Muscarinic Agonists and Antagonists in Schizophrenia

Recent Therapeutic Advances and Future Directions

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Abstract Existing therapies for schizophrenia have limited efficacy, and significant residual positive, negative, and cognitive symptoms remain in many individuals with the disorder even after treatment with the current arsenal of antipsychotic drugs. Preclinical and clinical data suggest that selective activation of the muscarinic cholinergic system may represent novel therapeutic mechanisms for the treatment of schizophrenia. The therapeutic relevance of earlier muscarinic agonists was limited by their lack of receptor selectivity and adverse event profile arising from activation of nontarget muscarinic receptors. Recent advances in developing compounds that are selective to muscarinic receptor subtypes or activate allosteric receptor sites offer tremendous promise for therapeutic targeting of specific muscarinic receptor subtypes in schizophrenia.

Keywords Acetylcholine • Allosteric • Cholinergic • Cognitive • Muscarinic • Psychosis • Schizophrenia

1 Schizophrenia Symptoms, Treatment, and Challenges

Schizophrenia is a chronic, debilitating neuropsychiatric illness affecting nearly 1% of the population, often requiring lifelong treatment. Symptoms of schizophrenia are broadly categorized into three domains: positive, negative, and cognitive symptoms. The positive symptoms include hallucinations, delusions, and

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disorganized behavior; negative (or deficit) symptoms reflect the absence of normal social and motivational functioning, for example, avolition, alogia, anhedonia, and blunted affect; and cognitive symptoms of schizophrenia include impaired attention, executive functioning, and working memory. Early recognition that antagonism of central dopamine receptors reduces the positive symptoms of the disorder, combined with the evidence that stimulation of the dopamine system by drugs such as amphetamine could induce psychosis, established dopamine as the neurotransmitter central to the disorder and had profound effects on drug development strategies in schizophrenia. Indeed, all clinically available antipsychotic drugs antagonize central dopamine receptors. However, while dopamine's integral role in the positive symptoms of schizophrenia is uncontroversial (see Howes and Kapur 2009), this is not the case with the other symptom domains. Increasing evidence suggests that while antipsychotic drugs can alleviate psychotic symptoms for many individuals with schizophrenia, recovery is often incomplete, leaving patients with residual positive clinical symptoms. For example, some 25% of schizophrenia patients do not respond to dopamine-targeted therapies (Hirsch and Barnes 1995).

In addition, a particularly critical barrier to improving outcomes is the elusiveness of adequate treatments for negative and cognitive symptoms. Even more than the positive clinical symptoms, cognitive deficits contribute to impaired social functioning and poor quality of life (Williams et al. 2008), and predict deficits in occupational functioning (Bellack et al. 1999; Dickinson and Coursey 2002; Gold et al. 2002; Green 1996). Moreover, cognitive deficits are associated with the onset of psychosis in individuals at risk for schizophrenia (Frommann et al. 2010). Finally, in a recent prospective longitudinal analysis, Reichenberg et al. (2010) revealed premorbid neurocognitive deficits in a wide variety of domains in individuals who went on to develop schizophrenia, including executive function, visual and verbal learning and memory, processing speed, attention, visuospatial problem solving, and working memory. These recent studies further underscore the pressing need for novel therapies to improve treatment of schizophrenia.

2 Muscarinic Acetylcholine Receptor System and Schizophrenia

Central cholinergic neurotransmission has long been known to be crucial in CNS functioning. The muscarinic acetylcholine receptor (mAChR) system plays a significant role in memory, learning, arousal, motivation, reward, and attention. Significant evidence links abnormalities in the muscarinic system to the pathophysiology of schizophrenia (for review, see Raedler et al. 2007) and to a number of other debilitating neuropsychiatric illnesses including Alzheimer's disease (Winkler et al. 1998). Moreover, neurochemical, pharmacological, and neuropathological evidence suggests that selective targeting of mAChRs may hold therapeutic potential for schizophrenia (Friedman 2004; Raedler et al. 2007; Sellin et al. 2008; Conn et al. 2009).

