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ORIGINAL INVESTIGATION

D-Cycloserine and performance under different states of anxiety in healthy volunteers

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Abstract
Rationale There is interest in the development of augmentation therapy in the treatment of anxiety disorders. Recent publications have shown that D-cycloserine can benefit exposure therapy in a group of acrophobic (height phobic) subjects and in patients with social anxiety disorder. These studies were based on the animal data suggesting that drugs acting to enhance glutamate function may be developed to accelerate the behavioural treatment of anxiety disorders. Perhaps by enhancing glutamate/*N*-methyl-D-aspartate receptor function, learning is thus enhanced. This study examines the effects of D-cycloserine 50 mg on a task that involves learning. We manipulated anxiety levels to model the effects of high anxiety.
Objectives To evaluate performance and learning, we used the Manikin task. Two groups of 24 healthy volunteers participated in a double-blind, placebo-controlled study. One group received the inhalation of CO_2 7.5% to model high anxiety, and the second group received air to represent lower anxiety. Subjects received D-cycloserine 50 mg or placebo, and the Manikin task was performed during the gas inhalation.
Results There were significant differences in the group inhaling air, but not CO_2, with the D-cycloserine group showing an increase in correct responses. This difference was apparent at several time blocks during the 20-min task. These findings were supported by subjective measures in that participants who received D-cycloserine reported that the task was easier.
Conclusions We have shown that at lower anxiety levels, D-cycloserine 50 mg improved the performance of this challenging visuospatial cognitive task. This increase in performance was not seen when anxiety was higher, and D-cycloserine did not appear to increase subjective anxiety. These data lend support to the use of D-cycloserine and related glutamate enhancers as cognitive modulators and suggest that the actions of D-cycloserine are not simply related to increased arousal or anxiety.

Keywords D-Cycloserine · NMDA · Learning · Fear · Glutamate · Anxiety

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Introduction

Glutamate is the main excitatory amino acid in the human central nervous system (CNS) and plays a critical role in synaptic plasticity and higher cognitive functions especially learning and memory. For this reason, there has been much recent interest in pre-clinical studies that show that a glutamate partial agonist, D-cycloserine, which enhances glutamate function through *N*-methyl-D-aspartate (NMDA) receptors, may accelerate the behavioural treatment of anxiety disorders (Davis and Myers 2002; Ledgerwood et al. 2003, 2005; Parnas et al. 2005; Richardson et al. 2004; Walker et al. 2002). Two recent human experiments have now shown significant effects of D-cycloserine to accelerate treatment response when used with behaviour therapies in people with a specific anxiety (Hofmann et al. 2006; Ressler et al. 2004).

The present study was designed to examine the issue of the relationship between the effects of glutamate manipulation using D-cycloserine and anxiety in humans. This is an important question for several reasons. Firstly, glutamate stimulation has been proposed to increase anxiety, and drugs that block glutamate function are potential anxiolytic

agents (Anthony and Nevins 1993; Rorick-Kehn et al. 2005; Swanson et al. 2005). Secondly, anxiety itself can markedly affect learning and memory (Kalueff and Nutt 1996), and it is important to know if the effects of D-cycloserine are anxiety-related, as in extinction paradigms such as the one used by Hofmann et al. (2006) and Ressler et al. (2004), anxiety is necessarily produced.

We can reliably induce fear and anxiety in otherwise healthy subjects by using the procedure of 7.5% CO_2 inhalation for a 20-min period, during which a learning task can be administered (Bailey et al. 2005). The state produced by inhaling 7.5% CO_2 mimics the symptoms seen in generalised anxiety disorder, and some of these symptoms can be attenuated by anxiolytic medication (Bailey et al. 2007). The control condition in this paradigm is air inhalation delivered in the same way.

To evaluate performance and learning we used the Manikin task, which is a validated test that requires individuals to cognitively manipulate a humanoid shape to determine in which hand a paddle is held (Leifflen et al. 1997). Because we were interested in learning, performance was measured in subjects who were task-naïve either under conditions of normal or CO_2-heightened anxiety.

