for review see Arslan et al. 1992). So far, only one human study has addressed this issue, examining the effects of the non-competitive NMDA antagonist ketamine on cortisol and prolactin secretion in healthy subjects and reporting a dose-related increase in both cortisol and prolactin plasma levels (Krystal et al. 1994). However, ketamine also induced behavioral changes: ketamine was in the dose that stimulated cortisol and prolactin secretion in general anxiogenic. Therefore, it cannot be excluded that these hormonal effects are secondary to the behavioral effects.

D-cycloserine, an antibiotic used in the treatment of tuberculosis (Rivas Salazar 1970), is a partial agonist of the NMDA receptor (Thompson et al. 1992) and crosses the blood-brain barrier (Hanngren et al. 1961). Comparing neuroendocrine responses induced by D-cycloserine between schizophrenic patients and normal controls could serve to test human NMDA receptor function in these groups. D-cycloserine dosage and blood level are critical variables in this challenge paradigm, because they determine D-cycloserine availability at the NMDA receptor site. Thus, this study examined the behavioral and neuroendocrine effects of D-cycloserine in healthy subjects. Selection of dosage was based on prior studies in humans, indicating that 15, 50, and 100 mg doses of D-cycloserine were well tolerated in human subjects (Jones et al. 1991; Goff et al. 1995; van Berckel et al. 1996).

MATERIALS AND METHODS

Subjects

Sixteen healthy male volunteers were recruited through university newspaper advertisements. Only physical

healthy subjects without a personal or family history in first-degree relatives of psychiatric illness could participate. All responders to the advertisement were first interviewed by telephone and, if suitable, were invited to the University Hospital Utrecht to complete the screening procedure. All potential research subjects underwent physical and psychiatric examination, using the Comprehensive Assessment of Symptoms and History (CASH; Andreasen 1985) and the Structured Interview for DSM-III-R Personality Disorder-Revised Dutch version (van den Brink and de Jong 1992). Subjects all had an electrocardiogram and routine laboratory tests, including complete blood count, thyroid function tests, urine analysis, and urine toxicology screen for drugs of abuse. All subjects had a body mass index (BMI) between 20 and 25, were between 18 and 31 years, and had an average level of physical exercise. The study was approved by the Human Ethics Board of the University Hospital Utrecht. After written and oral information had been given, written informed consent was obtained from all subjects before enrollment in the study.

Experimental Design

In a randomized, double-blind, Latin-square design, 16 men with a mean age of 24 years (SD, 3.3 years; range, 18 to 31 years; weight, 76.5 ± 7.9 kg; height, 183 ± 0.8 cm; BMI, 22.6 ± 1.9) each received 3 oral doses of D-cycloserine (15, 50 and 150 mg) and one of placebo on four separate occasions, a minimum of 1 week apart, between April and August 1995. The 16 subjects were randomly allocated to 4 Latin Squares, chosen in such a way that all dosages were given 4 times on the first, second, third, and fourth test day. Furthermore, none of the subjects received the same sequence of dosages. Neuroendocrine, D-cycloserine plasma levels, physiological, and behavioral measure were collected over a 4.5-hour period during each session.

Procedure

Subjects arrived at the Metabolic Ward of the Department of Psychiatry, University Hospital Utrecht at 8:30 A.M., having fasted since 11:00 P.M. the preceding day. They reclined on a bed until 1:00 P.M. They were not allowed to eat, sleep, smoke, or watch television until the procedure was completed. Between 8:30 and 8:45 A.M., one indwelling intravenous catheter was inserted into the antecubital vein and kept opened with 1 ml heparin (100 U/ml), infused after each blood sample and removed before the following blood sample. After inserting of the intravenous catheter, baseline blood samples were obtained following a 45-minute rest period at 9:30 A.M. and again 30 minutes later at 10:00 A.M. to determine baseline hormone concentrations. Immediately following the collection of the last baseline sample at

10:00 A.M., subjects received an oral dose of D-cycloserine or placebo. Additional blood samples were collected 30, 60, 90, 120, 150, 180, and 240 minutes after the oral dose. In addition, at these time points, sublingual body temperature, blood pressure, and heart rate were assessed. Furthermore, at 0, 60, 120, 180, and 240 minutes behavioral measurements were performed. Blood samples were collected in 10-cc plastic tubes containing EDTA. They were centrifuged (10 minutes at 3,000 rounds/minutes at 4°C) within 5 minutes of sampling. Plasma was allocated into plastic tubes and stored at -80°C until the time of the assays.

