Amino Acids (1994) 6: 247–260

Amino
Acids

D-Cycloserine: Agonist turned antagonist

Review Article

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Accepted October 4, 1993

Summary. D-Cycloserine can enhance activation of the NMDA receptor complex and could enhance the induction of long-term potentiation (LTP). In animals and humans, D-cycloserine can enhance performance in learning and memory tasks. This enhancing effect can disappear during repeated administration. The enhancing effects are also lost when higher doses are used, and replaced by behavioral and biochemical effects like those produced by NMDA antagonists. It has been reported that NMDA agonists, applied before or after tetanic stimulation, can block the induction of LTP. This may be the result of feedback inhibition of second messenger pathways stimulated by receptor activation. This may explain the antagonist-like effects of glycine partial agonists like D-cycloserine. In clinical trials of D-cycloserine in age-associated memory impairment (AAMI) and Alzheimer's disease, chronic treatment provided few positive effects on learning and memory. This may be due to inhibition of second messenger pathways following chronic stimulation of the receptor complex.

Keywords: Amino acids – D-Cycloserine – Glycine site – Partial agonist – Learning and memory – Long-term potentiation – Alzheimer's disease

Dementia, and other disorders of learning and memory, affect millions of people and create a tremendous burden on family and society. Until relatively recently, experimental treatments for learning and memory disorders have had to be based on whole animal testing in presumed learning and memory tasks. While this approach can be effective it has also produced many false positives. This is probably due to the large number of variables involved in whole animal behavior.

Long-term potentiation (LTP), a persistent enhancement of synaptic responses, is a candidate for a physiological mechanism underlying learning and memory. The conditions and pattern of stimulation which induce long-term

potentiation are reminiscent of those which produce conditioning (Levy and Steward, 1979, 1983; Kelso et al., 1986). In addition, the very long persistence of LTP (weeks) is reminiscent of memory (Bliss and Gardner-Medwin, 1973; Bliss and Lømo, 1973). If LTP is a critical physiological mechanism of learning and memory, then specific modulation of LTP may both underlie disorders of learning and memory and their treatment.

The pharmacologies underlying LTP are presently being worked out. However, it is widely accepted that at some synapses activation of the N-methyl-D-aspartate (NMDA) receptor/channel complex is necessary for the induction of LTP (Collingridge et al., 1983; Harris et al., 1984). This has been demonstrated by use of selective antagonists of the NMDA complex including antagonists of the NMDA recognition site (Harris et al., 1984; Walker and Gold, 1991), uncompetitive (with respect to L-glutamate) antagonists of the PCP/MK-801 site (Stringer et al., 1983; Coan et al., 1987), and noncompetitive (with respect to L-glutamate) antagonists of the NMDA receptor-associated glycine site (Izumi et al., 1990; Oliver et al., 1990; Watanabe et al., 1992). Involvement of the NMDA receptor complex is also suggested by the pattern of stimulation which is most favorable to inducing LTP (Larson et al., 1986). This pattern involves a single stimulus followed by a short train about 200–250 msec later. The first stimulus blocks subsequent activity through the inhibitory GABA system, thus disinhibiting responses, while the short train of stimuli produce a cumulative depolarization. This combination of disinhibition and depolarization are sufficient to both activate the NMDA acidic amino acid and glycine recognition sites and to remove the tonic magnesium block of the NMDA receptor-associated channel. The most effective intervals between the first stimulus and the short train correlate well with the frequency of the theta rhythm, an endogenous 4–7 Hz EEG rhythm which, in the hippocampus, has been correlated with learning (Berry and Thompson, 1978; Winson, 1978). This endogenous rhythmic activity appears to be perfectly designed to activate the NMDA receptor complex.

It has been shown that NMDA receptor complex antagonists can block learning as would be predicted if LTP is critical for learning (Morris et al., 1986; Danysz et al., 1988; Danysz and Wroblewski, 1989). More importantly, Davis et al. (1992) have shown that an NMDA complex antagonist, D-AP5, blocks learning at concentrations very similar to those which block the induction of LTP. NMDA antagonists do not block memory consolidation, i.e. do not affect performance once learning has occurred (Danysz et al., 1988; Watanabe et al., 1992). If the maintenance of LTP is the basis for memory, then this result would be predicted since NMDA antagonists do not block LTP once it has been established (Collingridge et al., 1983).

