D-Cycloserine, a positive modulator of the NMDA receptor, enhances acquisition of a conditioned taste aversion

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Pharmacological manipulations using agents that affect the action of the *N*-methyl-D-aspartate (NMDA) receptor have been demonstrated to modulate acquisition and retention in experimental animals. Although it is well established that antagonists of this receptor debilitate acquisition of many experimental tasks, the effects of agonists of the receptor site have not been thoroughly examined, except for those of D-cycloserine (DCS), a partial agonist of the NMDA receptor. In the present study, DCS is demonstrated to enhance acquisition of a conditioned taste aversion (CTA) in rats, extending the findings of facilitation of learning with this agonist to a CTA paradigm. DCS itself did not cause a taste aversion nor did it summate with lithium chloride, the unconditioned stimulus, to increase avoidance of the conditioned stimulus in experimental animals. It appears that modulation of the NMDA receptor can affect gustatory learning.

Pharmacological manipulation of the *N*-methyl-D-aspartate (NMDA) receptor has been shown to affect acquisition and retention in experimental animals (Izquierdo & Medina, 1995; Maren & Baudry, 1995). For example, antagonists of this receptor site have deleterious effects on learning, including place learning in the water maze (Morris, Anderson, Lynch, & Baudry, 1986), learning in the radial-arm maze (Butelman, 1990), imprinting in chicks (McCabe, Davey, & Horn, 1992), delayed matching-to-sample (Pontecorvo, Clissold, White, & Ferkany, 1991), and Pavlovian fear conditioning (Kim, DeCola, Landeira-Fernandez, & Fanselow, 1991).

Although the detrimental effects of NMDA antagonists on the acquisition of a variety of tasks are well documented, explorations of modulation of learning with agonists of this receptor site are limited (Thompson, Moskal, & Disterhoft, 1992). There is some evidence that one positive modulator of the NMDA receptor, D-cycloserine (DCS), facilitates learning. DCS is a partial agonist of the strychnine-insensitive glycine recognition site on the NMDA receptor (Hood, Compton, & Monahan, 1989), activation of which seems crucial for induction of LTP, or long-term potentiation, a putative mechanism of learning and memory (Abe, Xie, Watanabe, & Saito, 1990; Oliver, Kessler, Larson, Schottler, & Lynch, 1990). In one investigation involving this drug, peripheral administration of

DCS immediately before classical conditioning trials of the hippocampus-dependent rabbit nictitating membrane response improved acquisition (Thompson et al., 1992). Notably, the acquisition of this task is impaired by pre-training administration of an antagonist of this receptor, MK-801 (Cox, Guthrie, Macrae, & Kehoe, 1994). Also, co-administration of DCS and scopolamine attenuates the typical deficit in learning produced by this muscarinic antagonist (Fishkin, Ince, Carlezon, & Dunn, 1993). Thus, DCS may not only enhance learning, but block the retarding effects of other modulatory agents.

DCS also enhances learning of passive avoidance. When rats were administered DCS before the learning trial, after the unconditioned stimulus (shock), or before retention testing, their latencies to cross into the chamber in which they had been shocked were significantly higher than those of controls receiving injections of saline (Monahan, Handelsmann, Hood, & Cordi, 1989). These investigators also found that DCS did not enhance place learning in a T-maze, but did facilitate learning of a subsequent reversal task.

In a recently conducted delayed matching-to-position task in rats, DCS was found to increase performance only at a long delay; no improvement in retention was noted at a short delay (Ruske, Harper, Colombo, & White, 1995). Furthermore, DCS administration did not enhance discriminability performance and did not slow the rate of forgetting. Thus, despite reports indicating that DCS can enhance learning, the evidence is somewhat mixed regarding its efficacy in doing so.