Materials and methods

Ethical considerations

The local research ethics committee approved the study protocol. All subjects gave written informed consent before their participation. The subject information sheets provided details on the expected effects of inhaling CO_2 such as dizziness, headache and feelings of anxiety and breathlessness.

Participants

All participants gave written informed consent before inclusion. Potential participants were recruited via a database of volunteers or from responses to advertisements displayed around the university and hospital campus. A total of 48 participants were recruited; the first 24 were randomised to receive either placebo or 50 mg of D-cycloserine, and they inhaled CO_2 (the "CO_2 group"); the second 24 were randomised to receive either placebo or 50 mg of D-cycloserine, and they inhaled air (the "air group"; see Table 1 for further details). All were screened for good mental and physical health before inclusion, and those entered into the CO_2 study also underwent a physical examination and electrocardiogram recording. Exclusion criteria included history or current mental illness, specifically panic disorder or relatives with panic disorder or severe anxiety; history of or current medical conditions, including respiratory or cardiovascular disease; history of or current drug or alcohol abuse; smoking more than five cigarettes per day; drinking more than the recommended level of alcohol per week (the British Medical Association suggests that men should consume no more than 21 and women no more than 14 units of alcohol per week); intake of any other medication; previous knowledge of the Manikin task; and pregnant or breast-feeding women. All subjects were paid (£25) for their participation.

Study design and procedure

Each study was double blind and placebo controlled. Participants were told to avoid alcohol for 24 h before the study day and to avoid drinking caffeinated drinks 2 h before testing. At a designated time (morning or afternoon), subjects reported to the Psychopharmacology Unit clinical research facility and were questioned to assure continued informed consent and to determine that health status had not changed since the screening day. The medication (D-cycloserine 50 mg or placebo [PLAC]) was administered orally under supervision. Peak plasma levels of D-cycloserine are reached between 90–120 min (Van Berckel et al. 1997), so participants were able to read or work before baseline measures. In addition, before the start of the study, participants completed the following questionnaires—the Spielberger State and Trait Anxiety Inventory (SSAI, STAI; Spielberger 1983), the Beck Depression Inventory (BDI; Beck et al. 1988) and the Anxiety Sensitivity Index (ASI; Reiss et al. 1986).

Gas delivery procedure

The gas mixture for the CO_2 group was CO_2 7.5%/O_2 21%/N 71.5%. For the air group, we used medical air. Both gases were piped from the cylinder and delivered via a nasal–oral exercise facemask (Hans Rudolf), which was attached to a 500-l bag. Two investigators remained with the subject throughout the procedure.

Subjective ratings

Visual analogue rating scales (VAS) were used, measured on a 100-mm line and anchored from 0: "not at all" to 100: "the most...ever." The individual items were labelled as: alert, anxious, fearful, relaxed, happy, feel like leaving the room and worried. These types of scales provide a good estimate of rapid changes of aspects of mood states (Bond and Lader 1974). These individual items were used as they are sensitive to the effects of CO_2 (Bailey et al. 2005). Before the procedure, baseline assessments were made, and then, at the end of the inhalation, subjects were asked to rate how they felt when they most noticed the effects of the gas,

this rating being "peak." A further VAS scale was used to rate how easy it was to perform the Manikin task (see later).

The panic symptom inventory (PSI) lists 34 symptoms related to panic anxiety and the associated autonomic arousal, with the option of rating 0=not at all, 1=slight, 2=moderate, 3=severe and 4=very severe. It has been used in studies of panic provocation (Nutt et al. 1990; Bell et al. 2002) and our previous CO_2 studies (Argyropoulos et al. 2002; Bailey et al. 2005, 2007). The PSI was administered at baseline, for peak effects and at the end of gas inhalation.

The SSAI (Spielberger 1983) was used to measure state anxiety at baseline and at the end of the study.

