Muscarinic $M_1$ receptor agonists: can they improve cognitive performance?

Elizabeth Scarr$^{1,2}$

$^1$ Department of Psychiatry, The University of Melbourne, Victoria, Australia
$^2$ Molecular Psychiatry Laboratories, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Victoria, Australia

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Muscarinic receptors as drug targets

Due to their potential roles in the pathophysiologies of a number of central nervous system disorders such as depression (Dilsaver, 1986), schizophrenia (Raedler et al. 2006), Alzheimer’s disease (Araujo et al. 1988) and Parkinson’s disease (Ruberg et al. 1982), modulation of the muscarinic system has been a focus of drug discovery for decades. Particular attention has been paid to developing ligands for the muscarinic $M_1$ receptor because of the role it is thought to play in cognition (Anagnostaras et al. 2003) and the molecular processes associated with it (Giessel & Sabatini, 2010). Given the potential markets for a cognitive enhancer, especially in Alzheimer’s disease and schizophrenia, where not only are cognitive impairments key features (Coyle et al. 1983; Nuechterlein et al. 2004) but $M_1$ function also appears to be compromised (Dean et al. 2002; Harrison et al. 1991; Mancama et al. 2003; Overk et al. 2010; Scarr et al. 2009; Shiozaki et al. 2001; Zavitsanou et al. 2004), it is not surprising that the $M_1$ receptor has been the focus of significant drug development. However, the orthosteric binding site of the muscarinic receptors has been highly conserved during evolution (Langmead et al. 2008), hindering the design of subtype selective ligands and resulting in unacceptable side-effect profiles due to the off-target activation of peripheral, predominantly $M_4$ and $M_5$, muscarinic receptors (Bymaster et al. 2003).

Drug target fidelity

Such constraints were highlighted by trials of xanomeline, a partial agonist reported to have higher affinities for $M_1$ and $M_5$ receptors than for other muscarinic receptors (Bymaster et al. 1997). In trials for Alzheimer’s disease (Bodick et al. 1997) and schizophrenia (Shekhar et al. 2008), the xanomeline treatment groups had promising outcomes; showing both cognitive and clinical improvements at the end of the trials. However, in the Alzheimer’s disease trial, 59% of the patients who received the effective dose discontinued treatment; 7% had their treatment stopped by a third party, and the remaining 52% of the patients discontinued because of adverse effects. These events were mainly gastrointestinal in nature (nausea, vomiting, dyspepsia), but 13% of the patients receiving xanomeline had elevated hepatic function markers and over 12% experienced a loss of muscle tone and consciousness; these side-effects resulted in further development of xanomeline being discontinued. While these clinical findings are often interpreted as evidence that agonism of $M_1$ and $M_4$ receptors will be beneficial in treating cognition and psychosis, respectively, it should be noted that xanomeline binds to other $G$ protein-coupled receptors (Shannon et al. 1994). It is a functional agonist at the serotoninergic 1A and 1B receptors and an antagonist at the 2A receptor as well as binding to other cloned human receptors with varying affinities (Watson et al. 1998). Therefore, at the doses used in the clinical studies, it is possible that some of the outcomes are due, at least in part, to effects at receptors other than $M_1$ and $M_4$.

Advances in drug design

The drive for muscarinic ligands with increased subtype selectivity received extra impetus with the discovery that muscarinic receptors (Clark & Mitchelson, 1976), like many other receptor families, had alternative binding sites known as allosteric binding sites. However, it was some time before the full impact of this discovery was realized – the allosteric sites are not conserved between human receptors with varying affinities (Watson et al. 1998). Therefore, at the doses used in the clinical studies, it is possible that some of the outcomes are due, at least in part, to effects at receptors other than $M_1$ and $M_4$. The potent $M_1$ receptor allosteric agonist GSK1034702 improves episodic memory in humans in the nicotine abstinence model of cognitive dysfunction.
In drug discovery, most interest has focused on ligands that will activate the receptor, particularly the positive allosteric modulators (PAMs), which have no intrinsic activity but enhance the effects of ligands binding to the orthosteric site. The perceived advantage of utilizing such ligands as drugs is that their effects will primarily be driven by the normal activity of the central cholinergic system, rather than imposing an external driver on the system. Such an approach is in keeping with the concept proposed by Professor Arvid Carlsson of moving from the complete agonism or antagonism of central neurotransmitter systems towards a more subtle modulation of these systems (CINP World Congress, 2012, Stockholm).