Although, according to most reports, modulation of the NMDA receptor appears to affect the acquisition of a variety of tasks, it is not clear from the available evidence whether or not manipulation of these receptors can affect gustatory learning. Myhal and Fleming (1990) demon-

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strated the impairment of a socially mediated food preference with administration of the NMDA antagonist dizocilpine maleate (MK-801). One-trial learning of a conditioned taste aversion (CTA), in which presentation of a distinctive flavor is followed by the administration of an illness-inducing toxin, is impaired by administration of the noncompetitive NMDA antagonist ketamine (Welzl, Alessandri, & Bättig, 1990). In their experiment, a nonanesthetic dose of ketamine was injected either before presentation of the conditioned stimulus (CS; saccharin solution) or immediately prior to injection of the illness-inducing agent (lithium chloride; LiCl). When injected before the taste, ketamine impaired learning of the taste aversion; however, if ketamine was injected before the toxin, learning was not affected. Other investigations of the effects of an NMDA receptor blockade on taste learning have shown no impairment of acquisition (Robinson, Crooks, Shinkman, & Gallagher, 1989; Willner, Gallagher, Graham, & Crooks, 1992).

A similar set of experiments has failed to support evidence implicating NMDA receptors in taste learning (Aguado, San Antonio, Perez, del Valle, & Gomez, 1994). Using the NMDA antagonist ketamine and sucrose as the CS, these investigators attempted to replicate the finding of Welzl et al. (1990). Animals injected with ketamine before conditioning did show a diminished aversion to sucrose, but a control group for state dependency indicated that at least part of the effect was due to a change in drug state from training to test. Attenuation of neophobia was also investigated, and the results indicated that ketamine does not interfere with habituation to a novel flavor. It was not clear whether ketamine affected latent inhibition, by which exposure to a novel taste reduces a subsequent taste aversion when that flavor is paired with illness.

The purpose of the present experiments was to extend the findings involving DCS to a CTA paradigm in order to investigate the generality of NMDA agonists with respect to other learning tasks, as well as to accumulate additional evidence in an attempt to resolve the ambiguity regarding the role of NMDA-related modulation of gustatory learning. Toward this end, rats were given DCS prior to conditioning in a CTA paradigm. In addition, experiments were conducted to eliminate alternative explanations for the facilitation of performance. If DCS does affect acquisition of CTA, this outcome would provide further evidence that NMDA receptors are implicated in gustatory learning.

EXPERIMENT 1

The present experiment represents an attempt to extend to a CTA paradigm the previous findings of facilitation of learning with DCS. Like the passive avoidance task employed by Monahan et al. (1989), CTA tasks can involve one-trial learning, making them suitable for studying the pharmacological modulation of learning (Gold, 1986). And, like passive avoidance, CTA involves aver- sively motivated acquisition. If modulation of the NMDA

receptor can affect taste learning, pretraining injections of DCS should enhance avoidance of the CS in a taste aversion paradigm.

Method

Subjects. Thirty male Sprague-Dawley albino rats (Hilltop), weighing 290–340 g at the time of testing, were used in the experiment. All subjects were 128 days old at time of training. The animals were single-caged and maintained on a 14:10 h light:dark cycle. Food was available ad libitum throughout the experiment, which was conducted during the light portion of the cycle, between 0800 and 1100 h.

Procedure. The animals were randomly assigned to one of three groups based on injections. Partial water deprivation was begun 3 days before experimentation; subjects were allowed 15 min of water each day prior to training. Consumption was measured on each of these days to ascertain that there were no differences in drinking among the groups. Subjects were weighed immediately before training injections. All procedures occurred in the animals' home cages.

At training, animals were first injected interperitoneally (i.p.) with either saline (Group SAL) or DCS (0.3 or 0.6 mg/kg; Groups DCS-0.3 and DCS-0.6, respectively). All doses were mixed so that injection volumes would be identical. Immediately afterward, sucrose (10%) was presented and the rats were allowed to drink for 15 min. After the bottles were removed, all rats were injected i.p. with 2-mg/kg LiCl (0.5 M). Standard water bottles were replaced for 60 min to replenish body fluids.

