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 Gardiner-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.