Cardiovascular measures

Beat-to-beat blood pressure and heart rate measures were obtained using the Finapres (Ohmeda). The subject wore a finger cuff with a photosensitive cell connected via a servo-controlled pump, which inflates the cuff to maintain a constant pressure in the finger (see Coupland et al. 1995 for further details). A constant recording was made during the inhalation of each gas mixture. During this time, the subject's non-dominant hand rested on the arm of the chair to minimise movement.

Manikin task

This task was provided to the University of Bristol by QinetiQ and the Centre for Human Sciences (Farnborough, UK) for the purposes of this study only. The Manikin task was developed at the Royal Air Force Institute of Aviation Medicine to measure cognitive performance with minimum motor involvement (Benson and Gedye 1963) and has been used in studies of mild (Paul and Fraser 1994) and severe (Leifflen et al. 1997) hypoxia. This PC-based task consists of the appearance of a manikin shape on the screen, holding a red ball in one hand and a blue ball in the other. The manikin appears in different positions—standing upright or upside down and facing out or facing away. At the bottom of the screen, a coloured (red or blue) bar appears, and the participant has to make a decision based on which hand that coloured ball is held. The response is made via the dominant hand with a corresponding left or right mouse click.

The task was performed during the 20 min of gas inhalation, which meant there were ten blocks of trials lasting 90 s each with 30 s between each block. Each block contained 32 trials. For the purposes of this study, participants were naïve to the Manikin task, so each were briefly shown the task in action before proceeding to ensure they understood the rules, and each received matching printed instructions. The lack of prior practice ensured there was a strong learning element to the performance of the task in that all participants found it difficult at first but easier after 20 min. The data from the Manikin task was collected in time blocks (1–10) representing 90 s, and from this, two variables were identified: the number of correct responses and reaction time.

In addition, we measured subjective task performance in two ways: (1) with a simple VAS card as described above, with 0 being not at all easy and 100 being the easiest ever, and (2) the Defence Research Agency Workload Scale (DRAWS) questionnaire, which measures workload stress (Jordan and Farmer 1995). In this, there are four questions relating to mental demand, each requiring a response from 0 representing no demand to 100 representing great mental demand.

Drugs

D-Cycloserine 50 mg and placebo were prepared and stored in identical packaging. The dose used in this study was based on the work by Ressler et al. (2004), who included two doses of D-cycloserine (50 and 500 mg) but showed no difference in response between high and low dose D-cycloserine. Each participant received one capsule 90 min before baseline measures and the study procedure. Oral D-

Table 1 Baseline variables of research participants

Variable	DCS/air	PLAC/air	DCS/CO_2	PLAC/CO_2
Age	25.7 (6.6)	24.5 (4.7)	21.6 (2.9)	24.8 (6.0)
Sex f/m	3/9	4/8	4/8	5/7
STAI	34.5 (11.0)	38.4 (7.1)	36.7 (9.5)	31 (4.8)
SSAI	33 (9.5)	33.1 (9.0)	34.5 (7.8)	29.2 (6.2)
BDI	5.7 (6.7)	5.6 (4.6)	4.5 (3.5)	2.7 (2.6)
ASI	18.5 (12.6)	18.3 (6.8)	16.7 (7.1)	9.6 (5.6)*

Total n=48, 12 in each group; data are mean±standard deviation for group.

f/m Female/male; *STAI* Spielberger trait anxiety inventory; *SSAI* Spielberger state anxiety inventory; *BDI* Beck depression inventory; *ASI* anxiety sensitivity index; *DCS* D-cycloserine 50 mg

*Significantly lower than other groups, p=<0.05, adjusted for multiple comparisons ANOVA.

cycloserine is readily absorbed and shows a dose-related increase in plasma concentration (Van Berckel et al. 1997).

Statistics

Statistical analyses were performed for the four separate groups (Group 1=D-cycloserine/air, Group 2=PLAC/air, Group 3=D-cycloserine/CO_2 and Group 4=PLAC/CO_2) using multivariate analysis of variance (ANOVA) for between-subjects factors. In addition, this allowed for pairwise comparisons between drug and placebo in each study (air group and CO_2 group). All data were analysed using SPSS Version 11.5 for Windows.