Forty-eight hours later, subjects were presented with sucrose for 15 min in a single-bottle test. To allow for individual differences in drinking, the dependent variable employed was a difference score, obtained by subtracting training day consumption from test day consumption. A negative score indicates that the subject drank less at test than at training (aversion); a positive score or one of zero indicates no aversion.

Results and Discussion

In a one-way analysis of variance (ANOVA), comparison of pretraining water consumption indicated no differences in drinking among the groups [$F(2,22) = 2.258$, $p = .128$; means: SAL, 17.67 ($SD = 1.1$); DCS-0.3, 19 ($SD = 1.9$); DCS-0.6, 16.5 ($SD = 2.4$)]. Neither were differences found among the groups of initial (training) sucrose consumption [$F(2,23) = 2.337$, $p = .119$; means: SAL, 18.11 ($SD = 5.1$); DCS-0.3, 23 ($SD = 3.36$); DCS-0.6, 20.1 ($SD = 4.5$)]. As is shown in Figure 1, when a one-way ANOVA was conducted on relative sucrose consumption at test, however, there was a significant difference among the groups [$F(2,23) = 6.289$, $p = .007$]. Subsequent Tukey tests indicated that Group DCS-0.3 suppressed drinking of sucrose significantly more than did the saline group ($p < .005$). No significant difference was evident between Groups DCS-0.3 and DCS-0.6 ($p = .212$), nor were differences found between Groups DCS-0.6 and SAL ($p = .134$). Thus, it seems that DCS had an enhancing effect on acquisition of a taste aversion, but the effect was seen clearly only at the lower dose (0.3 mg/kg).

The facilitation observed in the present experiment could not be attributed to state dependence, a concern raised by Aguado et al. (1994), since DCS was administered before acquisition only. If DCS did induce state dependency, experimental animals should have consumed more at testing than the saline group; that is, the transfer

Figure 1. Mean difference scores of consumption of sucrose. Animals administered 0.3-mg/kg DCS prior to training consumed less at testing than did animals receiving saline before training.

from a drug to nondrug state would impair their retrieval of the aversion conditioning.

EXPERIMENT 2

Ingestion of high doses of DCS can induce nausea (Sigma Chemical, 1994). It has also been demonstrated that administration of the NMDA antagonists phencyclidine (PCP) and MK-801 following consumption of a novel saccharin solution can induce taste aversion (Jackson & Sanger, 1989). Therefore, it is important to investigate the toxic quality of DCS at the concentrations employed in these experiments. If these doses are illness inducing, any enhancement of a taste aversion with DCS may simply be the effect of a larger unconditioned stimulus (UCS). Accordingly, Experiment 2 was conducted to determine whether DCS, at either 0.3 or 0.6 mg/kg, can itself cause a taste aversion when paired with sucrose.

Method

Subjects. Fifteen male Sprague-Dawley albino rats (Hilltop), weighing 250–370 g at the time of training, were used in the experiment. Housing conditions were identical to those of Experiment 1. Procedures were conducted during the light portion of the cycle (0800–1100 h).

Procedure. Water deprivation was begun 3 days prior to training, with access to water daily for 15 min. On Day 4, rats were given 15 min of sucrose access, immediately followed by an i.p. injection of either DCS (Sigma Pharmaceuticals) or saline (NaCl; Sigma Pharmaceuticals). Animals were randomly divided into three groups characterized by the following injections: Group DCS–0.3

received 0.3 mg/kg DCS following sucrose; Group DCS–0.6 received 0.6 mg/kg DCS after sucrose; Group SAL was injected with saline after sucrose consumption. The animals were injected with DCS following sucrose consumption in order to optimize the possibility of detecting a conditioned taste aversion.

Forty-eight hours later, single bottles of sucrose were again presented for 15 min on the home cages of the animals. The dependent variable was a difference score, derived by subtracting test consumption from initial sucrose intake.

