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Reduction in Muscarinic M_1-Mediated Hypercholinergic State and Beneficial Cognitive Effects of Muscarinic Agonists in Schizophrenia

TO THE EDITOR: In their excellent editorial, published in the August 2008 issue of the *Journal*, Jeffrey A. Lieberman, M.D., Jonathan A. Javitch, M.D., Ph.D., and Holly Moore, Ph.D. (1) stated that the "cognitive benefits of xanomeline are thought to result from its stimulation of M_1 receptors in the neocortex and hippocampus, an action that facilitates acetylcholine and dopamine release in these regions" (1, p. 934). However, the Li et al. study (2), which the authors cited in support of this mechanism of action, examined the acute effects of xanomeline. Consequently, these neurotransmitter effects may not be pertinent to the recent 4-week treatment trial among schizophrenia patients conducted by Shekhar et al. (3). Acute and chronic treatment with muscarinic M_1 agonists, even with weak agonists such as choline, is also known to produce rapid downregulation and desensitization of these receptors that could actually result in a reduction in M_1-mediated transmission. There is also evidence that the relationship between cholinergic activity, including that associated with M_1 stimulation, and cognition has an inverted U-shaped dose response, in a manner in which both low and high activity can impair cognition. Taken together, these observations raise the possibility that brain region-specific reductions in M_1-mediated transmission and a reduction in hypercholinergic state might have also contributed to the beneficial cognitive effects of chronic treatment with xanomeline in schizophrenia in the Li et al. study.

Although there is presently no evidence of a generalized hypercholinergic state in schizophrenia, it is interesting to note that Crook et al. (4) ascribed their findings of reduced M_1 and M_4 receptors in the prefrontal cortex of schizophrenia patients to increased activity of cholinergic input to this region, leading to downregulation of these receptors. Consistent with this hypothesis, indices of extrinsic presynatic cholinergic input, including the nucleus of Meynert, and choline acetyltransferase activity in the prefrontal cortex are preserved.

Results from sleep studies, some of which were cited by Shekhar et al., have also provided evidence of cholinergic hyperactivity in pathways modulating rapid-eye-movement sleep in schizophrenia patients.

There are currently no techniques to determine region-specific presynaptic cholinergic activity in vivo. However, studies of the functional status and sensitivity of M_1 receptors in brain regions implicated in cognition (especially memory), which are presently feasible, may provide an indirect measure.

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Drs. Lieberman, Javitch, and Moore Reply

TO THE EDITOR: Dr. Pomara raises a very important issue regarding the evaluation of the potential efficacy of xanomeline, or any candidate molecule, as an antipsychotic therapy in the treatment of schizophrenia, particularly pertaining to its effects on cognition. The standard preclinical screening strategies often do not include evaluation of the effects of chronic administration of a candidate drug. Although the reduced throughput and increased immediate costs would seem pro-

hibitive, the actual cost of failing to assess a drug's chronic effects on physiological and cognitive processes relevant to the disease is a reduction in predictive validity, particularly with regard to cognitive, behavioral, and/or physiological effects that may interfere with the drug's therapeutic effects (1).

We were able to find very few studies examining the behavioral, neurochemical, or neurophysiological effects of the chronic administration of xanomeline or other M_1 agonists. Reported effects of the chronic administration of xanomeline and other compounds with M_4 agonism include a reduction in the proportion of spontaneously active dopamine neurons in the ventral tegmental area (2, 3)—an effect that would be predicted based on studies of other antipsychotic drugs—leading to decreased dopamine efflux in the striatum (4). In the case of M_4 agonists, since medial dopamine neurons are more affected, the action of the drug in "clamping" dopamine release would be predicted to affect the medial striatum more than the lateral nigrostriatal pathway. This effect on mesostriatal dopamine release, which may be mediated via xanomeline's actions on both midbrain dopamine neurons and in the striatum, must be considered as a potential mechanism underlying the ability of the drug to control psychosis.

Another issue to consider in assessing the mechanisms underlying the effects of xanomeline is the extent to which these effects result from M_1/M_4 agonism as opposed to effects of the compound on other molecular targets. For example, similar to clozapine, xanomeline is a relatively potent antagonist at serotonin 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors, with affinities for these receptors comparable with those for muscarinic receptors. Xanomeline also has moderate affinity for dopamine D_3 receptors. The recent discovery of highly selective allosteric potentiators of M_1 and M_4 receptors (5–7) presently allows for a determination of the contribution of M_1/M_4 agonism to the beneficial effects of xanomeline.

An important "site of action" of xanomeline, as highlighted by Dr. Pomara, is the chronic regulation of acetylcholine release in the neocortex and hippocampus. In a number of studies, schizophrenia patients have exhibited decreased binding at M_1 and M_4 receptors, an effect consistent with chronically increased extracellular levels of acetylcholine (8). Many of these studies were conducted among medicated patients, and we have no way of knowing whether chronic "overstimulation" at M_1 and M_4 receptors is the mechanism by which receptor binding is reduced in schizophrenia. Nevertheless, this finding, as well as other findings, has led some investigators to postulate that chronic and/or intermittent hyperactivity of cortical cholinergic transmission plays a role in the attentional deficits and psychotic symptoms in schizophrenia (9). However, more recent studies have indicated that a higher resting "set point" for extracellular acetylcholine in the cortex may be beneficial as long as the system retains the capacity for phasic increases in cholinergic transmission (10). Increases in acetylcholine in response to (and contingent upon) cognitive demands are essential for normal attentional processing. Disruptions of attentional mechanisms produced by a loss of responsivity of cholinergic transmission in the cortex may contribute to inappropriate encoding of environmental contingencies.