Results

Participants

All subjects recruited into the studies completed the procedure. Table 1 shows that there was a balance of age, sex and baseline psychopathology, measured by questionnaires, in all four groups. The only significant difference across the groups was that the CO_2/PLAC group scored lower on the ASI scale. All participants were right-hand dominant.

Manikin task

Analysis was performed on data for reaction time (RT) and the number of correct responses (CR) made.

Multivariate measures ANOVA for correct responses showed a significant effect of time (F 3.39, $p<0.005$), no effect of D-cycloserine or CO_2 and of group (PLAC/air group less than others F 3.63, $p=0.021$) but not group× time. However, ANOVA performed on each time block revealed no differences in the CO_2 group between D-cycloserine and PLAC; however, there was significant differences in the air group, with D-cycloserine/air showing a significant increase compared with PLAC/air in correct responses in several time blocks (see Fig. 1).

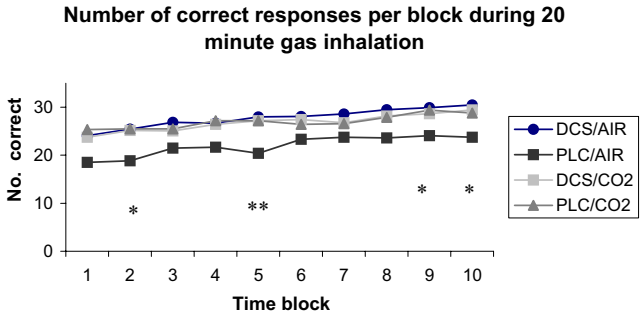

Fig. 1 Data are means for each time block; ANOVA shows significant effect of the group at four time blocks; *single asterisk* indicates $p<0.05$; *double asterisks* indicate $p<0.01$

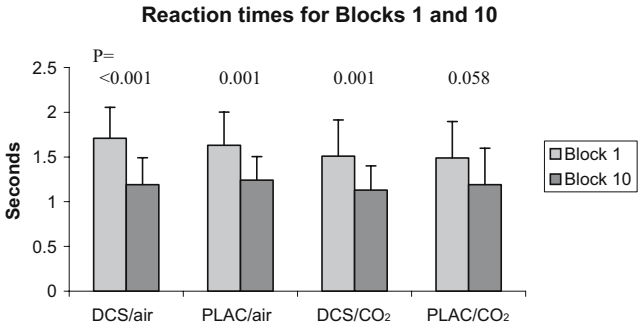

Fig. 2 There is a decrease in RT in all groups; data are mean and standard deviations; within group analysis used Paired Samples Test. *P* value represents difference between *Block 1* and *Block 10*

In the reaction time measures, there was a significant decrease in RT in each condition across time (multivariate ANOVA F 32.3, $p<0.001$; see Fig. 2).

This finding is consistent with the subjective reports of how demanding the performance of the task was. ANOVA revealed an overall group effect for "ease of task" VAS ($p=0.003$, $F=3.259$) with a significant difference between D-cycloserine/air and PLAC/air reported for peak effects. However, there was no difference between D-cycloserine/CO_2 and PLAC/CO_2 (see Fig. 3).

The DRAWS questionnaire was completed at the end of the 20-min session and, retrospectively, for the peak gas effects (Table 2). Again, there was no difference between D-cycloserine/CO_2 and PLAC/CO_2. However, there was a significant difference between D-cycloserine/air and PLAC/air for central demand (how much demand was imposed by the mental, e.g. memorisation, calculation, decision-making, operation required by the task) and output demand (how much demand was imposed by the responses, e.g. mouse clicks, control adjustments, required by the task) for both time points.