Results and Discussion

DCS at the present doses did not induce a taste aversion, nor did it create any differences in consumption among groups [one-way ANOVA, $F(2,9) = 0.016$, $p = .984$; mean difference scores: SAL, 7 ($SD = 2.94$); DCS–0.3, 6.75 ($SD = 1.89$); DCS–0.6, 6.8 ($SD = 1.708$)]. Therefore, it seems unlikely that the facilitation of acquisition observed in Experiment 1 can be attributed to an illness-inducing quality of DCS.

However, the enhancement of learning could be interpreted as an increase in the strength of the UCS as a result of an interaction between the two drugs, LiCl and DCS. This possibility was considered in the following experiment.

EXPERIMENT 3

Although administration of DCS at the doses utilized in the CTA paradigm does not induce a taste aversion (see Experiment 2), the interaction of this drug with LiCl could produce excessive malaise in subjects receiving both agents. If this were the case, the greater avoidance of sucrose exhibited by DCS subjects in Experiment 2 could be due not to enhanced acquisition, but to the result of a larger UCS. Amount of conditioning in a classical conditioning paradigm varies directly with the intensity of the UCS (Scavio & Gormezano, 1974). Thus, if the illness experienced by subjects receiving DCS was greater, so would be their subsequent aversion to the sucrose. Accordingly, a measure was employed to quantify the degree of illness experienced by the subjects. After injection of a toxin, rats typically retire to the back of the home cage and assume a posture termed “lying on belly,” which persists for the duration of the sickness (Meachum & Bernstein, 1990).

It is a reasonable assumption that an animal's approach and consumption of a preferred substance will vary inversely with the amount of illness it experiences. Animals feeling more ill will remain in the lying-on-belly posture longer. In the present experiment, we took advantage of this response to illness by recording the latency to approach a preferred substance (10% sucrose solution) after injection of both DCS and LiCl or LiCl alone. Once drinking began, test consumption of sucrose was also measured; differences between DCS and saline groups could indicate differences in illness. Thus, this paradigm did not involve conditioning of an aversion to sucrose, but assessed the tendency of DCS and LiCl to suppress approach and consumption activity toward a highly palatable substance.

Method

Subjects. Fifteen male Sprague-Dawley rats (Hilltop) were used, weighing 310–380 g at the time of testing. Housing conditions were identical to those of the preceding experiments. Training and testing was conducted between 0800 and 1100 h, during the light portion of the animals' cycle.

Procedure. The animals, randomly divided into three groups, were partially water deprived beginning 4 days prior to experimentation. Each day the subjects were allowed 15 min of sucrose, in order to establish a strong preference and approach tendency. Consumption was measured daily so as to ascertain that there were no group differences prior to experimental manipulations. On Day 4, the animals were given i.p. injections of 0.3-mg/kg DCS (Group DCS-0.3), 0.6-mg/kg DCS (Group DCS-0.6), or saline (Group SAL). After 15 min, all subjects were injected with LiCl (0.5 M; 2 mg/kg). The delay between injections was intended to mimic the conditions of Experiment 2, where sucrose access for 15 min occurred between injections. After administration of the toxin, sucrose bottles were placed on the home cages for 120 min and latency to drink as well as consumption of sucrose were measured. It was expected that if the DCS-0.3 and DCS-0.6 animals experienced greater malaise, they would exhibit longer latencies to drink relative to controls. Consumption differences might also vary with degree of sickness.

Results and Discussion

There were no differences among groups in pretesting consumption of sucrose [one-way ANOVA, $F(2,16) = 2.656$, $p = .101$; means: SAL, 17.33 ($SD = 2.503$); DCS-0.3, 15.7 ($SD = 1.83$); DCS-0.6, 12.6 ($SD = 3.29$)]. On test day, all the animals initially approached the proffered sucrose but immediately retired to the back of the cage and assumed the lying-on-belly position. A one-way ANOVA indicated no differences among groups in drinking onset after sickness [$F(2,9) = 2.033$, $p = .187$; means: SAL, 33 min; DCS-0.3, 18.5 min; DCS-0.6, 24.4 min]. The saline-injected animals actually took longer to drink, but these differences were not reliable. Neither were differences found in postsickness sucrose consumption [$F(2,9) = 0.760$, $p = .496$; mean consumption: SAL, 20.6; DCS-0.3, 18; DCS-0.6, 20].