Neuroendocrine, D-cycloserine Plasma Levels, Behavioral, and Physiological Measurements

Assessment of D-cycloserine Plasma Levels. D-cycloserine plasma levels were determined using a fully automatic high-performance liquid chromatographic (HPLC) analysis with fluorescence detection. In the D-cycloserine assay, a fully automated precolumn derivatization was performed. The HPLC system consisted of a Pharmacia-LKB pumpmodel 2249 (Pharmacia, Woerden, the Netherlands) equipped with a low-pressure mixing module, a Gilson 231 XL auto-sampler (Meyvis, Bergen op Zoom, the Netherlands) supplied with a Rheodyne injection valve 7010 and a 20- μ l loop. Detection was performed with an Applied Biosystems fluorometer model 980 (Excitation 230 Nm, Emission > 470 Nm, Separation B.V., Waddinxveen, the Netherlands) connected to a data-integrating system. Analyses were performed on a 5- μ m Supelcosil 8-DB 25cm \times 4.6 mm (Id) column from Supelchem (Leusden, the Netherlands). The detection limit of the assay was 2 μ M.

Neuroendocrine Measurements. At the end of all tests of one subject, all measurements were carried out in one assay to avoid interassay variation by a technician blind to the order and nature of drug sequence. Prolactin was measured by the Enzymun-Test Prolactin, a noncompetitive enzyme immunometric assay (IEMA, Boehringer Mannheim Immuno-diagnostics, Germany). The prolactin standard has been calibrated against the WHO-standard 84/500 (3rd IRP). The interassay variation was between 3.1% and 7.1%, the detection limit was 0.03 U/l. LH was measured by the Enzymun-Test (Boehringer Mannheim Immuno-diagnostics, Germany) also an IEMA. The LH standard has been calibrated against the NIBSC standard 2nd ISP 80/552. Interassay variation was between 2.4% and 6.7%, detection limit was 0.2 U/l. Prolactin and LH assays are automated on the ES600. Cortisol was measured using a competitive fluorescence polarization immunoassay (FPIA, Abbott Laboratories, ILL, USA). Calibrators are referenced against Abbott Reference Standards. Interassay variation was between 3.8% and 4.6%, and detection limit was 0.01 μ mol/l.

Assessment of Temperature and Cardiovascular Responses. Sublingual body temperature was assessed with a digital thermometer. Blood pressure and pulse were measured with an Omega 1400 noninvasive, fully automatic blood pressure method.

Assessment of Mood and Other Psychological Responses. Three rating scales were used to assess psychological and somatic changes associated with D-cycloserine administration: The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), the Adverse Event Checklist and Visual Analog Scales (VAS; Bond and Lader 1974). From the VAS afterward three factors were calculated: alertness, contentedness, and calmness.

Drugs

D-cycloserine was provided by Eli Lilly in capsules of 250 mg. Capsules of 5, 50, and 150 mg D-cycloserine and placebo were prepared in identical capsules by the pharmacy department of the University Hospital Utrecht. According to good laboratory practice, a sample of these capsules was analyzed in the Laboratory of Biological Psychiatry, University Hospital Utrecht, by a technician blind to content of the capsules.

Statistical Analysis

Biochemical, neuroendocrine, and behavioral effects and vital signs were analyzed by means of multivariate analysis of variance (MANOVA) with repeated measures on the within-subjects factors time and dosage. Time, dosage, and time-by-dosage effects were evaluated. The latter, being of special interest, was examined post hoc for contrasts among dosages. In addition, areas under the concentration-time curve (AUC) for the biochemical and neuroendocrine variables, as well as the maximum change from baseline for vital signs, biochemical, and neuroendocrine measurements, were analyzed by analysis of variance (ANOVA) with repeated measures on dosage. Polynomial contrasts were used to detect possible dose-response relationships. Analysis of covariance (ANCOVA) was used to correct for subject-related variables, such as BMI.