Agonists of the glycine site on the NMDA receptor complex increase the probability of activating the NMDA receptor-associated channel (Johnson and Ascher, 1987; Kleckner and Dingledine, 1988). Given that activation of the NMDA receptor complex is important for the induction of LTP, then glycine agonists, which increase its activation, should increase the probability of inducing LTP. It has been reported that the glycine site agonist, D-serine, will increase the magnitude of LTP *in vivo* (Thiels et al., 1991). Presumably this was due to increasing the probability of inducing LTP in some higher threshold units.

However, since a substantial amount of LTP was induced by the stimulation alone, the true potential for a glycine agonist to enhance the induction of LTP was probably not assessed in this study.

The potential for a glycine agonist to increase the induction of LTP will be dependent on the endogenous level of glycine. If the glycine site is saturated, further increases in the concentration of agonists cannot increase the probability of induction of LTP. Several pieces of data, including the effects of D-serine mentioned above, suggest that the glycine site is not normally saturated (Thomson, 1990). However, the true concentration of glycine near its binding site is difficult to assess. D-cycloserine is an antibiotic which has been used mainly as a tuberculostatic (Mandell and Sande, 1985). Recently it has been found that D-cycloserine interacts with, and is a partial agonist of, the glycine site of the NMDA receptor complex with an EC_{50} of about 3 μM (Monahan et al., 1989; Hood et al., 1989; Watson et al., 1990). D-cycloserine has been reported to have an efficacy of 40–70% of that of glycine (Hood et al., 1989; McBain et al., 1989; Watson et al., 1990; Henderson et al., 1990). In the presence of low levels of glycine, D-cycloserine will increase the probability of activation of the NMDA receptor-associated channel. At higher levels of glycine, D-cycloserine will reduce activation of the NMDA receptor-associated channel – down to the efficacy of D-cycloserine itself. Based only on its interaction with the glycine site itself, D-cycloserine should never completely block activity at the NMDA receptor complex.

D-cycloserine has a number of features which make it especially attractive for investigating the role of the glycine site in learning and memory *in vivo*. It is very bioavailable (Anderson et al., 1956; Conzelman, 1956; Nair et al., 1956; Spencer and Payne, 1956). In addition, it is brain-bioavailable, with CSF levels similar to plasma levels (Hanngren et al., 1962). Its partial agonist character suggests that D-cycloserine will not potentiate toxicity associated with excessive stimulation of the NMDA receptor complex. Its partial agonist character can also be used to estimate the functional level of activation of the glycine site. If the glycine site is normally saturated, then D-cycloserine should provide no enhancement of learning – it may even be somewhat deleterious. However, if the glycine site normally encounters a low concentration of glycine, then D-cycloserine may enhance learning.

Another attractive feature of D-cycloserine is the fact that it has been used clinically for many years and its side-effect profile is well-known. At the high doses used for tuberculostatic treatment (e.g. 500–2,000 mg/day) D-cycloserine can produce a number of side-effects. Many of the side-effects involve the CNS (Mandell and Sande, 1985), confirming its entry into the CNS. These side-effects include grand mal seizures and psychosis (Lewis et al., 1957). At these same doses, it has been reported that D-cycloserine can be antidepressant and anxiolytic (Crane, 1959, 1961). These side-effects appear to be dose-related and are mainly associated with doses of greater than 250 mg at one time (Nair, 1957). CNS side-effects mainly occur at plasma levels above 30 μg/ml (Lewis et al., 1957; Epstein et al., 1958–9; Simeon et al., 1970), about 300 μM D-cycloserine.

