Xanomeline and the Antipsychotic Potential of Muscarinic Receptor Subtype Selective Agonists

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ABSTRACT

Binding studies initially suggested that the muscarinic agonist, xanomeline, was a subtype selective muscarinic M₁ receptor agonist, and a potential new treatment for Alzheimer’s disease. However, later in vitro and in vivo functional studies suggest that this compound is probably better described as a subtype selective M₁/M₄ muscarinic receptor agonist. This subtype selectivity profile has been claimed to explain the limited classical cholinomimetic side effects, particularly gastrointestinal, seen with xanomeline in animals. However, in both healthy volunteers and Alzheimer’s patients many of these side effects have been reported for xanomeline and in the patient population this led to a >50% discontinuation rate. Clearly, the preclinical studies have not been able to predict this adverse profile of xanomeline, and this suggests that either xanomeline is not as subtype selective as predicted from preclinical research or that there are differences between humans and animals with regard to muscarinic receptors. Nevertheless, in Alzheimer’s patients xanomeline dose-dependently improves aspects of behavioral disturbance and social behavior including a reduction in hallucinations, agitation, delusions, vocal outbursts and suspiciousness. The effects on cognition are not as robust and mainly seen at the highest doses tested. These effects in Alzheimer’s patients have given impetus to the suggestion that muscarinic agonists have potential antipsychotic effects. The current review assesses the antipsychotic profile of xanomeline within the framework of the limited clinical studies with cholinergic agents in man, and the preclinical research on xanomeline using various models commonly used for the assessment of new antipsychotic drugs. In general, xanomeline has an antipsychotic-like profile in various dopamine models of psychosis and this agrees with the known interactions between the cholinergic and dopaminergic systems in the brain. Moreover, current data suggests that the actions of xanomeline at the M₄ muscarinic receptor subtype might mediate its antidopaminergic effects. Particularly intriguing are studies showing that xanomeline, even after acute administration, selectively inhibits the firing of mesolimbic dopamine cells relative to dopamine cell bodies projecting to the striatum. This data suggest that xanomeline would have a faster onset of
action compared to current antipsychotics and would not induce extrapyramidal side effects. The preclinical data on the whole are promising for an antipsychotic-like profile. If in a new formulation (i.e., transdermal) xanomeline has less adverse effects, this drug may be valuable in the treatment of patients with psychosis.