RESULTS

D-cycloserine Plasma Levels

The different D-cycloserine dosages produced a dose-dependent rise in D-cycloserine plasma levels (Figure 1). Multivariate analysis for AUC data revealed a significant dose effect (Wilks's $F_{2,14} = 48.37$, $p < .001$). Paired t -tests revealed a significant rise in AUC of the 50-mg dose ($t = -7.56$, $df = 15$, $p < .001$) and the 150-mg dose ($t = -9.87$, $df = 15$, $p < .001$) compared to the 15-mg dose. The 150-mg D-cycloserine produced a signifi-

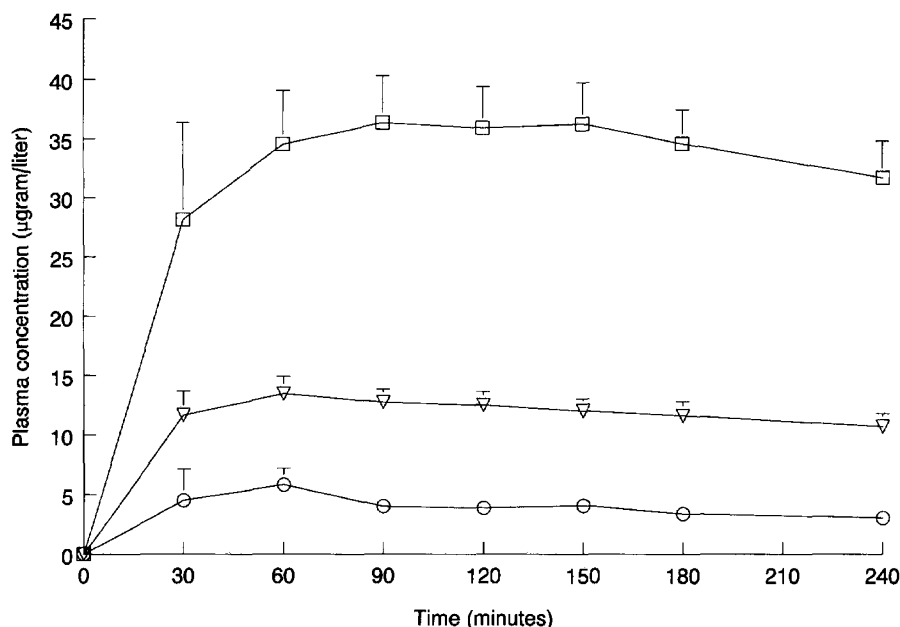


Figure 1. D-cycloserine plasma concentrations after oral administration of 15 mg (circles), 50 mg (triangles), and 150 mg (squares) D-cycloserine.

cantly higher AUC ($t = -8.44$, $df = 15$, $p < .001$) than the 50-mg dose.

Neuroendocrine Measurements

LH. D-cycloserine did not induce a change in LH plasma levels (Figure 2A). Multivariate analysis for plasma levels revealed no time or dose effect nor an interaction (dose \times time). An ANOVA of AUC data with repeated measures on dosage revealed no effect of D-cycloserine ($F = 0.47$, $df = 2$, $p = .628$).

Cortisol. D-cycloserine did not induce a change in cortisol plasma levels (Figure 2B). Multivariate analysis revealed a significant time effect (Wilks's $F_{7,9} = 5.97$, $p = .008$), but no effect for dose or interaction (dose \times time). A repeated-measures ANOVA on dose for AUC data revealed no effect of D-cycloserine ($F = .22$, $df = 2$; $p = .80$).

Prolactin. None of the D-cycloserine dosages produced a change in circulating prolactin (Figure 2C). Multivariate analysis revealed a significant time effect (Wilks's $F_{7,9} = 8.26$, $p = .003$), but no effect for dose or interaction (dose \times time). A repeated-measures ANOVA on dose for AUC data revealed no effect of D-cycloserine ($F = 0.27$, $df = 2$, $p = .76$).