2.1 Overview and Distribution of mAChRs

mAChRs are 7-transmembrane G-protein-coupled receptors (GPCRs). Five muscarinic receptor subtypes have been identified (M_1–M_5). The oddly numbered receptors, M_1, M_3, and M_5, are excitatory and couple predominantly through the $G_{q/11}$ pathway to stimulate phosphoinositide hydrolysis and increase intracellular calcium. M_2 and M_4 receptor subtypes have inhibitory effects and couple predominantly with $G_{i/o}$ proteins to inhibit cAMP. The anatomical distribution of these mAChRs places them in key dopamine pathways implicated in psychotic symptoms of schizophrenia, as well as in brain regions relevant to cognitive functioning, especially attention and memory. The M_1 and M_4 mAchR subtypes are concentrated heavily in the forebrain, including cerebral cortex, striatum, and hippocampus. M_4 receptors are also prominently expressed in the midbrain, where their interaction with midbrain dopaminergic mechanisms in VTA and striatum suggests that they influence dopamine release into the nucleus accumbens (Langmead et al. 2008a). The M_2 and M_3 receptor subtypes are located in the periphery as well as in the central nervous system (CNS) and are involved in parasympathetic functions including bronchoconstriction, salivation, smooth muscle relaxation, vasorelaxation, appetite, bradycardia, akinesia, and tremor. Within the brain, M_2 receptors are especially dense in forebrain and hippocampus where they regulate acetylcholine release (Billard et al. 1995; Stoll et al. 2003). Like M_1 receptors, M_4 receptors are also heavily concentrated in the cortex, striatum, and hippocampus. The M_5 receptor subtype is expressed primarily on dopaminergic neurons in the substantia nigra pars compacta, where it modulates dopamine release to the striatum (Weiner et al. 1990). It is also prominently expressed in the ventral tegmental area, which provides dopaminergic input to limbic structures such as the nucleus accumbens (Eglen 2005). However, dissociating the relative contributions of different muscarinic receptor subtypes within the CNS has been challenging, especially in the absence of subtype-specific ligands. Major obstacles include the fact that mAChRs are often co-localized within the same brain regions, often on the same cells (Levey et al. 1991), and sometimes with opposing actions. Of the 5 mAChRs, subtypes M_1 and M_4 have been the target of the most widespread interest for schizophrenia.

2.2 mAChR Manipulations Influence Symptoms of Schizophrenia

One source of evidence for a role of mAChRs in schizophrenia comes from observations that muscarinic antagonists can induce an “antimuscarinic syndrome” that includes psychotic features (Bolden et al. 1991). The hallucinations induced by muscarinic antagonists are remarkably similar in character to those experienced by individuals with schizophrenia (Yeomans 1995). Atropine, scopolamine, quinuclidinyl benzilate, ditran, and other centrally acting antimuscarinic agents

have been known to induce hallucinations in multiple sensory domains, as well as cognitive symptoms that bear marked resemblance to those observed in schizophrenia, including profound disturbances in attention and concentration, impaired memory, and confusion (Abood and Biel 1962; Granacher and Baldessarini 1975; Mego et al. 1988; Gershon and Olariu 1960; Neubauer et al. 1966; Clarke et al. 2004; Fisher 1991; Perry and Perry 1995; Fredrickson et al. 2008). Nonspecific muscarinic antagonists also induce learning and memory deficits in animals (Senda et al. 1997; Rasmussen et al. 2001). Finally, anticholinergic load is also associated with reduced cognitive function in schizophrenia (Minzenberg et al. 2004).

Clinical trials of mAChR agonists provide additional evidence for the putative role of mAChRs. Xanomeline, a relatively selective M_1/M_4 agonist, improved cognition and reduced psychotic symptoms in both schizophrenia (Shekhar et al. 2008) and Alzheimer's disease (Bodick et al. 1997). The nonspecific muscarinic agonist arecoline has also shown cognition-enhancing effects in Alzheimer's disease patients (Christie et al. 1981). Moreover, increasing evidence indicates that some atypical antipsychotics, namely, clozapine and olanzapine (Bymaster et al. 2003a), are partial muscarinic agonists, which has contributed to a new recognition that cholinergic facilitation may contribute to their cognition-enhancing and antipsychotic efficacy. Atypical antipsychotics drugs (i.e., ziprasidone, risperidone, clozapine, and olanzapine), but not conventional antipsychotics, increase acetylcholine release in prefrontal cortex (Ichikawa et al. 2002), which may be one mechanism by which these drugs exert their somewhat modest cognition-enhancing effects. This review will describe evidence suggesting that the muscarinic acetylcholine system is a compelling therapeutic target for schizophrenia, summarize recent progress in understanding the role specific muscarinic receptors may play in schizophrenia, and detail advances in selectively targeting receptors implicated in the pathophysiology of schizophrenia.

2.3 mAChR Abnormalities in Schizophrenia

The anatomy of the CNS cholinergic projections is consistent with a possible role in schizophrenia. The mesopontine cholinergic projection has been most associated with psychotic symptoms. It originates in the pedunculopontine and laterodorsal tegmental nuclei and projects most densely to thalamic nuclei, as well as to the substantia nigra and basal forebrain cholinergic nuclei, lateral hypothalamus, and limbic frontal cortex (Yeomans 1995). The basal forebrain cholinergic system, by virtue of its projection to hippocampal and cortical areas involved in learning and memory, has been strongly associated with cognition.