These results suggest that LiCl and DCS at either 0.3 or 0.6 mg/kg do not summate to produce a greater illness and thus a larger UCS for experimental group animals. Therefore, the improved acquisition of the taste aversion seen in DCS rats in Experiment 2 was not likely due to a more intense UCS.

EXPERIMENT 4

It seems clear that modulation of the NMDA receptor site can influence taste learning. However, what is not apparent from the foregoing investigations is the manner in which DCS modulates acquisition. If DCS influences learning by altering the representation of the memory, one manifestation of this alteration may be that the memory of the flavor is more enduring. A lingering representation of the flavor could be revealed by delaying the administration of the UCS (LiCl). Postponing administration of LiCl can attenuate an aversion in normal animals. Rats first given DCS may retain the integrity of the CS representation longer and thus show a greater aversion than do control animals. The following experiment

was conducted to investigate this possibility. If DCS animals do show less attenuation of the aversion, one interpretation might be that the representation was rendered more enduring by DCS. This experiment also served as a partial replication of the enhancement of CTA by DCS reported in the first experiment.

Method

Subjects. Forty-nine male Sprague-Dawley albino rats (Hilltop Farms), 121 days old and weighing 290–420 g, were used in the experiment. Housing conditions were as noted earlier, and all experimentation was conducted during the light portion of the rats' cycle, between 0800 and 1100 h.

Procedure. The subjects were partially water deprived beginning 3 days before experimentation. They were randomly divided into four groups: Group DCS-Immediate (DCS-IMM) received DCS (0.3 mg/kg) before conditioning, and LiCl (0.25 M; 2 mg/kg) was administered immediately after consumption of the CS (10% sucrose). Group Saline-Immediate (SAL-IMM) was injected with saline before conditioning and received LiCl directly after consumption of the CS as well. Group DCS-Delay (DCS-DEL) was injected with DCS (0.3 mg/kg) prior to conditioning and received the LiCl injection 30 min following sucrose consumption; Group Saline-Delay (SAL-DEL) received a preconditioning saline injection instead of preconditioning DCS. Thus, this experiment included a partial replication of Experiment 1 (Groups DCS-IMM and SAL-IMM) and a comparison with animals receiving a delay between the CS and UCS (Groups SAL-DEL and DCS-DEL). A lower dose of LiCl, 0.25 M solution, was employed in order to avoid ceiling aversion scores that would obscure differences due to a delay. DCS-IMM animals should suppress consumption at test more than SAL-IMM, as was seen in Experiment 1. If DCS extends the representation of the flavor, DCS-DEL animals should drink considerably less than those in the SAL-DEL condition. Again, a

Figure 2. Mean difference scores of sucrose consumption. DCS (0.3-mg/kg) rats consumed much less at testing than did animals that received saline, regardless of the delay between the CS and UCS.

difference score was used to control for individual differences in consumption.

Results and Discussion

The animals receiving DCS drank much less than the saline animals, which was confirmed by a two-way ANOVA [$F(1,45) = 5.827, p < .02$; see Figure 2]. However, although the effect of drug was significant, the interaction between the time interval (immediate or delay) and DCS was not [$F(1,45) = .706, p = .40$], nor was the effect of a delayed administration of LiCl [$F(1,45) = 0.160, p = .691$]. The delay was not sufficient to attenuate acquisition. Thus, DCS seemed to enhance retention, but not more so in animals receiving a delay of UCS administration. It is possible that a longer delay could have revealed differential effects of DCS at the long interval. Although the primary objective of this experiment was not realized, the results do serve to underscore the effectiveness of the 0.3-mg/kg DCS dosage in enhancing learning of a taste aversion.

