D-Cycloserine Facilitation of Fear Extinction and Exposure-Based Therapy Might Rely on Lower-Level, Automatic Mechanisms

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Exposure-based therapy, a leading technique in the treatment of a range of anxiety disorders, is facilitated by D-cycloserine (DCS), a partial *N*-methyl-D-aspartate receptor agonist. This review discusses the potential mechanisms involved in this facilitation and its implications for developing theories of fear conditioning in humans. Basic research in rodents suggests that DCS acts by speeding up extinction. However, several laboratory-based investigations found that DCS had no effect on extinction in humans. This report proposes that these observations can be accounted for by a dual-model theory of fear conditioning in humans that engages two complementary defensive systems: a reflexive lower-order system independent of conscious awareness and a higher-order cognitive system associated with conscious awareness of danger and expectation. The DCS studies in animals seem to have explored lower-order conditioning mechanisms, whereas human studies have explored higher-order cognitive processes. These observations suggest that DCS might act preferentially on lower- rather than higher-order learning. This report presents evidence suggesting that, in humans, DCS might similarly affect lower-order learning during exposure-based therapy and, consequently, might be less effective during cognitive therapy (e.g., cognitive restructuring). Finally, it is recommended that extinction studies using DCS in humans be conducted with fear-relevant stimuli (e.g., snakes), short conditional stimulus–unconditioned stimulus intervals and intense unconditioned stimulus to promote lower-order conditioning processes.

Key Words: Anxiety disorders, D-cycloserine, DCS, extinction, exposure-based therapy, fear conditioning, phobia

The finding that D-cycloserine (DCS), a partial *N*-methyl-D-aspartate (NMDA) receptor agonist, enhances exposure-based therapy (EBT) for height phobia generated considerable excitement for its use as a novel treatment strategy for anxiety disorders (1). Whereas traditional anxiolytics such as the benzodiazepines or selective serotonin reuptake inhibitors reduce symptom expression, DCS facilitates the effectiveness of EBT (1–5).

The strategy of combining EBT with DCS is based on two assumptions. First, basic research in rodents shows that DCS facilitates extinction, defined as the decrease in conditioned fear that occurs after the repeated presentation of a conditioned stimulus (CS) in the absence of a noxious unconditioned stimulus (US) with which it had been initially paired. Second, EBT, which consists of confronting patients with the feared stimulus without adverse consequences, relies on extinction principles (1,6). Thus, DCS facilitates the extinction learning that takes place during EBT (7–9). However, DCS has no effect on laboratory-based extinction in humans (see following), raising questions regarding the precise nature of the learning process via which this agent operates.

As this review will discuss, the contradictory findings regarding DCS's effectiveness in extinction studies can in fact be used to refine our thinking of how fear conditioning and EBT operate in humans. On the basis of these disparities, this review presents evidence of a dual-model theory of fear conditioning in humans that can engage two complementary defensive systems: a basic, lower-order, automatic process independent of conscious awareness; and a higher-order cognitive system associated with conscious awareness of danger and anticipation (10,11). Evidence suggests that conditioning in rodents is essentially a low-level, automatic process (12), whereas laboratory-based conditioning in humans relies essentially on high-level cognitive learning (13,14). The fact that DCS influences extinction in rodents but not in humans suggests that DCS might act preferentially on lower- rather than higher-order learning. If so, DCS might similarly affect lower-order learning during EBT. Support for these hypotheses and implications for our understanding of the effects of DCS on the psychological treatment of anxiety disorders are discussed in the following.

Fear Conditioning

Fear conditioning has long been a cross-species model paradigm to study the learning and unlearning of fear. During fear conditioning, a CS is repeatedly paired with an aversive US. Subsequent presentation of the CS can evoke a conditioned fear response (CR), which progressively extinguishes when the CS is no longer reinforced with the US. Most of our knowledge regarding conditioning mechanisms is based on rodent studies, raising the question of the generalizability of findings to humans. Of special relevance is the role of lower-order subcortical automatic mechanisms as opposed to higher-order cognitive processes, which dominate in humans (13,14).