To date, the preclinical data for the allosteric ligands has been promising, supporting the xenomeline trials, suggesting that the clinical effects were due to actions at the M4 and M4 receptors. The M4 allosteric ligands are reported to be effective in animal models used to predict antipsychotic activity (Brady et al. 2008; Chan et al. 2008; Leach et al. 2010; Lewis et al. 2010), an effect shared by some M4 allosteric ligands (Jones et al. 2008; Vanover et al. 2008). In addition, the M1 ligands appear to be pro-cognitive, resulting in improved performances in a number of paradigms (Bradley et al. 2010; Budzik et al. 2010; Shirey et al. 2009; Vanover et al. 2008). Furthermore, the M4 ligands have been reported to promote non-amyloidogenic processing of amyloid precursor protein (Jones et al. 2008; Reid et al. 2011; Shirey et al. 2009), raising the possibility that they could reduce the amyloidogenic burden in the brains of people with Alzheimer’s disease, as well as improving cognition. These data strongly support the concept that a subtle modulation of the central muscarinic system could be beneficial in treating the cognitive problems that are core features of schizophrenia and Alzheimer’s disease and, furthermore, such drugs could have additional benefits in the treatment of both disorders.

Clinical test

The paper by Nathan et al. (2012) is the first report of the effects of a M1 allosteric agonist on cognitive performance in humans. GS1034702 has been shown, using calcium mobilization studies, to potently activate the M1 receptor, to have 100-fold selectivity for this site, relative to the other muscarinic receptors and to reverse scopolamine-induced amnesia in the passive avoidance test (Nathan et al. 2012). GS1034702 was administered in a randomized, double-blind, placebo-controlled, cross-over design, to healthy smokers participating in a nicotine abstinence model of cognitive dysfunction. Nicotine abstinence caused reductions in both immediate and delayed recall, the first of which was attenuated by the highest dose of the M1 agonist; this is in contrast to data from the m1<sup>−/−</sup> mice, which suggests that a lack of M1 receptors affects hippocampal/cortical interactions rather than hippocampal-dependent tasks (Anagnostaras et al. 2003). As pointed out by Nathan et al., preclinical data suggest that activating M1 receptors affects hippocampal-dependent paradigms. This disparity could be due to the cortical deficit purported to exist in m1<sup>−/−</sup> mice arising as a result of reduced cortical dendritic arborization (Zhang et al. 2005), which is thought to contribute to reduced cortical experience-dependent plasticity (Zhang et al. 2006). Interestingly, neither nicotine abstinence nor GS1034702 affected performance on any of the other cognitive tasks involved in this study; nicotine abstinence has previously been shown to affect a number of cognitive domains, suggesting nicotine abstinence has variable outcomes depending on the participant selection criteria and the cognitive paradigms used. Despite GS1034702 being described as a selective M1 allosteric agonist, the commonest adverse events were those typically caused by activation of muscarinic receptors, at the low dose these were predominantly gastrointestinal, while at the high dose the adverse events included body temperature fluctuations, flushing, increased perspiration, lachrymation, headaches and dizziness. These findings suggest that in humans, at the low dose GS1034702 activates other muscarinic receptors whilst at the high dose it also appears to block muscarinic receptors. However, these effects were described as mild and none of the participants withdrew as a result of these side-effects, which is encouraging for further development of these compounds.

Overall, the trial yielded modest, but promising data; GS1034702 reverses the cognitive impairment seen on one of the cognitive tests and although the side-effects appear to be due to off-target activation of other muscarinic receptors, they were not serious enough to necessitate treatment withdrawal. Although this preliminary trial adds support for the development of allosteric ligands for muscarinic M1 receptors, there are still issues to be addressed regarding the clinical use of such compounds. Of most concern is that the downstream effects of activating muscarinic M1 receptor appears to depend on the allosteric ligand involved (Marlo et al. 2009), possibly as the result of there being more than one allosteric site on the receptors (Spalding et al. 2006), and the orthosteric ligands used for the pharmacological assessment (Valant et al. 2012). This point is exemplified by a recent report that different M1 allosteric agonists did not activate all the downstream effector systems to the same extent (Digby et al. 2012), suggesting that the physiological outcomes of M1 allosteric ligands may vary from compound to compound. While these data indicate a through characterization of each individual compound is required before their full clinical utility can be realistically assessed, including the off-target effects, they also suggest that it may be possible to produce highly specific effects by stimulating the precise signalling system involved in the cognitive processes affected by psychiatric and neurological disorders.
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Statement of Interest

E. Scarr has co-authored a paper with J. Watson, who is a co-author of the study by Nathan et al. (2012). In addition, she has previously received honorarium from AstraZeneca and travel support from GSK.

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