Body Temperature, Blood Pressure, and Heart Rate

There was no significant effect of D-cycloserine at any dosage level or placebo on blood pressure, heart rate, or temperature.

Psychological Effects

Mood States. No effects of D-cycloserine administration were noticed on the sum scores of the times contributing to factor alertness, contentedness, and calmness.

BPRS. No effects of D-cycloserine were noticed on any of the BPRS items and clusters.

Side Effects. Adverse Events Listings report mild headache in six subjects, one during the placebo test, two after 15-mg D-cycloserine, one after 50-mg, and two after the 150-mg D-cycloserine dose. One subject reported blurred vision after receiving the 15-mg D-cycloserine dose, and one other subject complained of nausea after placebo administration. No relation between D-cycloserine administration and these reported effects is suspected. In general, D-cycloserine was well tolerated.

DISCUSSION

The main findings of this study are that 15, 50 and 150 mg D-cycloserine administered orally were readily absorbed and that the drug's plasma concentration increased dose-dependently in male healthy volunteers; that D-cycloserine was well tolerated and did not induce side effects; and that D-cycloserine failed to elicit a cortisol, LH, or prolactin response. These results are compatible with absorption characteristics and tolerance of D-cycloserine (Goff et al. 1995; van Berckel et al. 1996) used in the treatment of schizophrenic patients.