Fear Conditioning in Animals

In vertebrates, phylogenetically older neural structures detect and react rapidly and reflexively to danger cues (e.g., the CS). The amygdala plays a pivotal role in all aspects of fear conditioning (15). Detection and response to a CS can be learned and expressed in the absence of a cortex (16), suggesting low-level processing (17). Indeed, CRs in rodents can be mediated by a lower-level thalamo-amygdala pathway that provides a crude but rapid analysis of stimuli (17,18).

The amygdala is also the central neural node of response expression, facilitating and synchronizing rapid reactions to danger. Efferents from the central nucleus of the amygdala to the hypothalamus and various brainstem sites enable a rapid and integrated defensive response. These connections are hard-wired

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so that warning cues can automatically activate the fight and flight response (19). This bottom-up mechanism that facilitates automatic fear before full identification of the nature of the threat is advantageous for survival in the face of immediate danger. However, because it is impervious to conscious cognitive controls, it can become maladaptive and might constitute a substrate for phobic fears (20).

Fear conditioning can also involve higher-order processes in animals. In a seminal review, Rescorla (21) argued that conditioning involves learning the relationship between events as well as the memory representation of the US and that it is influenced by past experience and contextual variables. Furthermore, although rodents without cortices can learn a fearful response to a CS (16,18), the cortex is necessary for more elaborate learning involving complex stimuli. For example, rabbits undergoing differential conditioning procedures where only one of two tones was associated with a shock responded to both tones after lesions of the auditory cortex (22). Similarly, the hippocampus is necessary for conditioning to contextual stimuli (23,24). Thus, parallel conditioning mechanisms operate in animals; complex conditioning engages higher-order processing, whereas simpler forms of conditioning (e.g., single cue) rely on lower-order processing. This dual mechanism is particularly relevant to our understanding of drug effects on conditioning. Because lower- and higher-order fear-learning rely on different neural structures, a treatment that affects one type of conditioning would not necessarily be expected to influence the other type of conditioning. Notably, DCS studies in animals have mostly relied on single-cue fear conditioning, suggesting that DCS might operate largely on lower-order processes.

A Dual-Model Theory of Fear Conditioning

The extent to which animal conditioning findings apply to humans is of particular concern, precisely because humans are endowed with a well-developed cognitive system capable of relational learning, defined as the controlled reasoning ability to infer relationships between events (13,20). Although modern theories view fear conditioning learning in animals in terms of associative learning and anticipatory responses (21), the nature of conditioning in rodents and in humans is quite different. Cognitive processes in rodents might be the precursors of high-order cognitive processes and language in humans, but they are not equivalent. Human subjects enter the laboratory with unique motivations and expectations likely to influence the CR. Hence, a critical issue in human research involves the degree to which the CR depends on fast, automatic, and low-level processes versus a more cognitive response that could be couched in terms of relational learning, conscious thoughts, and anticipation (11,13,14,25). Most likely, both lower- and higher-order processes are involved; a dual-model theory of fear conditioning is the simplest explanation for conditioning data in humans (10,11).

A dual-model theory of conditioning is consistent with current conceptions of human learning and memory that distinguish between implicit, lower-order mechanisms that are rapid, automatic, and inaccessible to awareness and explicit, higher-order processes that are slow, deliberate, and conscious (12,26). An important difference between conditioning in humans and animals is that humans can report their awareness of the CS–US contingency. Several studies using various procedures demonstrate that conditioning can take place in the absence of contingency awareness (27). For instance, backward masking is a technique in which a visual test stimulus is briefly presented, then followed closely by another salient visual stimulus that "masks" the perception of the test stimulus. With this approach, it has been shown that CRs can be evoked by backwardly masked CS (28,29). In addition, neurological patients who cannot see the CS due to cortical blindness can exhibit a CR to a visual CS (30). Consistent with Ledoux's subcortical fear mechanism, a direct subcortical pathway to the amygdala that bypasses sensory cortices has been identified in humans (31), providing a substrate for automatic fears that arise independent of cognitive control.