Until the appropriate studies are conducted, we have no way of knowing the effects of chronic M_1 receptor stimulation on cognitive modulation of acetylcholine release in the cortex. However, it is encouraging to note that chronic administration of the M_1 agonist CI1017 resulted in improvement in the acquisition of a hippocampally dependent Pavlovian association, possibly through downregulation of an M_1-mediated after-hyperpolarization of hippocampal neurons. Thus, selective downregulation of M_1 receptor-mediated effects through chronic stimulation (and possible internalization [11]) of M_1 receptors may serve to increase responsivity of neocortical and hippocampal neurons to acetylcholine through nicotinic and other muscarinic mechanisms and leave intact modulation by other monoaminergic systems, including dopamine. Consequently, we might be tempted to postulate that xanomeline may represent an improvement over dopamine D_2 antagonists in that it controls striatal dopamine release without blocking D_2 receptors but also maintains—perhaps even therapeutically adjusts—a set point for cortical cholinergic transmission that also permits dynamic cholinergic transmission. The latter mechanism may serve to help improve or preserve attentional abilities and, in turn, reduce the probability of inappropriate association formation that may contribute to psychosis and reduced functional outcome (12). We hope that those vested in this therapy are moved to test these hypotheses with chronic drug studies in animal models.

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Drs. Shekhar, McKinzie, and Felder Reply

TO THE EDITOR: Dr. Pomara suggests that the clinical efficacy of xanomeline treatment for improving cognitive deficits in schizophrenia patients in our study (1) may not have been a result of sustained M_1 receptor agonist properties, as hypothesized by Dr. Lieberman et al. (2), but rather a result of chronic agonist-induced desensitization and downregulation of cortical M_1 receptors. Although M_1 receptor desensitization contributing to the clinical efficacy of xanomeline is certainly possible, which is supported by some of the evidence cited by Dr. Pomara, such a hypothesis is difficult to test directly. On the other hand, it is equally possible that direct agonist effects of xanomeline may contribute to cognitive benefits for the following reasons.

First, the postmortem studies by Crook et al. (3) measured 3H-pirenzapine binding, a ligand that is not a highly selective M_1 receptor antagonist and does not distinguish high versus low affinity states of the M_1 receptor. Second, muscarinic M_1 receptors appear to have a high receptor reserve requiring only a 15% occupancy to attain full signal transduction, suggesting that a significant decline in receptor number can possibly occur without causing functional consequences (4). Thus, the conclusion by Crook et al. that reductions in M_1 receptor density in limbic regions were a result of hypercholinergic state has not been directly tested and remains speculative.

Interestingly, preclinical testing of another M_4 receptor agonist, BuTAC, demonstrated that it possesses antipsychotic-like properties similar to xanomeline. However, unlike xanomeline, BuTAC is an antagonist at the M_1 receptor and does not exhibit efficacy in spatial learning in rats. This may support the hypothesis that the cognitive benefits of xanomeline may well be the result of its agonist properties at the M_1 receptor. Unfortunately, utilizing direct orthosteric agonists of receptors, it is difficult to conclude whether the effects of chronic administration of the drug are a result of continued agonism or desensitization of its receptors. Recently published data using muscarinic receptor potentiators further support a role for M_1 and/or M_4 positive modulation, rather than antagonism, as the primary mechanism driving antipsychotic efficacy (5, 6). With positive modulators, M_1 and M_4 receptors would be less sensitive to downregulation as a result of the allosteric mechanism of action. Indeed, positive allosteric modulation would be less prone to desensitization and would preserve spatial and temporal regulation of M_1 receptor activation (4). Therefore, based on the high receptor reserve for the M_1 receptor, and most likely for M_4 receptor, and evidence based on recent M_1 and M_4 selective positive allosteric modulators, it is unlikely that orthosteric agonist-mediated desensitization is the sole explanation for muscarinic-based mechanisms of antipsychotic therapeutics.

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Risperidone-Associated Increase in Triglyceride Levels

TO THE EDITOR: Second-generation antipsychotics are frequently associated with metabolic adverse effects, such as weight gain and elevations of triglyceride or total cholesterol levels (3). Although minor changes in lipid levels have previously been reported during risperidone treatment (2), we observed the following case of pronounced risperidone-induced hypertriglyceridemia.

"Mr. A" was a 27-year-old man who suffered from DSM-IV paranoid schizophrenia for 9 years and had been previously treated with perazine and flupentixole. Upon his hospitalization, the patient presented with normal triglyceride (97 mg/dl) and total cholesterol (121 mg/dl) levels