In light of the strong mechanistic basis for a salutatory effect of D-cycloserine in learning and memory disorders, along with its excellent bioavailability, inves-

tigators at G. D. Searle & Co. (and others) sought to study its effects in animals and in humans. Handelmann et al. (1988) first reported that D-cycloserine (3–30 mg/kg, ip) would enhance performance of rats on a passive avoidance task when given prior to the training session. This result is consistent with an enhancement of learning. The performance-enhancing effects of D-cycloserine were dose-dependent, but exhibited an "inverted-U" dose-response relationship, i.e. both low and high doses were ineffective. It is useful to note that the type of passive avoidance task used, one in which there is a strong motivation to leave the initial position, is dependent on activity of the hippocampus. LTP at the Shaffer collateral/commissural-CA1 synapse in the hippocampus is known to be dependent on activation of the NMDA receptor complex. Also of note, the experimental parameters used by Handelmann et al. (1988) produced only a very weak aversion for the shock compartment. Monahan et al. (1989) further showed that 3 mg/kg, ip, D-cycloserine could enhance reversal learning in rats on a T-maze task. This result is also consistent with activity in the hippocampus since reversal learning, but not initial position learning, in a T-maze, is adversely affected by a hippocampal lesion (O'Keefe and Nadel, 1978).

A number of other investigators have also reported that D-cycloserine can enhance performance given prior to training, when it can affect learning. Thompson et al. (1992) reported that 6 mg/kg, im, D-cycloserine strongly enhanced acquisition of a delay classical conditioning task in young rabbits, cutting the number of trials to criterion in half. Interestingly, they showed similar results with an antibody that also has the characteristics of a glycine site partial agonist (Haring et al., 1991). More recently, Disterhoft et al. (1993) have found that D-cycloserine also enhances acquisition of the same task in aged rabbits. Aged rabbits show a marked deficit in this task. D-cycloserine can improve their performance to the level of normal young rabbits. In both young and aged rabbits, D-cycloserine's effect was dose-dependent. In the young rabbits, evidence for an 'inverted-U' dose-response relationship was seen. This was not seen in the aged animals. This may have been due to the limited number of doses studied since the downward swing of the dose-response relationship in young animals occurred only at the highest dose of D-cycloserine tested and D-cycloserine appeared to be less potent in the aged rabbits. Delay conditioning is different from standard trace conditioning in that a short delay (600 msec) is interposed between the end of the conditioned stimulus and the onset of the unconditioned stimulus. This change in experimental parameters changes the task from one in which hippocampal activity tracks the task, but is not critical for performance – trace conditioning – to one in which a hippocampal lesion severely reduces the ability of the rabbits to acquire the task (Moyer et al., 1990). Thompson and Disterhoft (1991) have also shown that phencyclidine, an uncompetitive antagonist of the NMDA receptor complex, can disrupt acquisition of the delay conditioning task.

Quartermain et al. (1993) have found that D-cycloserine strongly enhances performance in mice on a linear maze when given prior to training. Mice given 3 mg/kg, sc, D-cycloserine learned the task to criterion in half the number of trials taken by vehicle-treated mice. Although its involvement has not been tested directly, the hippocampus also can be expected to be involved in the

learning of this spatial task (O'Keefe and Nadel, 1978). A number of authors (Sirviö et al., 1992; Baxter et al., 1993; Fishkin et al., 1993; Lehmann et al., 1993; McNaughton and Barnes, personal communication) have used the spatially-cued version of the Morris water maze to investigate the effects of D-cycloserine in rats. Although positive effects have been reported by some of these groups in normal, scopolamine-treated, and aged rats, the magnitude of the enhancement is quite small. This is somewhat surprising given the involvement of the hippocampus and hippocampal LTP in learning this task. However, the quickness with which this task is acquired may make it difficult to produce large improvements in learning. Schuster and Schmidt (1992) reported that D-cycloserine was effective in ameliorating the deficit in learning an 8-arm radial maze produced by a quinolinic acid lesion of the hippocampus. The 8-arm radial maze is a standard task for testing the behavioral function of the hippocampus.

It is therefore clear that D-cycloserine can enhance performance when given prior to training. This is consistent with an effect on learning, and consistent with an increased probability of inducing LTP, especially in the hippocampus. Two investigations of the effects of D-cycloserine on LTP in rats have been carried out. Riekkinen (personal communication) found an increase in LTP after a single dose of 10 mg/kg, ip D-cycloserine in rats. However, McNaughton and Barnes (personal communication) reported no increase in the amplitude of LTP, and possibly a shortening of its time-course, during repeated exposure to 10 mg/kg, ip, D-cycloserine. Although this lack of concensus is not encouraging, it may be noted that the major predicted effect of D-cycloserine of LTP would be on probability of occurrence rather than magnitude. These studies were not specifically designed to investigate probability of occurrence. In addition, as discussed later, the repeated exposure paradigm used by McNaughton and Barnes may have contributed to the lack of effect of D-cycloserine.