In humans, conditioning can also rely on high-level cognitive factors involved in consciously learned causal relationships between events and anticipation. In fact, most studies show that CRs to nonmasked CSs rely strongly on awareness of CS–US contingency (14,28,29,32,33). Proponents of the cognitive view of conditioning postulate that CRs are mediated by anticipation of and preparation for the US (13,14).

Both low- and high-order processes are engaged by traumatic events (10), but these can also be dissociated in humans with rare brain lesions. Explicit learning requires an intact temporal lobe (hippocampus and related cortical areas), but implicit learning can be demonstrated in patients with hippocampal damage (12). For instance, Bechara *et al.* (34) reported that a patient with selective hippocampal damage showed no awareness of CS–US contingency but exhibited normal CR, whereas a patient with selective amygdala lesions could report the CS–US contingency but no CR. In addition to using backward masking techniques, implicit learning can also be facilitated in healthy subjects via the use of fear-relevant stimuli (e.g., snake) (28), a short CS–US interval (35), or intense US (36).

Social Learning: Vicarious Conditioning and Verbal Communication

Fear conditioning is one among several mechanisms of fear learning. Other fear learning mechanisms include vicarious conditioning and verbal information (37). Vicarious conditioning, which does not involve an encounter with an aversive stimulus, has been observed in several animal species (38–40) as well as humans (41). Verbal information, which also does not involve an encounter with an aversive stimulus, is a powerful way to acquire fears unique to humans (41). Subjects instructed to expect noxious stimuli display robust fear, even when no noxious stimuli are actually administered (42). Similarly, negative information provided by adults can greatly influence children's fear of an object with which they have no prior experience (43). Retrospective studies show that most normal and clinical fears in children are acquired through a combination of these three learning mechanisms (44).

A key question concerns the extent to which mechanisms of fear extinction differ among these different learning pathways. Differences in extinction mechanisms raise the possibility that they could be differently affected by a variety of therapeutic interventions, including DCS. There is preliminary evidence suggesting that fear and vicarious conditioning might involve automatic processes, whereas verbal information might not (36,41).

Effects of DCS on Extinction and EBT

Studies in rodents indicate that extinction can be blocked by NMDA antagonists via NMDA receptor-dependent neural plasticity within the basolateral amygdala (45,46). In rats, DCS, which is a partial NMDA agonist, facilitates extinction when administered just before as well as up to 60 min after extinction training

(7–9), suggesting that DCS facilitates the consolidation of extinction learning rather than extinction learning per se (47). In addition, single-dose treatments seem to be more effective than repeated treatments, perhaps because chronic treatment with DCS abolishes its activity at the NMDA receptor (48). In fact, the facilitating effect of DCS on extinction is suppressed by a single pre-exposure dose of DCS given shortly before treatment (48).

The facilitation of DCS on extinction has proven to be clinically useful. The first published study examined the effect of 50 mg and 500 mg DCS during two EBT sessions for height phobia (1). DCS significantly improved symptoms 1 week and 1 month after treatment. A second study showed greater improvement in social phobic subjects who received brief EBT combined with 50 mg DCS (2). These initial positive results were extended to the treatment of obsessive compulsive disorder (OCD) in two studies (4,5) but not in a third one (49). Overall, four of five clinical studies confirmed the efficacy of a treatment strategy combining DCS with EBT in humans.

In contrast to the positive results obtained in clinical studies of patients with a DSM-diagnosed anxiety disorder, investigations in nonclinical samples have surprisingly been unanimously negative. Two studies of individuals with nonclinical spider phobia found that 50 mg or 500 mg of DCS did not facilitate a one-session EBT when post-treatment assessment was conducted on the same day as treatment or 1 month later (50). The DCS's lack of same-day efficacy is consistent with animal data indicating that DCS does not facilitate extinction learning per se and requires a period of extinction consolidation; however, it cannot account for the negative effect at follow-up. This negative result was attributed to the use of a subclinical population with less severe symptoms as well as the substantial efficacy of EBT, which left little room for improvement (50).

