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Commentary

Allosteric Antipsychotics: M4 Muscarinic Potentiators as Novel Treatments for Schizophrenia

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The cholinergic system has been implicated in both the etiology and the treatment of schizophrenia for nearly 60 years (Rowntree *et al*, 1950). With regard to schizophrenia therapeutics, pioneering studies have shown a high correlation between the antimuscarinic properties of typical and atypical antipsychotic drugs and lack of extrapyramidal side effects (EPS) (Snyder *et al*, 1974); this finding led to the anticholinergic hypothesis of atypical antipsychotic drug action. However, it is now clear that antimuscarinic receptor activity cannot be the sole contributor to the lack of EPS as several atypical antipsychotic drugs exist, which have negligible affinities for all five human muscarinic receptors and low EPS (Roth *et al*, 2004). A chance observation that xanomeline (a pan-muscarinic receptor agonist with substantial off-target actions at other biogenic amine receptors; Figure 1) diminished psychotic symptoms in patients with Alzheimer's disease (Bodick *et al*, 1997) led to the proposal that the modest antipsychotic effects of xanomeline might be attributed to M1/M4 receptor agonism (Shannon *et al*, 2000). Similarly, the pan-muscarinic agonist properties of *N*-desmethyl-clozapine (Davies *et al*, 2005) provided additional support for the hypothesis that muscarinic receptor agonism might be antipsychotic (Figure 1).

A major impediment to testing the 'muscarinic agonism' hypothesis of antipsychotic drug therapeutics has been the fact that broad-spectrum muscarinic agonists frequently have debilitating side effects (eg, excessive sweating, piloerection, nausea, vomiting, seizures). Given the prominent roles of M1 and M4 muscarinic receptors in the regulation of dopaminergic neurotransmission (Gerber *et al*, 2001; Gomeza *et al*, 1999), M1 and/or M4 selective agonists have been postulated to be potentially safe and effective antipsychotics, although their development has been an elusive goal.

One recent approach for creating drugs, which are highly selective for previously intractable targets, has been to create allosteric modulators, which can either potentiate or inhibit the activity of the receptor (see Christopoulos (2002) for a review). In this issue of *Neuropsychopharmacology*, a team led by Arthur Christopolous and Patrick Sexton at the University of Monash in collaboration with Eli Lilly report on the molecular mechanisms and potential antipsychotic actions of a novel M4 allosteric potentiator LY2033298.

A recent report by this group (Chan *et al*, 2008) provided the tantalizing preliminary findings that LY2033298 had antipsychotic actions in various rodent models. Although these findings were interesting, the molecular and cellular mechanism(s) of action of LY2033298 were unclear. Indeed, a key unanswered question from the initial report of Chan *et al* (2008) was whether LY2033298 was a *bona fide* allosteric potentiator.

The *sine qua non* for allosteric potentiation of agonist activity is the demonstration that the drug enhances agonist-binding potency at the receptor. In a series of carefully controlled and quantitatively analyzed studies, Leach *et al* (2010) showed that LY2033298 potentiates the agonist potency of acetylcholine in both transfected cells and neuronal cell lines, which endogenously express M4 receptors. One of the strengths of this approach is the rigorous quantitative analysis of various parameters associated with allosterism. Indeed, the group of Sexton and Christopolous are major contributors to the current renaissance of quantitative molecular pharmacology.

Leach *et al* (2010) then showed that LY2033298 potentiates the effect of oxotremorine (a nonselective muscarinic agonist) in the conditioned avoidance response paradigm in WT mice, whereas this potentiation was attenuated but not abolished in M4 KO mice. These findings indicate that in addition to M4 potentiation, there may be a non-M4 component to the activity of LY2033298. The study by Leach *et al* (2010) stands as a paradigm for the molecular pharmacological characterization of drug-like compounds,

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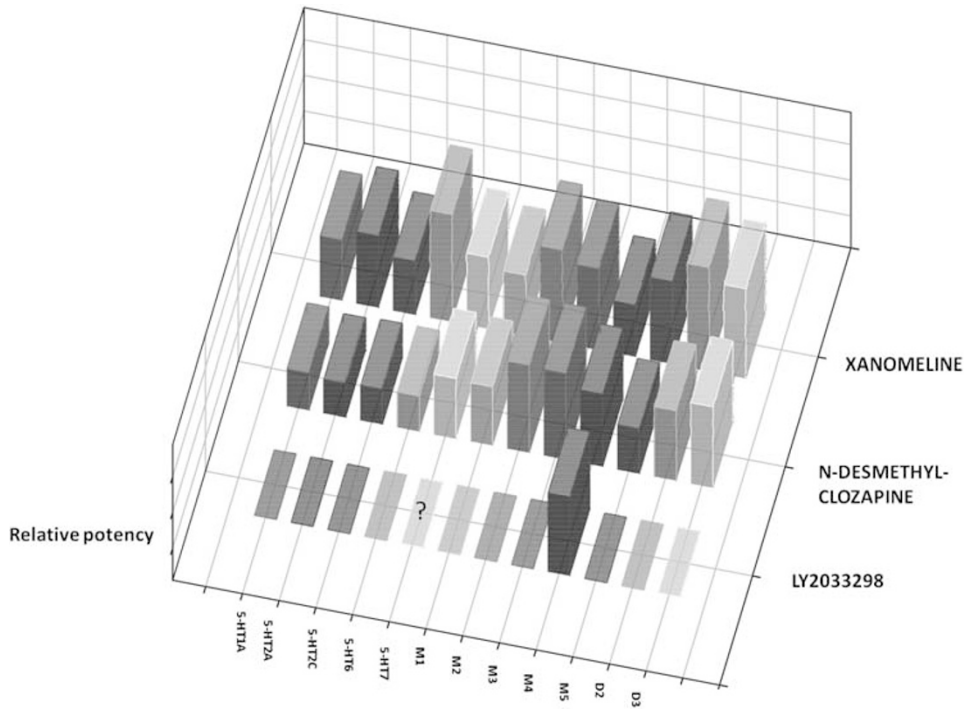

Figure 1 GPCR profiles of 'selective' muscarinic agonists. The relative comparative activities of xanomeline, *N*-desmethylclozapine, and LY2033298 at GPCRs implicated in atypical antipsychotic drug actions are shown. As can be seen, only LY2033298 has significant selectivity for muscarinic and nonmuscarinic GPCRs implicated in antipsychotic drug actions. '?' represents unknown activity at 5-HT7 receptors.

which therapeutically modulate GPCR signaling. However, the potential antipsychotic activity of this compound must be considered 'putative' until it can be validated in other models (eg, primates) and tested in humans.

DISCLOSURE

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