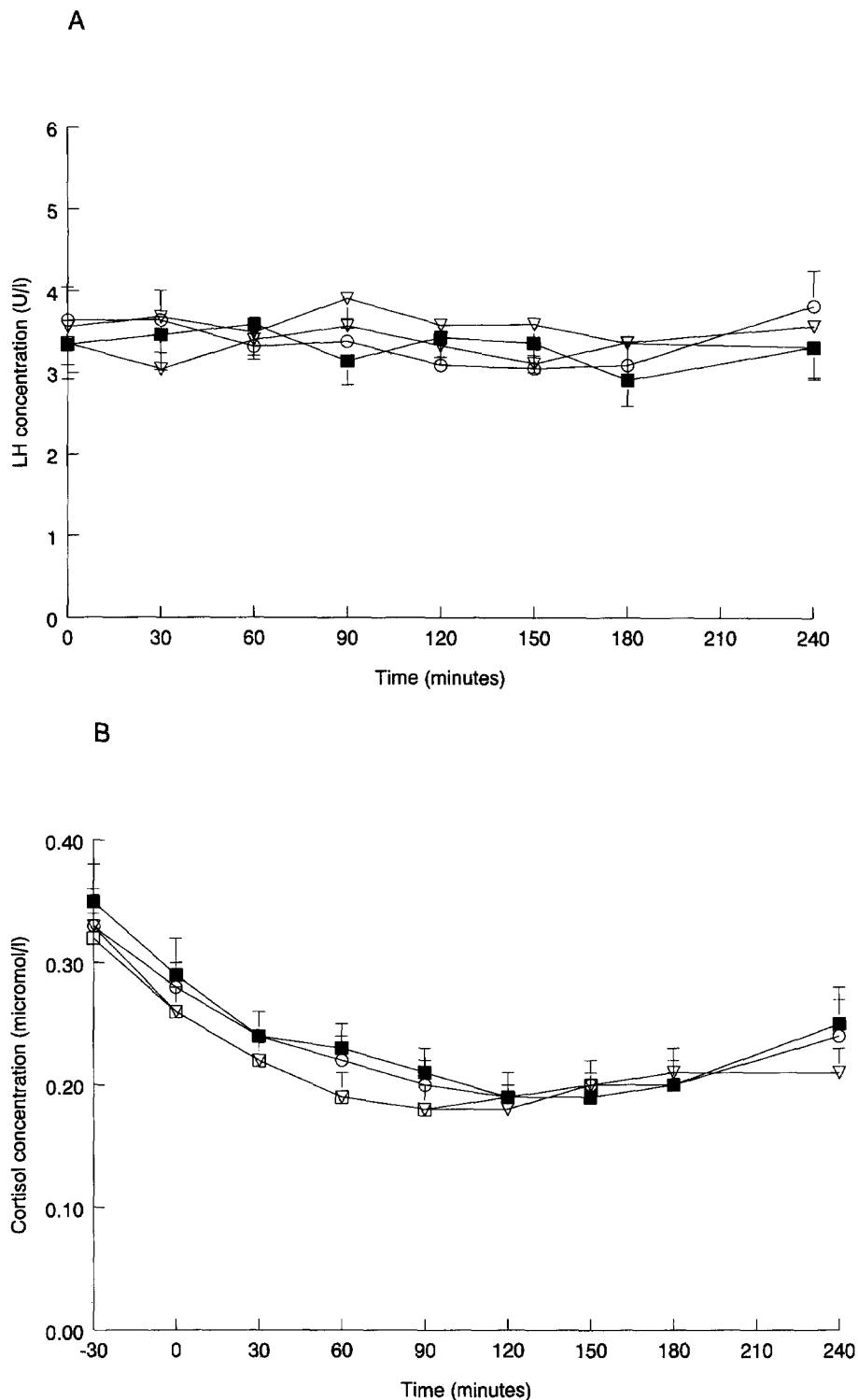


Figure 2. Plasma levels of LH (A), cortisol (B), and prolactin (C) following oral administration of placebo (solid squares) and 15 mg (circles), 50 mg (triangles), and 150 mg (open squares) D-cycloserine. Each point represents mean \pm SEM obtained from 16 healthy volunteers.

Thus, D-cycloserine in this dose range can readily be administered to human subjects.

A possible explanation for the lack of stimulation of neuroendocrine secretion is the weak efficacy of D-cycloserine as an agonist for the glycine recognition site of the NMDA receptor: D-cycloserine shows only 60% of the

agonistic potency as compared to the endogenous agonist glycine (Chessel et al. 1991). Thus, as a weak, partial agonist of the glycine binding site of the NMDA receptor (Hood et al. 1989; Monahan et al. 1989; Watson et al. 1990; Emmett et al. 1991; Sirvio et al. 1992; Thompson et al. 1992; Pittaluga et al. 1993; Pitkanen et al., 1994),

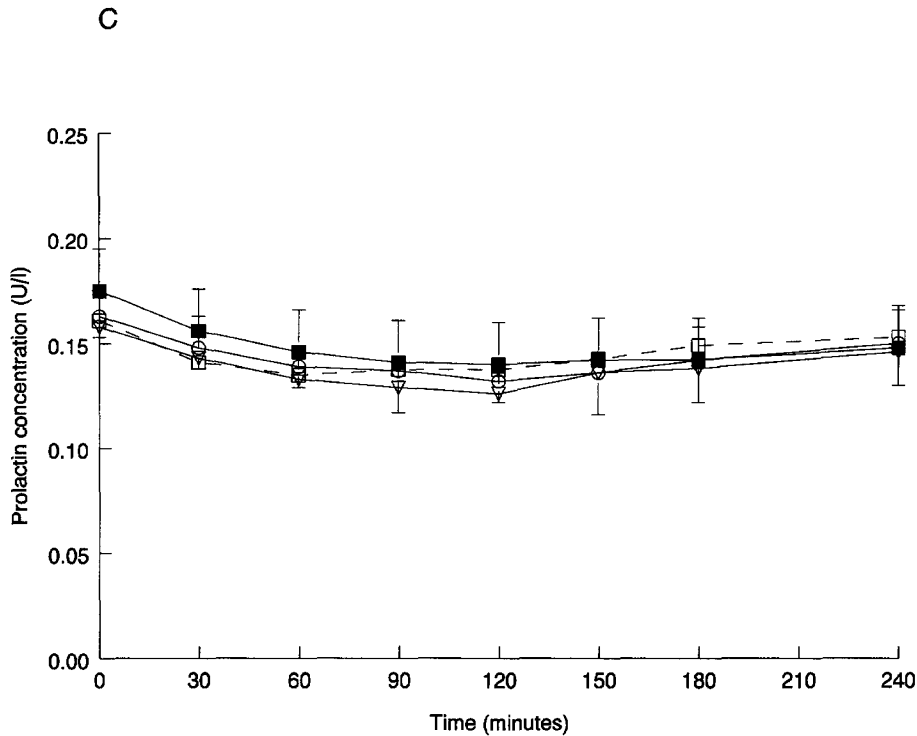


Figure 2. Continued.