Unexpectedly, the performance-enhancing effects of D-cycloserine are not restricted to learning. Monahan et al. (1989) reported that D-cycloserine enhanced performance on a passive avoidance task when given immediately after training or just prior to testing. The effects were almost as large as when it was given prior to training. Flood et al. (1992) reported that D-cycloserine enhanced weakly trained performance in mice on a T-maze shock avoidance task when given immediately after the training trials. The significantly effective doses in mice were 10-40 mg/kg, sc. An 'inverted-U' dose-response relationship was found. On the other hand, in studies to determine the appropriate dose-range, Flood (personal communication) found that 40 mg/kg, ip, D-cycloserine could disrupt test performance when given following training which resulted in a strong memory. This amnestic effect is seen with most cognitive enhancing agents under these conditions (J. Flood, personal communication). Quartermain et al. (1993; personal communication) have reported that D-cycloserine can improve performance of mice and rats when given following training or just prior to testing on a number of tasks, including passive avoidance, 2-way active avoidance, a brightness discrimination task, and the linear maze mentioned above. An 'inverted-U' dose-response relationship was seen when dose-response studies were carried out. In most cases, the active doses were between 3 and 20 mg/kg. ip. In contrast to the results of Monahan et al. (1989), Quartermain et

al. reported that the effects of D-cycloserine (on linear maze performance) were greater when administered prior to training than when administered following training. On the other hand, Rupniak et al. (1992) reported that D-cycloserine did not reverse scopolamine or PCP-induced impairments in rhesus monkeys on a well-learned delayed spatial matching to sample test when administered in similar doses (on a mg/kg basis) as were effective in some tests with rats and mice. It may be worth noting that the half-life of D-cycloserine in rhesus monkey is much longer than in small mammals (Conzelman and Jones, 1956), so that the real doses may have been significantly higher in the rhesus. Taken together, these results indicate that D-cycloserine can enhance (with some exceptions) performance by affecting processes other than learning, in particular it may enhance memory consolidation and memory retrieval. In some cases, the effects of D-cycloserine are largest when given prior to training, i.e. when it could enhance learning as well as memory consolidation.

Although NMDA antagonists have no effect on performance when administered following training, indicating that NMDA receptor activity is not critical to memory consolidation, it may be that NMDA receptor-containing circuits may be able to facilitate the process of consolidation. The effects of NMDA antagonists on test performance have not been specifically studied. However, it is well-known that NMDA antagonists can impair motor activity, suggesting that they could have motor or sensory effects that could affect learned behavior (e.g., Mondadori et al., 1989; Davis et al., 1992). It is also known that the tonic discharge of visual cortex neurons can be reduced by NMDA antagonists (Fox et al., 1989). This also suggests that NMDA antagonists can produce sensory deficits. It has been suggested that the overall effects of D-cycloserine may be consistent with an enhancement of selective attention (Handelmann, personal communication). However, a specific test for selective attention is not available. Many of the effects of D-cycloserine could also be explained if it possessed either reinforcing or aversive properties. However, Herberg and Rose (1990) found no indication that it affected self-stimulation rates suggesting that it was neither reinforcing or aversive.

In light of what is known about NMDA receptor complex-dependent LTP and neural structures critical to learning, it is reasonable to predict that tasks involving the hippocampus would be especially, and in some cases selectively, affected by D-cycloserine. In particular, NMDA antagonists block acquisition of the spatially-cued Morris water maze, but not a visual discrimination in the water maze (Morris et al., 1986). This is consistent with the effects of hippocampal ablation on these same types of tasks. However, the effects of D-cycloserine do not appear to be restricted to hippocampally mediated tasks (O'Keefe and Nadel, 1978). Quartermain et al. (personal communication) have found that D-cycloserine can enhance a brightness-signaled lever press reversal task. Performance on this type of task would probably not be affected by a hippocampal lesion or by NMDA antagonists. In addition, the T-maze avoidance task used by Flood et al. (1992) is also a task for which the hippocampus is not likely to be critical for learned performance. While it is not unreasonable that an agonist may have effects beyond that of an antagonist, these results do make it clear that additional neural processes are involved in the effects of D-cycloserine. Whether

such effects can be subsumed under one psychological process, such as selective attention, is not clear at this time.

