Comments on “Memantine Blocks α7* Nicotinic Acetylcholine Receptors More Potently Than N-Methyl-D-aspartate Receptors in Rat Hippocampal Neurons”

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The following is a response to the report by Aracava et al. (2005) entitled “Memantine Blocks α7* Nicotinic Acetylcholine Receptors More Potently Than N-Methyl-D-aspartate Receptors in Rat Hippocampal Neurons” (J Pharmacol Exp Ther 312:1195–1205). It is our view that the authors do not present a balanced discussion with respect to the physiological/clinical relevance of antagonizing α7 nicotinic acetylcholine receptors (nAChRs) in the central nervous system, especially within the context of Alzheimer’s disease (AD). It is the authors’ contention that memantine’s apparent inhibition of α7 nAChRs would be “counterproductive” for the treatment of AD, especially at early stages of the disease; however, recent clinical study results have demonstrated beneficial effects of memantine on cognitive function in patients with mild-to-moderate AD (Peskind et al., 2004; Potkin et al., 2004). In addition, the expression of α7 nAChRs has been shown to be relatively unaffected in AD regardless of the disease severity (Sugaya et al., 1990; Kem, 2000). Although it has been shown that α7 nAChR agonists enhance cognition and are neuroprotective, it is not clear whether these effects are the result of receptor activation per se or activation-induced receptor desensitization, because α7 nAChRs are known to rapidly desensitize following activation (Quick and Lester, 2002). Furthermore, some effects of α7 nAChR agonists can be mimicked by selective α7 nAChR antagonists (Fujii and Sumikawa, 2000; Ferchmin et al., 2003). Thus, although the authors demonstrate that memantine inhibits α7 nAChR-mediated currents in rat hippocampal neurons, the statement drawn from these data are not supported either by the current state of the field or recent clinical experience.

In the rodent hippocampal tissue, both α7 nAChR agonists and antagonists were found to be neuroprotective against N-methyl-D-aspartate (Ferchmin et al., 2003). Furthermore, there have been many studies that have shown that activation of α7 nAChRs may be involved in processes that contribute to AD pathophysiology and neuropathology. For example, in rodent hippocampal preparations, Aβ peptides impair hippocampal signaling in an α7 nAChR-dependent manner and are thought to result from increased Ca2+ influx and chronic activation of signal transduction cascades (e.g., extracellular signal-regulated kinase 2/mitogen-activated protein kinase) (Dineley et al., 2001, 2002). In addition, these α7 nAChR-dependent activities have also been shown to mediate Aβ-induced τ hyperphosphorylation, an effect that is attenuated by α7 nAChR antagonism (Wang et al., 2003). Therefore, one can hypothesize that memantine-induced decreases in α7 receptor-mediated activity may contribute to its clinical benefits by interfering with the pathological processes suggested to be involved in AD.

Another important consideration is the reported species differences with respect to the pharmacology of α7 nAChRs, also acknowledged by the authors. For example, Aracava et al. (2005) report a noncompetitive inhibition of rat hippocampal α7 receptor-mediated currents by memantine with an IC50 of 0.34 μM. By contrast, Maskell et al. (2003) have shown that memantine inhibits human α7 nAChRs expressed in Xenopus oocytes with an IC50 approximately 5 μM. The therapeutic concentration of memantine achieved at clinical doses in AD patients is ~1 μM (Kornhuber and Quack, 1995).

Aracava et al. (2005) also cited a clinical study conducted by Schugens et al. (1997) where memantine was found to impair the eye-blink conditioning response in healthy young subjects, a response presumably modulated by the cholinergic system. Although there is evidence that AD patients may exhibit an altered eye-blink conditioning response, there is neither any data indicating that the eye-blink conditioning response is mediated by α7 nACh receptors nor any clinical evidence that memantine alters eye-blink response in AD patients. Furthermore, the Schugens study used a single dose of 30 mg of memantine, whereas the recommended dose of memantine in AD patients is 10 mg b.i.d. using a 4-week up-titration scheme starting at 5 mg once daily (Reisberg et al., 2003).

Aracava et al. (2005) also state that memantine can impair short-term memory processing in rats since memantine reduced accuracy in fixed consecutive number tasks (Willmore et al., 2001). However, the cited study also states that memantine reduced the accuracy in the above task only at doses that reduced response rates, indicating that this was a non-specific effect of memantine, and at high doses that are not clinically relevant.

ABBREVIATIONS: nAChR, nicotinic acetylcholine receptor; AD, Alzheimer’s disease.
Thus, although Aracava et al. (2005) argue that inhibition of α7 nAChRs by memantine may oppose the benefits of inhibiting excessive activation of N-methyl-D-aspartate receptors and would be counterproductive in the treatment of early stages of AD, there is ample evidence to suggest the opposite; i.e., a reduction in α7 nAChR-mediated activity may actually provide benefits within the context of the pathophysiology of AD. This is further supported by the observed clinical benefits of memantine in AD patients.

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References