Subjective measures

Univariate ANOVA showed a significant group effect for VAS measures at peak effect of anxiety, fear, worry and

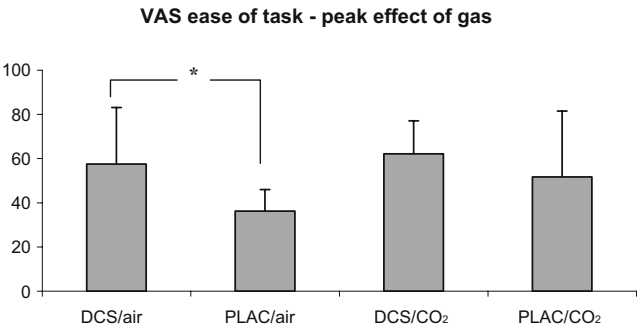

Fig. 3 A higher score indicates that the task was experienced as being easier; data are mean and standard deviations; *PLAC/air* is significantly different from D-cycloserine/air (*Asterisk*, $p=<0.02$)

Table 2 Score on DRAWS questionnaire for peak effects of gas

Measure		DCS/air	PLAC/air	DCS/CO_2	PLAC/CO_2
Central demand	+20	51.3 (21.8)[a]	69.2 (15.6)	59.6 (18.0)	64.5 (23.4)
	Peak	49.6 (24.5)[b]	69.2 (13.8)	69.3 (20.6)	72.5 (19.2)
Output demand	+20	20.8 (27.1)	45.0 (26.1)[b]*	25.8 (19.3)	22.7 (17.4)
	Peak	23.7 (25.9)[a]	46.7 (21.9)	35.0 (23.6)	32.5 (19.0)

Data are mean and standard error for each group; On DRAWS scale, 0 represents no demand, and 100 represents great mental demand; p=<0.05 adjusted for multiple comparison ANOVA.
[a] Significantly less than PLAC/air group
[b] Significantly different to all groups
*p=0.052

happy and the PSI scale. These can mostly be attributable to the known effects of CO_2 rather than any effect of D-cycloserine or PLAC. There were no significant differences between groups on VAS measures of "feel like leaving the room" and "alert," or total SSAI score at the end of the inhalation/task condition. Data are shown in Table 3.

Cardiovascular measures

Univariate ANOVA showed a significant group effect for systolic blood pressure (SBP) in that CO_2 increased SBP regardless of drug condition, and D-cycloserine showed no effect on these measures under either condition.

Discussion

The main goal of this work was to evaluate the effect of D-cycloserine on a learning task conducted under conditions of low anxiety (air group) and higher anxiety (CO_2 group). We found that, as predicted, the inhalation of 7.5% CO_2 for 20 min produced a significant and robust increase in anxiety as per earlier studies (Woods et al. 1988; Bailey et al. 2005). This 50-mg dose of D-cycloserine itself had no significant effect on subjective anxiety levels and did not change the predicted cardiovascular responses to CO_2. There were some between-group differences in task performance, and this was further supported by two different self-reports of task performance.

In the air group or low anxiety state, the Manikin task showed the predicted learning effect with more correct responses and shorter reaction times in later sessions. D-Cycloserine/air group showed more correct responses at most time points and significantly at some time points without affecting the improvement over time. In addition, further evidence of a beneficial effect of D-cycloserine was shown by the self-reports of demand, which revealed that the D-cycloserine/air group found the task considerably easier to perform with less demand on mental function. In neither condition did D-cycloserine affect physiology measures or alter the actions of CO_2 to increase blood pressure and heart rate.

In contrast, in the CO_2 group or high anxiety state induced by CO_2, there was no difference between D-cycloserine/CO_2 or PLAC/CO_2 on task performance, perhaps because the arousal caused by the inhalation of CO_2 produced a ceiling effect on performance. In addition, the difference observed in baseline ratings of anxiety sensitivity did not appear to impact on subjective response to CO_2 in this study. However, reports by ourselves and others have shown that individuals who have a higher score on the anxiety sensitivity index are more sensitive to the effects of CO_2 (Bailey and Nutt 2005; Schmidt and Mallott 2006).