Similarly, studies of laboratory-based fear conditioning in healthy control subjects unanimously failed to show that DCS facilitates extinction. It is important to note at the outset that all these studies used conditioning procedures that tap into higher-order cognitive processes. In the first two studies of a three-study investigation, DCS was administered between acquisition and extinction training that took place on the same day (51). DCS did not facilitate extinction when tested 1 day later. The negative findings were attributed to DCS influencing both acquisition and extinction. This possibility was eliminated in the third study, where DCS was given before extinction training conducted 1 day after acquisition. Again, DCS did not facilitate extinction. Similar results were found in an analysis restricted to individuals with the best conditioning, eliminating the possibility that a floor effect masked DCS's effect.

A recent study used a complex design to examine the effect of 500 mg of DCS on conditioning (52). DCS was administered during a session that involved acquisition training in one context followed by extinction training in a different context. As noted earlier, one problem with such a design is that DCS could influence both learning processes. Results showed retention of fear conditioning in the acquisition and extinction contexts only in the DCS group during a recall test 72 hours after the acquisition/extinction session; according to the authors, this finding suggested that DCS facilitated fear acquisition (52). However, the persistence of conditioned fear in the extinction context could also be interpreted as suggesting that DCS actually impaired rather than facilitated extinction.

Basic methodological differences could explain disparities between human and animal findings. One key difference is the method used to measure conditioned fear in humans and in animals. Human studies traditionally rely on the skin conductance response (51,52), whereas rodent investigations use freezing or the startle response to assess fear. Notably, skin conductance is a rather indirect index of fear that reflects orientation to a stimulus as a function of its relevance and not necessarily its emotional significance (14,53). The negative findings in humans might thus have been due to the use of indirect measures of conditioned fear. In contrast, the startle reflex, a well-validated cross-species measure of fear conditioning (54), might be a more sensitive index of the type of conditioning that DCS influences; however, this possibility was not substantiated by two recent studies that found that DCS did not facilitate extinction as measured with the startle reflex (J.P.M. Bass, unpublished data, August 2008; C.G., unpublished data, January 2007). Both studies involved differential fear conditioning with a noxious shock as the US. Additionally, in both studies the dose of DCS (250 mg) (C.G., unpublished data, January 2007) or 50 or 500 mg (J.P.M. Bass, unpublished data, August 2008) was administered 2 hours before a short extinction training trial that took place 24 hours after acquisition; the test of extinction retention was conducted 48 hours after extinction, to allow consolidation of extinction learning. The negative findings obtained by these two studies are especially puzzling, given that the initial finding of DCS-induced facilitation of extinction in rodents was based on fear-potentiated startle (9).

The conflicting results between human and animal conditioning studies do not seem to be caused by significant methodological differences. Most of the general procedures used in rodent investigations (i.e., DCS dose, time of administration, separate sessions for acquisition and extinction training as well as retention testing) were replicated in several of the human studies. However, one potentially important difference between conditioning procedures used in DCS studies in animals and humans is that animal studies rely on only one CS (single-cue conditioning), whereas human studies involve at least two CS (e.g., differential conditioning). It is possible that single-cue and differential conditioning engage different mechanisms (lower- and higher-order processes, respectively) that are differentially sensitive to DCS.

Interpreting Therapeutic Effects of DCS During EBT: Implications from a Two-Level Theory of Fear Conditioning

A dual-model theory of fear conditioning implies dissociable neural systems that might be affected differently by DCS and other therapeutic treatments. All laboratory-based DCS/fear conditioning experiments in humans have examined higher-order cognitive learning with negative results. The positive results in rodent studies suggest that DCS acts on lower-level learning mechanisms—as the single-cue conditioning studies suggest. Hence, DCS might affect lower-order but not higher-order processes. Consequently, DCS might affect the implicit learning that takes place during EBT.

Both implicit and explicit cognitive processes are important in the etiology and treatment of anxiety disorders (55–57). Cognitive bias theories posit that vulnerability to anxiety stems from dysfunctional, early, preattentive mechanisms that assess the threat value of stimuli; a later stage of attentional allocation is affected by the exaggerated output of the former mechanism and thus becomes excessively active (28,58). Similarly, conditioning models of fear and phobia place a strong emphasis on implicit learning in phobic- and trauma-related emotional memories (10,59). These models assume that a traumatic or frightening stimulus (i.e., a US) becomes associated with a benign stimulus

(i.e., a CS) without formation of explicit memory. Subsequent exposure to the benign stimulus with minimum sensory input leads to a fast and automatic activation of the subcortical fear network, which occurs with little or no conscious awareness of the stimulus. One aim of EBT is to deactivate these automatic fear responses (55,57,60,61).