Most of the performance-enhancing effects of D-cycloserine exhibit an 'inverted-U' dose-response relationship. The loss of an effect at higher doses is often attributed to a toxicity or lack of specificity at these higher doses. However, this is difficult to assess using whole animal behavior. This 'inverted-U' dose-response relationship has also been reported for D-cycloserine's effects on biochemical measures, in particular, its effects on cerebellar cGMP. Emmett et al. (1991) have reported that D-cycloserine can increase cerebellar cGMP, but that at higher doses this effect diminishes. In fact, at higher doses, D-cycloserine reduces the basal level of cGMP. It can also completely block the increase in cGMP expected following administration of D-serine (a full-efficacy glycine site agonist). A detailed time-course of the effects of a high dose of D-cycloserine revealed that there was an increase in cGMP early on followed by a reduction in content thereafter. These antagonist-like effects have been attributed to the partial agonist character of D-cycloserine (Emmett, 1991). However, these effects are not consistent with partial agonism. In the face of a constant concentration of endogenous glycine, D-cycloserine should produce either a submaximal agonist or submaximal antagonist effect, but not both. In order to produce both effects, it must be producing additional effects, e.g. changing the concentration of glycine. Moreover, under no condition should D-cycloserine produce complete antagonism either of cGMP or learned performance. However, both effects have been reported. This strongly suggests that D-cycloserine must produce effects in addition to increasing the probability of opening the NMDA receptor-associated channel.

Activation of the NMDA receptor complex can be required for the induction of LTP. However, at the same synapses, it has been reported that inappropriately timed stimulation of the NMDA receptor complex can block the subsequent (or previous) induction of LTP by a tetanic stimulus (Coan et al., 1989; Huang et al., 1992; Izumi et al., 1992a). Inappropriately timed means activation of the NMDA receptor complex at times other than during the tetanic stimulus. Therefore, NMDA and the endogenous NMDA agonist (L-glutamate?) can act like an NMDA receptor complex antagonist. Izumi et al. (1992b) have provided evidence that the antagonist effects of NMDA on LTP are due to the production of NO since they are mimicked by NO-releasing compounds and blocked by NO synthase inhibitors. These investigators have also reported that prior stimulation of the NMDA receptor complex does not reduce the NMDA-dependent portion of the synaptic EPSP in CA1. This suggests that activity of the NMDA receptor-associated channel *per se* is not reduced by prior activation of the receptor complex, and that only certain biochemical processes, normally enhanced by NMDA complex stimulation, are blocked. It is not known whether this inhibition of second messenger-initiated events (i.e., LTP) is due to end-product feedback inhibition of biochemical pathways.

Emmett et al. (1991) have reported that D-cycloserine can completely inhibit increases in cerebellar cGMP following administration of D-serine. Increases in cGMP are known to result from the release of NO. Therefore, the antagonist-like effects of D-cycloserine on cGMP may be part of the same mechanism by which

