TOXICOLOGICAL HIGHLIGHT
From Anticholinesterase Toxicity to Alzheimer’s Disease: Important Interactions of Cholinergic and NMDA Receptor Systems

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The article highlighted in this issue is “Dizocilpine Improves Beneficial Effects of Cholinergic Antagonists in Anticholinesterase-Treated Mice,” by Andrzej Dekundy, Rafał M. Kaminski, and Waldemar A. Turski (pp. 289–295). It explores the relationship between cholinergic and N-methyl-D-aspartate (NMDA) receptors as mediators of anticholinesterase toxicity. The following review summarizes these findings and discusses their broader implications for central nervous system pharmacology. Alzheimer’s disease is discussed as an example of how knowledge of the interactions between NMDA and cholinergic receptors may lead to a better understanding of human disease.

In the study by Dekundy et al., mice received the anticholinesterase pesticides dichlorvos or methomyl alone, or following pretreatment with atropine (a muscarinic-cholinergic antagonist), mecamylamine (a nicotinic-cholinergic antagonist), or dizocilpine (an NMDA receptor antagonist also known as MK-801). Consistent with existing literature, dichlorvos and methomyl each induced dose-dependent seizures and lethality in mice. Atropine, a preferred treatment for anticholinesterase poisoning in humans, diminished the lethality of both pesticides but failed to attenuate seizures. Mecamylamine also reduced lethality and attenuated only those seizures induced by methomyl. These results suggest that a dissociation exists in the mechanisms which underlie anticholinesterase toxicity. More specifically, these results suggest that lethality associated with anticholinesterase poisoning may be a direct result of cholinergic receptor stimulation, whereas seizures associated with anticholinesterase poisoning may involve other mechanisms.

The role of N-methyl-D-aspartate (NMDA) receptors in mediating these results was investigated in mice treated with MK-801 prior to the administration of dichlorvos or methomyl. When administered alone, MK-801 prevented seizures induced by dichlorvos but did not affect seizures induced by methomyl. Contrary to the effects of atropine and mecamylamine, and consistent with the hypothesized dissociation in the mechanisms underlying anticholinesterase toxicity, MK-801 failed to reduce lethality induced by either pesticide. When MK-801 was co-administered with either atropine or mecamylamine, it had a significant augmenting effect; MK-801 enhanced the protective effect of both cholinergic antagonists.

The results of this study have important implications for the understanding of anticholinesterase toxicity. First, these findings suggest that lethality associated with anticholinesterase poisoning may involve NMDA receptor activation as well as cholinergic stimulation. Second, and perhaps more importantly, these findings suggest that current approaches to treating anticholinesterase poisoning may be less than optimal. The authors conclude that combined administration of cholinergic and NMDA receptor antagonists may be more effective in preventing anticholinesterase toxicity than is anti-cholinergic treatment alone.

The notion that multiple physiologic processes can underlie toxic effects is not new. Mechanisms of toxicity are often diffuse, involving intra- and extracellular processes and multiple “downstream” effects. However, the relationship between the cholinergic and NMDA receptor systems, as implied by the present work, is particularly noteworthy. The literature of the past several years contains numerous reports of NMDA receptor involvement in cholinergic function (Shoaib et al., 1997; Sziraki et al., 1998). Similarly, there is evidence to suggest that altered cholinergic function can impact events mediated by NMDA receptors (Court et al., 1990; Aizenman et al., 1991; Levin et al., 1998; Terry et al., 2002). Nicotine, a nicotinic-cholinergic agonist, has been shown to inhibit the binding of MK-801 to cerebral cortical membranes and to inhibit NMDA-mediated currents in cultured rat cortical cells (Aizenman et al., 1991; Court et al., 1990). Other nicotinic agonists have been shown to offset deleterious effects of MK-801 on learning and memory in rats, and on attention and distractibility in non-human primates (Levin et al., 1998; Terry et al., 2002). Such reports have helped to focus attention on the importance of cholinergic-NMDA receptor interactions and their implications for the treatment of human disease. Alzheimer’s disease, in particular, provides a useful context in which to examine the role of the NMDA receptor in a disease with significant cholinergic etiology.

