acetylcholine release, but are without effect on NMDA evoked spermidine release. This profile is shared by magnesium, polyamine spider toxins and the relatively less psychostimulant NMDA channel blockers dextrorphan and dextromethorphan while dizocilpine, phencyclidine, CGP37849 and L-689,560 block both responses with equal potency. Finally, in immature rat cerebellar Purkinje cells, dizocilpine, 2APV and 7-Chlorokynurenate totally block NMDA-induced calcium entry, which is however only partially blocked by ifenprodil or eliprodil.

Ifenprodil or Eliprodil protect against the neurotoxic effects of NMDA receptor activation in vitro; their protective effects in cortical culture can be reversed by spermine or spermidine. Eliprodil has been shown to be neuroprotective in mouse (ip,po), rat (po) and cat (iv) models of focal ischaemia and also provides extensive neuroprotection in a rat model of cerebral trauma. The window of therapeutic opportunity in the mouse focal ischaemia model is from 2-4hrs post-occlusion and considerably longer in cerebral trauma (~18hrs).

Antagonists at each other site of the NMDA receptor (channel, glutamate and glycine) have also been shown to exert neuroprotective effects in animal models of stroke or cerebral trauma. Unfortunately, NMDA receptor antagonism can be accompanied by a battery of undesirable side effects including, in varying degree, phencyclidine-like psychostimulation, amnesia, neurotoxicity, hypertension and tachycardia. These effects are particularly intense with certain NMDA channel blockers (although less so in the case of dextrorphan-like compounds), and can also be observed with competitive NMDA antagonists. Glycine antagonists appear to have a more favourable profile at neuroprotective doses, while eliprodil is completely devoid of such side-effects. The reasons for this favourable profile are likely to reside in its mechanism of action - antagonism of the effects of modulatory polyamines whose influence is increased in the ischaemic or traumatised brain. The fact that ifenprodil and eliprodil act at a specific NMDA receptor subtype, and that non-stimulant channel blockers also show a degree of native NMDA receptor subtype selectivity suggests that NMDA receptor subtype targetting could provide neuroprotective NMDA antagonists with a favourable therapeutic index.

Cholinesterase Inhibitors in Alzheimer's Disease

Kenneth L. Davis

Department of Psychiatry, Mount Sinai School of Medicine, New York

Data generated to date by a number of large studies (Eagger et al, Davis et al, Farlow et al, and Murphy et al) indicate that aminoacridines, as a class of compounds, have a statistically significant effect to diminish, slightly, some of the cognitive symptoms of Alzheimer's Disease. The clinical significance of this acetylcholinesterase induced change is the central issue that will determine whether regulatory bodies will ultimately approve these agents. Clinical global improvement has been found in some of these studies, but not others. However, the possibility exists that patients have been underdosed, as a consequence of the potential hepatotoxicity that reflected in the elevation of transaminase levels that occur in a substantial number of patients. Nonetheless, higher doses of the amino acridines, if tolerated, might produce larger effects that would be more apparent to the clinician, or, alternatively, other cholinesterase inhibitors than aminoacridines that are devoid of the hepatic problems so far encountered might be administered in larger doses, particularly if they are relatively brain selective, to produce a level of enhancement of central cholinergic activity that would maximize symptom improvement.

There is little doubt that responsivity to cholinesterase inhibitors exists in only a subgroup of patients, and is robust in a further subgroup. Thus, a critical question is the biological substrate for the absence of efficacy of cholinesterase inhibitors in many Alzheimer's patients. One obvious explanation is that Alzheimer's disease is far more than simply a cholinergic deficit. Animal models have been utilized to address the heterogeneity of responsivity.

The efficacy of cholinesterase inhibitors to reverse the deficit in passive avoidance learning that is caused by a nucleus basalis lesion has been studied in animals in whom either a noradrenergic, serotonergic, or somatostatinergic deficit has been added to the cholinergic deficit. These data indicate that cholinomimetic compounds are just as efficacious in reversing the deficit in learning on a passive avoidance task following a nucleus basalis lesion when that lesion is combined with either a serotonergic or a somatostatinergic deficit. However, the combination of a noradrenergic lesion produced by either the injection of 6-hydroxydopamine or DSP-4 into the ascending noradrenergic bundle from the locus coeruleus, with a nucleus basalis lesion, completely obliterates the ability of a cholinergic compound to reverse the passive avoidance learning deficits. However, by combining drugs that enhance noradrenergic activity with those that enhance cholinergic activity it is once again possible to normalize the behavior of these animals with both noradrenergic and cholinergic deficiencies on passive avoidance learning tasks. Thus, these data encourage the use of drugs that will reverse multiple neurotransmitter deficits.