Exposure-based therapy attempts to correct dysfunctional cognition, emotion, and behaviors with various techniques such as flooding, systematic desensitization, and implosive therapies. These techniques are highly effective for the treatment of a range of anxiety disorders (62–66), but there is little agreement as to how they work (67,68). Exposure-based therapy can be traced back to Mowrer's two-factor theory of avoidance learning (69) and to classical conditioning principles positing that anxiety can be eliminated through extinction via direct experience with the unreinforced fear-producing CS acting via lower-order processes (60). Interpretations relying essentially on cognitive processes have also been proposed (68). More likely, EBT engages both implicit and explicit mechanisms. Current connectionist models consider that fear is represented in memory-based networks of associations or nodes that integrate perceptual, cognitive, and behavioral tendencies leading to implicit processing bias (56,69). These models are consistent with the view that therapeutic effects of EBT entail activation of implicit and explicit mechanisms leading to synaptic changes that alter how the fear network functions and reduces processing bias (67). In fact, changes in lower-level automatic bias are postulated to be keys to treatment effectiveness (55). Supporting evidence has been recently reported. Specifically, changes in automatic fear association during the course of treatment predict symptom improvement in phobic (61) and in panic disorder (57) patients. These automatic fear associations might be the target of DCS's effects.

If DCS enhances EBT in phobias, why was no such facilitation observed in the study of individuals with nonclinical fear of spiders described in the preceding text (50)? It is possible that DCS's effectiveness is restricted to severe phobic fears in DSM-diagnosed clinical samples; specifically, because fears are less severe and persistent in nonclinical phobias, EBT might reduce fear to a floor level so that further improvement cannot be gained with DCS (70). More speculatively, the lower-order, automatic mechanisms on which DCS operates might play a more pivotal role in clinical phobias than in nonclinical fears. This could be caused by differences in the mode of fear acquisition. Because experiential/vicarious conditioning can lead to automatic CR but verbal communication cannot (41), it is possible that clinical phobias result from the former type of conditioning and nonclinical phobias from the latter. Preliminary evidence suggests that experiential/vicarious conditioning plays a greater role in clinical phobias than in common developmental fears in children (71). In addition, childhood phobias are far more likely to be associated with experiential or vicarious conditioning than with verbally mediated information (72). For example, 41%, 19%, and 5% of children with spider phobia attribute their phobia to direct conditioning, observational learning, and verbal information, respectively (73).

Little is currently known about the effect of DCS on cognitive processes in general in humans. The effects of DCS on explicit learning and memory, if any, seem to be very limited. For instance, DCS (50 mg) do not affect verbal and continuous performance tasks (74) and has no effect on verbal and nonverbal explicit cognitive tasks with nonemotional stimuli (75). Clearly, research needs to be extended to investigate DCS effects on implicit forms of learning and memory.

Alternative Possibilities

At least three variables seem to play a key role in DCS's effectiveness: dose, the time of administration relative to extinction learning, and the number of extinction trials. First, the dose of DCS must be optimal; too little might not affect NMDA receptors and too much might reduce NMDA receptor function (76). However, a recent meta-analysis indicated that, within the range used in human and animal studies, the dose of DCS was not significantly associated with its effect, including in nonpatient studies (70).

Second, DCS should be given at a time that ensures that peak plasma levels are highest during postextinction memory consolidation; according to rodent studies, this occurs 1 to 2 hours after learning (77) but continues in waves lasting 1 to 2 days (78). In addition, extinction retention testing should take place during the postconsolidation period. These two requirements have been fulfilled in several nonpatient studies. For instance, DCS was given shortly before (1 to 2 hours) extinction learning or to EBT in all nonpatient studies. The DCS levels peak 4 to 8 hours after oral administration, which corresponds to the peak period of postextinction memory consolidation in these studies (70). Furthermore, extinction testing took place 24–48 hours after extinction learning in several studies ([51] and J.P.M. Bass, unpublished data, August 2008; C.G., unpublished data, January 2007). Thus, the failure to find an augmenting effect for DCS on extinction in nonpatients cannot be attributed to inadequate timing of drug ingestion or extinction testing.