Our study did reveal that D-cycloserine 50 mg appeared to improve performance on the Manikin task compared with the PLAC/air control group. This complex task measures spatial processing, psychomotor performance, reaction time and accuracy of response, and it does demand

Table 3 Subjective VAS and PSI for peak effect of gas and SSAI for the end of study

Peak VAS	DCS/air	PLAC/air	DCS/CO_2	PLAC/CO_2	ANOVA group Df, F, Sig
Anxiety	10.0 (9.5)	21.7 (27.6)	47.5 (28.3)	53.3 (22.0)	3, 9.6, 0.0001
Fear	5.8 (6.7)	10.4 (15.1)	45.4 (29.6)	32.9 (29.6)	3, 8.3, 0.0001
Worry	9.2 (10.0)	13.8 (22.9)	43.8 (28.5)	32.1 (27.9)	3, 5.6, 0.002
Happy	51.7 (21.2)	48.3 (20.7)	33.3 (28.4)	28.8 (19.6)	3, 2.9, 0.045
PSI	6.2 (6.1)	7.1 (11.0)	32.7 (18.2)	24.1 (14.5)	3, 11.7, 0.0001
SSAI	31.4 (7.1)	34.8 (13.4)	38.1 (11.1)	35.5 (9.2)	3, 0.98, 0.407

Data are mean and standard deviation.

the ability to learn a strategy to improve performance. Published studies of the Manikin have required that the research subject reach a plateau in performance before the test procedure to examine deterioration in performance rather than an increased ability to perform (e.g. Hearon and Brinkley 1985; Bunnell and Horvath 1989; Gibson and Allan 1979). However, by using it in a different way, we have shown preliminary evidence that it can be used to estimate both performance, measured by reaction time and speed of learning, as measured by the improvement in the number of correct responses when given to naïve subjects. Although this is a novel approach, it may also be a limitation to our findings as we cannot be sure that any pre-existing baseline differences somehow affected outcome.

No studies have specifically examined the effects of D-cycloserine on learning. One study examined the effects of D-cycloserine 50 mg on performance and learning of a verbal and a continuous performance task (D'Souza et al. 2000) where there was no effect of D-cycloserine. Although in this study, the healthy participants were also subjected to lumbar puncture and a battery of blood tests and behavioural ratings, so the study was not specifically designed to test cognitive function. One functional magnetic resonance imaging study has shown that in patients with schizophrenia, 8 weeks treatment of D-cycloserine 50 mg daily, compared with placebo, improved word fluency, and a significant increase in temporal lobe activation was demonstrated (Yurgelun-Todd et al. 2005). However, this study used a small number of patients, and these findings are yet to be duplicated in a non-patient population.

The studies that have shown a beneficial effect of D-cycloserine are those that have used it in conjunction with behaviour therapy to accelerate extinction of phobic responses (Ressler et al. 2004; Hofmann et al. 2006). These differ from ours in several ways—patients rather than normal volunteers, extinction rather than procedural learning and differences in dosing and times of testing—so they are difficult to compare. Of interest is the fact that they did not show improved performance under D-cycloserine; rather, they found improvement between test sessions, which may suggest a different effect of D-cycloserine on different forms of performance. Their finding of enduring effects suggests that future studies in volunteers using similar designs to ours might wish to look for effects that extend beyond the test session. At the least, we can say that anxiety, at least that induced by CO_2, did not appear to affect the actions of D-cycloserine in a negative way.

Conclusion

We have shown preliminary evidence that in a challenging visuospatial cognitive task of procedural learning, D-cycloserine 50 mg improved performance, although not learning, and reduced the subjective cognitive demands of the task. An equivalent increase in performance was not seen when the task was conducted under a condition of raised anxiety caused by a CO_2 inhalation, perhaps because the CO_2-induced increase in anxiety was itself associated with improved performance on the task. D-Cycloserine did not appear to affect anxiety levels and, in the lower anxiety air condition, appeared to reduce the cognitive demands of this difficult task. These data give further support to the use of D-cycloserine and related glutamate enhancers as cognitive modulators and suggest that the actions of D-cycloserine are not simply related to increased arousal or anxiety.

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