EXPERIMENT 5

As demonstrated in Experiment 1, DCS seems to facilitate the acquisition of CTA. The present experiment represents a partial replication and extension of previous investigations involving passive avoidance learning. Monahan et al. (1989) found that DCS enhanced learning of a passive avoidance task. In their experiment, a Y-shaped runway with gray and black chambers was used, and the animals were allowed to explore both chambers the day before training. At training, the animals were permitted to enter a chamber; the door was closed, and they were shocked. Twenty-four hours later, latency to enter the chamber in which the animal had previously been shocked was assessed as the dependent variable. The present experiment differed from that of Monahan et al. in that a two-compartment shuttlebox was used: one side was black; the other, white with a clear lid. Training involved allowing the rat to cross to the black side, where it was then shocked and permitted to escape to the white side. Animals were trained during their initial exposure to the apparatus, and the dependent variable was the proportion of time spent on the safe side of the apparatus during a 600-sec test conducted the following day; no shocks were administered at this time. The dosages of DCS administered in this experiment (3 and 6 mg/kg) were compatible with those of Monahan et al., as well as with Experiment 1 of this paper (0.3 and 0.6 mg/kg). Thus, as well as providing a replication, this experiment was an attempt to extend the findings to a different training method, apparatus, and dosage. If DCS does enhance learning of this aversively motivated task, it should be evidenced by more time spent in the side of the apparatus where the animal had not been shocked.

Method

Subjects. Fifteen male Sprague-Dawley albino rats (Hilltop) were used; they were 121 days old at time of testing, and they

weighed 360–450 g. Food and water were available ad lib throughout the experiment, which was conducted during the light portion of the day: night cycle, between 0800 and 1100 h.

Apparatus. A Plexiglas shuttlebox with two compartments, one white with a clear lid and one completely black, served as the conditioning and testing chamber. The compartments were separated by a guillotine door, and a 30-W lightbulb was suspended 12 in. above the center of the apparatus. The floor was composed of stainless steel grids, spaced 1.5 cm apart. The grids on the black side were connected to a shock generator.

DCS was mixed with saline at either 3:1 or 6:1 in order for the volume of all injections to be identical.

Procedure. Subjects were randomly assigned to five groups characterized by their pretraining injections. At time of training, each subject was removed from his home cage, given an i.p. injection of either saline (Group SAL) or DCS (3 mg/kg, Group DCS-3; 6 mg/kg, Group DCS-6; 0.3 mg/kg, Group DCS-0.3; 0.6 mg/kg, Group DCS-0.6). The rat was then placed in a litter-filled plastic shoebox until passive avoidance training 5 min later. The subject was transported via the plastic shoebox to the experimental room, held by the experimenter for 30 sec in the room, and placed on the white side of the apparatus for 30 sec. At this time the guillotine door was raised, and latencies to cross to the black side were recorded. After 10 sec on the black side, a 2-sec 90-V shock was administered. Following an additional 10 sec, the door was raised simultaneously with a second (escapable) 2-sec 90-V shock. All animals escaped the shock by crossing into the white side before the shock ended. They were then removed from the white side and returned to their home cages.

Testing was conducted 24 h later. The subjects were transported to the experimental room and placed on the white side of the shuttlebox. The door to the black side was then lifted. Total time on white (TTW) during a 600-sec test was the dependent variable. High scores on this measure were considered indicative of good retention.

Groups receiving DCS at 3 and 6 mg/kg were run separately from those given 0.3 and 0.6 mg/kg, so the analyses were conducted separately.

Results and Discussion

A Kruskal-Wallis ANOVA, used in analysis because of an asymmetrical distribution resulting from ceiling scores, indicated a significant difference among the groups ($H = 6.655, p = .036$). Figure 3 indicates that DCS-3 animals spent a greater amount of time on the white side during testing. This outcome was confirmed by a Mann-Whitney U test, which showed a significant difference between the DCS-3 and SAL groups ($U = 19, p = .027$). Group DCS-6 evidenced higher TTW scores than did Group SAL, but this difference was not reliable ($U = 21, p = .055$). No difference was found between Groups DCS-3 and DCS-6 ($U = 8, p = .20$).