Third, excessive numbers of extinction trials could reduce fear, so that such trials would not benefit from DCS augmentation (50,70). As noted in the preceding text, several nonpatient studies found that DCS had no beneficial effects despite significant recovery of fear during the extinction test phase ([51] and C.G., unpublished data, January 2007). These results are inconsistent with the view that DCS does not affect extinction in humans due to inappropriately low fear levels.

Although too many extinction trials can lead to too much extinction, too few trials might reactivate conditioned fear rather than extinguish it. In rodents, DCS facilitates retention of extinction only if there is successful extinction underway during extinction training (79–81). In fact, with too few extinction trials, DCS can lead to increased rather than decreased fear, perhaps because DCS facilitates memory reconsolidation (81) (but see [79]). Human studies usually rely on small numbers of extinction trials, but this does not prevent initiation of extinction, as shown by a progressive reduction in CR during extinction learning ([51] and J.P.M. Bass, unpublished data, August 2008; C.G., unpublished data, January 2007). It is unlikely that DCS's failure to facilitate extinction in humans is due to reduced number of extinction trials. Nevertheless, there might be an optimal number of extinction trials required for DCS to operate, and future studies should investigate whether DCS's effectiveness depends on this variable.

Conclusions

Despite the effectiveness of DCS as an adjunct to EBT in clinical studies, the learning mechanisms on which DCS operates remain largely unknown. The lack of efficacy of DCS on extinction in human laboratory-based experiments and as a treatment for subclinical fears provides important clues as to the potential learning mechanisms that it affects. More specifically, DCS might facilitate extinction and EBT specifically by modulating low-order, automatic learning. One implication of this view for

psychological treatment is that DCS's effectiveness would be expected to be greater for EBT compared with cognitive therapy (e.g., cognitive restructuring).

A more general implication of a two-level theory of fear conditioning for translational research is that investigators should be mindful of important cross-species differences when conducting conditioning studies. First, the nature of conditioning (e.g., single-cue vs. differential or contextual conditioning) might promote the use of lower-order or higher-order processes. In addition, noxious US must be perceived to be potentially lethal in animals. In human experiments, US are comparatively mildly aversive and pose no threat to survival. Mild US are less likely to activate automatic CRs than more intense US (35). Second, the nature of the cognitive processes involved in rodents (21) and humans are likely to be very different; volitional attention strongly influences CR in humans. Human research would more greatly benefit from basic research if more complex conditioning procedures engaging higher-level cognitive processes were used in animals (e.g., context conditioning, differential conditioning). Similarly, human research should devote greater efforts to developing robust conditioning experiments that are more impervious to cognition. Ideally, the best way to examine the effect of DCS on extinction in laboratory-based conditioning in humans would be to use fear-relevant CS, short CS–US intervals during acquisition, an intense US, and masked CS presentation during extinction.

Many practical questions remain unanswered concerning the mechanisms of action of DCS on conditioning processes, and the specific factors that affect DCS's effectiveness, such as the dose/time of treatment or the number of exposure/extinction trials. These questions can also be extended to other therapeutic interventions that might influence conditioning processes (acquisition, extinction, consolidation, reconsolidation) with potential implications for human mental health (e.g., β-blockers, cortisone). Traditionally, these issues have been addressed via clinical trials, but clinical trials with patients are challenging, costly, and time-consuming. As an alternative, laboratory-based fear-conditioning procedures present several advantages (e.g., low cost, easy-to-recruit nonclinical samples). Thus, fear conditioning in humans is an important step toward better characterization of drug effects on conditioning processes to inform clinical treatment. However, for the cross-fertilization of basic science and psychological science to benefit clinical science, the need to develop a better understanding of fear-conditioning mechanisms and refine conditioning procedures in humans and in animals is key.

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