the effect of D-cycloserine on the NMDA receptor depends on the occupancy of the glycine binding site by (the endogenous agonist) glycine: if this site is not fully saturated, D-cycloserine in low dosages could enhance the stimulating effects of the endogenous glycine on the NMDA receptor, whereas in higher dosages it is expected to compete with glycine and act as a relative antagonist of this receptor. Indeed, in animals, low dosages of D-cycloserine in a narrow dose range appeared to be able to stimulate the NMDA receptor, as measured in several memory paradigms in animals, indicating that (in animals) endogenous glycine does not fully occupy the glycine recognition site *in vivo* and that this receptor therefore can be stimulated by low dosages of D-cycloserine (Watson et al. 1990; Chessell et al. 1991; Jones et al. 1991; Flood et al. 1992; Sirvio et al. 1992; Thompson et al. 1992; Pittaluga et al. 1993; Pitkanen et al. 1994). Thus, another explanation for the lack of neuroendocrine effects of low doses of D-cycloserine in healthy subjects might be full occupancy of the glycine recognition site of the human NMDA receptor with endogenous glycine. Furthermore, the highest D-cycloserine dose used in this experiment, 150 mg, might have been too low to compete with the endogenous glycine to reveal the expected antagonistic properties of D-cycloserine. Interesting, in patients with schizophrenia D-cycloserine in low doses seems to be able to induce behavioral changes, suggesting that in schizophrenia the glycine recognition site of the NMDA receptor might not be saturated by glycine and, indeed, can be stimulated by D-cycloserine.

In addition, although it has been described that

D-cycloserine readily passes the blood-brain barrier (Hanngren and Hansson 1961), this has been reported only in animals. In humans, only the side effects originating in the central nervous system, like psychosis and epilepsy, after dosages used in the treatment of tuberculosis, that is, 500 mg daily and higher, suggest that D-cycloserine penetrates the blood-brain barrier in humans (Walker and Murdoch 1957; Vallade 1959). No information is currently available about the bioavailability of D-cycloserine in cerebral fluid in lower dosages. However, the behavioral effects of D-cycloserine in humans indirectly suggest that D-cycloserine in doses of 15, (Jones et al. 1991), 50 (Goff et al. 1995), and 100 mg (van Berckel et al. 1996) does pass the blood-brain barrier.

Finally, although in animals NMDA receptors are involved in the regulation of secretion of pituitary hormones (Carbone et al. 1996), this might not be the case in humans. Stimulation of neuroendocrine secretion after administration of the NMDA antagonist ketamine (Krystal et al. 1994) is the only indication currently available indicating that indeed NMDA receptors are involved in human neuroendocrine response. However, the interference of ketamine with other receptors might have contributed to this effect. Furthermore, the anxiogenic properties of ketamine could, as described before, also explain the stimulation of cortisol and prolactin secretion. Thus, the role of NMDA receptors in human neuroendocrine secretion still needs to be established.

The present results indicate that D-cycloserine can readily be administered to healthy volunteers but that, in the dosages used in this experiment, D-cycloserine

failed to elicit a neuroendocrine response. Limited penetration through the blood-brain barrier, weak efficacy of D-cycloserine, and a narrow dose range in which D-cycloserine can stimulate NMDA receptors could explain the lack of neuroendocrine response. Further investigations are needed to assess whether D-cycloserine in other dosages can be used as a probe for NMDA receptor function in humans.

ACKNOWLEDGMENTS

The authors thank C. Braams, A. Klompmakers, and S. de Graaf for their valuable technical assistance; A. F. A. M. Schobben, Pharm. Ph.D., H. G. M. Westenberg, Ph.D., and M. A. Blankenstein, Ph.D., for their critical advice.

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