These findings represent a successful replication of Monahan et al. (1989) and demonstrate that DCS can also enhance punishment learning in a go/no-go rather than discriminative choice paradigm. Further, the effect does not depend on prior exploration or exposure to the apparatus, as could have been the case in Monahan et al.

For the lower dosages, a Kruskal-Wallis ANOVA showed no differences among the groups in avoidance of the previously shocked compartment ($H = .854, p = .653$; mean TTW: SAL, 201.3 sec; DCS-0.3, 271.67 sec; DCS-0.6, 259.5 sec). Thus, learning of passive avoidance was not enhanced by the smaller dosage of DCS that facilitated CTA learning. So, although learning of this

Figure 3. DCS at 3 mg/kg enhanced the total-time-on-white (TTW) scores of experimental animals in comparison with saline animals.

task is sensitive to positive modulation of the NMDA receptor, greater doses of DCS apparently are required in order to observe enhancement of acquisition. Although similar in their aversive nature, CTA and passive avoidance have many differences. For example, not only are illness and shock very different UCSs, but CTA training occurred in the home cage, whereas passive avoidance was learned in a novel context. An important consideration from these results is the differences in modulation required in order to enhance learning with different tasks. Gustatory learning could be more sensitive to modulation of the NMDA receptor complex, or it may simply be easier to learn. Further investigation is needed to determine what mechanisms account for these differences.

GENERAL DISCUSSION

The results of these experiments confirm the ability of DCS to enhance learning of passive avoidance when administered prior to training, and they extend these findings to a CTA paradigm. The present study suggests that modulation of the NMDA receptor with an agonist of this site, DCS, can affect gustatory learning without altering the UCS, affecting initial consumption, or inducing state dependence.

Because different doses of DCS were used in testing passive avoidance and CTA, an interesting result emerged: Levels of DCS that facilitate learning of a taste aversion are not effective with passive avoidance. The latter task appears to require a higher dose to enhance acquisition. Again, these tasks differ along several dimensions, but a

possible implication is that the NMDA receptor plays a different role in different kinds of learning, and various amounts of modulation are required to affect acquisition with differing tasks (see Morris, Halliwell, & Bowery, 1989).

Another curious aspect of these results involves the doses effective at enhancing learning. In both Experiments 1 and 5, the lower dose (0.3 and 3.0 mg/kg, respectively) affected acquisition, but not the higher one (0.6 and 6.0 mg/kg, respectively). Although these data would fit a model postulating the typical nonmonotonic inverted-U dose-response relationship of drug effectiveness seen with agents such as epinephrine (Gold & VanBuskirk, 1975), it is impossible to draw such a conclusion from the use of only two levels of administration. Clearly, this issue is one to be addressed in future studies.

By what mechanism of acquisition and/or retention does DCS exert its effects? It is unclear from the present experiments whether this agonist of the NMDA receptor modulates the representation, storage, or retrieval processes. Although Experiment 4 was an attempt to clarify which aspect of the learning process was affected by DCS, the method was unsuccessful at providing an answer to this question. Delaying the administration of the UCS for several hours may allow for the effects of DCS upon the longevity of the representation to be assessed. Further investigation of the exact processes influenced by DCS will be necessary in order to adequately determine its precise role in acquisition and retention.

Regardless of its mechanism of action, in the present experiments, an NMDA agonist was shown to enhance learning of a conditioned taste aversion, which adds important evidence to the growing body of work showing improved acquisition when these agents are administered at time of training. DCS may have therapeutic value, especially for patients with Alzheimer's disease, who have a reduced sensitivity to NMDA receptor activation (see Fishkin et al., 1993). Further elucidation of the means through which this agent and others like it influence acquisition and retention processes has important implications and applications, both theoretical and clinical.

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