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Evidence of NMDA receptor involvement in the etiology of Alzheimer’s disease can be found molecularly, histologically, and behaviorally (see Table 1 for a summary of the literature referenced here). Greenamyre et al. (1987) reported significant reductions in NMDA receptor binding in postmortem hippocampal tissue of patients diagnosed with Alzheimer’s disease. Others have reported an association between Alzheimer’s disease and reductions in the encoding and the expression of specific NMDA receptor subunits. Bi and Sze (2002) for example, reported reductions in the expression of NR2 mRNA in the brains of Alzheimer’s disease patients relative to normal controls. They did not, however, report changes in the expression of NR1 mRNA, suggesting that the NMDA receptor changes associated with Alzheimer’s disease may be specific to the NR2 subunit. This interpretation is complicated however, by the results of Hynd et al., (2001) who reported significant reductions in encoding of two different NMDAR1 mRNA isoforms and by those of Sze et al. (2001) who reported changes in NR1, As well as NR2 receptor subunits (Sze et al., 2001).

Whether inconsistencies in the relationship between NMDA receptor expression and Alzheimer’s disease reflect differences in experimental method or heterogeneity in the progression of the pathology remains to be established. However, any difference in the distribution or function of NMDA receptors may have important implications for the progression and treatment of the disease. Recent studies indicate that NMDA receptor antagonists can block the uptake and internalization of β-amyloid peptide into cultured hippocampal cells (Bi et al., 2002). Others report that NMDA receptor antagonists can protect against neurotoxicity associated with intracerebroventricular administration of β-amyloid in vivo (Harkany et al., 2000). Because the accumulation of β-amyloid is of primary importance to the histopathology of Alzheimer’s disease, findings that NMDA antagonists can alter the uptake or effects of this peptide are of vital interest for the treatment of its associated symptoms. Reports that NMDA receptor antagonists can ameliorate behavioral and neurochemical deficits seen in animal models of Alzheimer’s disease are particularly encouraging (Harkany et al., 1999; Bachurin et al., 2001).

Despite increasing evidence to support the relationship between NMDA receptor function and the etiology of Alzheimer’s disease, many important questions remain. It is intriguing, for example, that blocking NMDA receptors pharmacologically can attenuate β-amyloid-induced toxicity, particularly given the fact that Alzheimer’s disease appears to be associated with a decrease, rather than an increase, in NMDA receptor expression and activity. Several theories have been proposed which address this apparent paradox. Olney et al. (1997) proposed that reduced NMDA receptor activity can trigger a disinhibition syndrome in which low-grade chronic excitotoxicity (fueled by acetylcholine and glutamate) can cause widespread neuronal degeneration resembling that seen in Alzheimer’s disease. Although this theory has yet to be fully supported empirically, it may ultimately help to reconcile the seemingly contradictory relationship between the molecular etiology of Alzheimer’s disease (as it pertains to NMDA receptor expression and function) and the potential therapeutic value of NMDA receptor antagonists.

Another important question regarding the role of the NMDA receptor in Alzheimer’s disease revolves around the issue of “causality”. As others have pointed out (Hynd et al., 2001), it has been difficult to determine whether the NMDA receptor changes associated with Alzheimer’s disease are a “cause”, preceding its onset and progression, or an “effect”, resulting from widespread neurodegeneration. The results of short-term animal studies, in which NMDA receptor antagonists were administered “therapeutically” (Harkany et al., 1999; Bachurin et al., 2001), are consistent with the interpretation that the pathophysiology of Alzheimer’s disease results in subsequent alteration in NMDA receptor expression and function. The results of other studies, however, in which NMDA receptor antagonists...
antagonists were administered “prophylactically,” suggest that alterations in NMDA receptor systems may play a role in initiating the neurodegenerative process by mediating the uptake and effects of β-amyloid (Bi et al., 2002). It is possible, of course, that both of these alternatives are true in part. Future studies, in which NMDA receptor antagonists are administered prophylactically, as well as therapeutically, may help to clarify this issue.

To summarize, the article by Dekundy and colleagues provides important insights into the role of NMDA receptors as mediators of anticholinesterase toxicity. When administered alone, dichlorvos and methomyl each induced seizures and lethality in mice. Lethality, but not seizure activity, was significantly reduced by pretreating rats with cholinergic receptor antagonists. The effects of these antagonists were significantly enhanced by concurrent administration of the NMDA receptor antagonist, MK-801. This pattern of results suggests that an important relationship exists between the NMDA and cholinergic receptor systems as they relate to anticholinesterase toxicity. Of additional importance are the implications that these findings may have for our broader understanding of the role that these two receptor systems may play in the etiology of disease. The study of Alzheimer’s disease, in particular, provides a salient example of how the NMDA and cholinergic receptor systems may interact to influence human health. NMDA receptor expression is altered in patients with Alzheimer’s disease and NMDA antagonists can ameliorate functional deficits associated with the presence of β-amyloid in rats. Future studies will help to clarify the relationship between the NMDA and cholinergic receptor systems as they relate to this, and other neurological disorders.

REFERENCES