NMDA agonists can block the formation of LTP. Thus high concentrations or prolonged stimulation of the glycine site, producing strong or prolonged stimulation of NMDA complex-linked biochemical processes, may result in an antagonist-like effect of glycine site agonists. Tentative support for this notion is provided by the clinical side-effects of high doses of D-cycloserine itself. These side-effects which include psychosis, antidepressant effects and anxiolytic effects (Crane, 1959; Crane, 1961; Simeon et al., 1970; Mandell and Sande, 1985) sound very much like effects of NMDA antagonists in humans and animals. For example, compounds acting at the MK-801/PCP site are well-known to be able to release a schizophrenia-like psychosis in humans (Luby et al., 1959). In animals, NMDA antagonists are active in a number of antidepressant, anxiolytic, and anticonvulsant models (e.g., Leander et al., 1988; Dunn et al., 1989; Trullas et al., 1989, 1990). In addition, D-cycloserine has been shown to possess anticonvulsant properties in animals (Peterson, 1992). In this regard, it is interesting to note that NMDA receptor complex antagonists, like the glycine antagonist 7-chlorokynurenate (Peterson, 1992), block the anticonvulsant effect of D-cycloserine. This is most easily understood if the anticonvulsant effect of D-cycloserine were a result of its agonist properties, but not if they were due to its antagonist effects. Therefore, it appears that D-cycloserine itself can induce activity similar to an NMDA antagonist. In order to test this more thoroughly, Anthony and Nevins (1993) investigated the effects of D-cycloserine in a test for anxiolytic potential, the potentiated startle test. At doses higher than those associated with enhancement of learned behavior, i.e. 30 mg/kg, ip, and above, D-cycloserine reduced potentiated startle in a manner similar to known anxiolytics like benzodiazepines and buspirone, and similar to NMDA complex antagonists. Therefore, at high doses, D-cycloserine can act similarly to NMDA antagonists.

In addition, Skolnick and colleagues (Skolnick et al., 1989; Trullas et al., 1989, 1990) have found that relatively high doses of 1-amino-cyclopropane-1-carboxylate (ACPC), a glycine partial agonist with nearly full efficacy (about 85%; Marvizon et al., 1989; Watson and Lanthorn, 1990) produces the same behavioral effects as NMDA antagonists, including activity in antidepressant tests, anxiolytic tests, and anticonvulsant tests. These results have also been suggested to be due to partial agonism. However, it is difficult to conceive how receptor antagonism of, at most, 15–20% can produce antagonist-like behavioral effects. It seems more reasonable to attribute these effects to the same mechanism by which NMDA agonists can act like antagonists, that is, feedback blockade of NO-mediated events. Taken together, the effects of high doses of D-cycloserine and ACPC suggest that strong agonist activity at the glycine site will result in a compensatory blockade of some biochemical pathways linked to NMDA receptor activity.

These ideas suggest that at high doses D-cycloserine might not enhance learning. This can explain the 'inverted-U' dose-response relationship seen in many behavioral studies. In addition, prolonged, or repeated, administration of D-cycloserine at acutely performance-enhancing doses may result in a loss of its effects since this would produce inappropriately-timed activation. This hypothesis has been tested by Quartermain et al. (1993). They administered 3 mg/kg, sc,

D-cycloserine to mice twice a day for two weeks before training them on their linear maze. The last dose of D-cycloserine was given just after the training session. This dose of D-cycloserine enhanced performance when administered acutely. Following the repeated injections, D-cycloserine (3,10 or 20 mg/kg, sc) did not enhance performance. D-cycloserine (3 mg/kg, sc), given after repeated injection of saline, was still effective. It is interesting that performance was not impaired, but simply not enhanced, in the animals receiving repeated injections of D-cycloserine. These results are strongly consistent with the notion that inappropriately-timed stimulation of the NMDA receptor complex can block some of its effects to subsequent stimulation.

It should be noted, however, that the enhancement of delay conditioning reported by Thompson et al. (1992) was during daily dosing of D-cycloserine which could last for several days. It may be speculated that the difference between the once-daily and twice-daily administration used by Thompson et al. (1992) and Quartermain et al., 1993) may be critical. Since the half-life of D-cycloserine is short in mice and rabbits (Conzelman and Jones, 1956) it is possible that the antagonistic effect of stimulation dissipated enough following once-daily dosing to allow the next day's dose to be effective, but that the interval was too short when twice-daily dosing was used. Measurement of the time-course of changes in (cerebellar) cGMP content may provide a means to test this hypothesis.

The effects of D-cycloserine on learning and memory tasks has recently been tested in humans using a single oral dose of 5, 15 or 50 mg (Jones et al., 1991). These doses (about 0.1–1 mg/kg, ig) yield blood levels similar to those in rodents with performance-enhancing doses of D-cycloserine (Burton, personal communication). In young adults volunteers given scopolamine, D-cycloserine reversed a number of the scopolamine-induced impairments. Older, normal adults given scopolamine were also tested. Because of an increased sensitivity to some effects of scopolamine, a lower dose was used which resulted in less impairment of learning and memory. D-cycloserine produced some reversal of the scopolamine effects, but less than seen with the young adults. However, no indication of enhanced performance was reported. These results suggest that D-cycloserine may improve performance in these tasks in people with impaired learning and memory functioning, but that it has little effect under normal conditions. Whether this is a difference between the response of rodents and humans to D-cycloserine or is a result of differences in the types of tasks used requires critical evaluation.

Examination of the effects of D-cycloserine (1–100 mg, b.i.d.) in humans with age-associated memory impairment and with Alzheimer's disease has just been completed (Herting et al., personal communication). These conditions are suspected to have specific impairments of the NMDA system. Many studies have reported that aged animals have reduced numbers of NMDA binding sites (e.g. Peterson and Cotman, 1989; Bonhaus et al., 1990; Kito et al., 1990; Pellymounter et al., 1990; Wenk et al., 1990; Magnusson and Cotman, 1993). D-cycloserine might be helpful by maximizing the activity of the remaining sites. The age-related decrease in NMDA receptor-mediated norepinephrine release in the rat hippocampus *in vitro* was partially overcome by treatment with D-cycloserine (Pittaluga et al., 1993). Alzheimer's disease is characterized by degeneration of

many neurons, especially neurons which are glutamatergic. The loss of these glutamatergic neurons reduces the level of stimulation of the remaining postsynaptic NMDA receptors (Francis et al., 1993). If this scenario characterizes Alzheimer's disease, then D-cycloserine may act like replacement therapy similar to L-DOPA for Parkinson's disease. On the other hand, the neurons which degenerate tend to be highly invested with NMDA receptors (Maragos et al., 1987; Monaghan et al., 1987). This may suggest that increased NMDA receptor activation is involved in the neuronal death itself. In this scenario, the effect of D-cycloserine is difficult to predict, but could decrease NMDA receptor activity and possibly exacerbate the dementia. In studies involving 3–6 month exposure to D-cycloserine, only a few positive effects on learning and memory tasks were seen in patients with AAMI or Alzheimer's disease (Herting et al., personal communication). In light of Quartermain et al.'s (1993) findings following repeated administration in mice and the blocking effect of NMDA agonists on LTP, it is quite possible that this was due to a compensatory blockade of NO-mediated events. Further studies will be necessary to examine this hypothesis.

In summary, D-cycloserine can facilitate learning, and also memory consolidation and retrieval, in animals on a number of tasks. However, these effects show an 'inverted-U' dose-response relationship. At higher doses, the enhancing effects disappear and D-cycloserine produces behavioral changes usually associated with antagonism of the NMDA receptor complex. A similar change in activity of D-cycloserine is seen when effects on cerebellar cGMP content are assessed. Another glycine site partial agonist, ACPC, also exhibits antagonist-like behavioral activity. Inappropriately-timed stimulation of the NMDA receptor complex can block the formation of LTP and thus can act similarly to antagonists of the NMDA receptor complex. It is likely that glycine agonists, i.e. D-cycloserine and ACPC, can also produce this antagonist-like activity and that this can account for the 'inverted-U' dose-response relationships. In addition, this can explain the fact that repeated exposure to a memory-enhancing dose of D-cycloserine blocks its ability to enhance learned performance. In humans, D-cycloserine can show some learning and memory enhancing effects, but these were not generally seen in chronic studies in patients with age-associated memory impairment or Alzheimer's disease. This may be explained by the concept of blockade of second messenger events following inappropriately-timed activation of the receptor complex. These findings call into question the hope that glycine site agonists can enhance learning and memory on a chronic basis, but further studies need to be carried out. Moreover, the fact that glycine site agonists can result in antagonist-like behaviors raises the specter that prolonged administration might release psychosis in some patients. High doses of D-cycloserine are already known to release psychosis in some patients (Simeon et al., 1970).

Acknowledgements

My grateful thanks to Drs. R. Herting, J. Disterhoft, T. Thompson, D. Olton, D. Quartermain, J. Lehmann, B. McNaughton, C. Barnes, J. Flood and M. Nevins for allowing me to cite their unpublished works on D-cycloserine.

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Received August 23, 1993