Notably, postmortem studies have suggested mAChR abnormalities in schizophrenia. Quantitative autoradiography studies measuring the binding of [(3)H] pirenzepine, a muscarinic antagonist that binds selectively to M_1 and M_4 receptors (Doods et al. 1987; Hulme et al. 1990), have consistently demonstrated reductions in the density of these muscarinic receptor subtypes in a number of brain regions

implicated in the pathophysiology of schizophrenia (Dean et al. 1996, 2000, 2002; Crook et al. 2000, 2001; Zavitsanou et al. 2004, 2005; Deng and Huang 2005; Newell et al. 2007; Scarr et al. 2007). For example, [(3)H]pirenzepine binding has revealed low mAChR binding density in prefrontal cortex from subjects with schizophrenia (Brodmann's areas 8, 9, 10, and 46); importantly, this decreased density is also observed in individuals with schizophrenia who had never been treated with anticholinergic drugs (i.e., benzotropine mesylate; Crook et al. 2001). Gene expression studies have also found decreased M_1 (Mancama et al. 2003; Dean et al. 2002) and M_4 (Dean et al. 2002) expression in prefrontal cortex in schizophrenia. In the hippocampus, while M_4 receptor expression levels were significantly decreased in schizophrenia, M_1 receptor levels were comparable to that in controls (Scarr et al. 2007). Reduced [(3)H]pirenzepine binding has also been reported in the anterior cingulate cortex in schizophrenia (Zavitsanou et al. 2004; Newell et al. 2007). A subsequent study by Zavitsanou et al. (2005) using the same cohort of participants tested in their 2004 study showed no differences between schizophrenia patients and other groups on [(3)H]AF-DX384 binding (Zavitsanou et al. 2005), which by inference implicates the M_1 receptor in the previously observed reduction in [^{3}H]pirenzepine binding. Schizophrenia patients also have decreased muscarinic receptor binding in the striatum (Dean et al. 1996, 2000) and throughout the hippocampal formation, including the dentate gyrus, areas CA1–CA4, subiculum, and the parahippocampal gyrus (Crook et al. 2000).

Given the almost ubiquitous exposure to antipsychotic drugs in the schizophrenia population, it is possible that alterations in muscarinic receptor density could be an artifact of medication use. However, in situ hybridization studies suggest that antipsychotic exposure is unlikely to underlie these findings. For example, in rats, M_1 mRNA expression *increased* in the substantia nigra, pars compacta, nucleus accumbens, and hippocampus following exposure to both typical and atypical antipsychotic drugs (Han et al. 2008). This finding supported an earlier study in which long-term exposure to antipsychotic drugs in rats either increased or had no effect on the density of [^{3}H]pirenzepine binding (Crook et al. 2001). Taken together, this evidence suggests that M_1 receptor alterations may be central to the pathophysiology of schizophrenia. It is also consistent with evidence that atypical antipsychotic drug actions at the M_1 receptor may play a critical role in their efficacy in schizophrenia. Similarly, with respect to the M_4 receptor, both typical and atypical antipsychotic drugs have either no effect or increase binding of [3H] pirenzepine and [3H]AF-DX384 (Crook et al.1999), suggesting that decreases in M_4 receptor density in schizophrenia is unlikely to be attributed to antipsychotic drug exposure.

Findings from a study by Raedler et al. (2003) further supported postmortem findings of reductions in muscarinic receptor density in schizophrenia in an in vivo study of 12 unmedicated patients using [I-123]iodoquinuclidinyl benzilate ([(123)I] IQNB) single photon emission computed tomography (SPECT). In comparison to healthy controls matched for gender and age, the schizophrenia group had significant reductions (ranging from ~20 to ~33%) in muscarinic receptor availability in the cortex, basal ganglia, and thalamus. These studies provide compelling evidence

that abnormalities in mAChRs, especially M_1 and M_4 subtypes, exist in schizophrenia independent of treatment effects from antipsychotic drugs.

3 Partially Selective mAChR Agonists

A number of relatively selective muscarinic agonists were developed in the 1990s, each of which preferentially activated either M_1 or M_4 (or both) subtypes. It has been suggested that compounds that selectively enhance M_1 activity are effective in treating cognitive deficits in schizophrenia, while M_4 agonism is effective in treating psychotic symptoms of the disorder (Felder et al. 2001; Bymaster et al. 2003a, b). Evidence in support of this hypothesis comes from studies showing that a number of these partially selective M_1 receptor agonists, including xanomeline, sabcomeline, and milameline, have also demonstrated efficacy in preclinical models of cognition (Bodick et al. 1997; Harries et al. 1998; Dean et al. 2003; Weiner et al. 2004). While the M1 receptor is primarily regarded as a target for enhancing cognition, preclinical studies also implicate this receptor in psychosis. For example, M1 knockout mice show disruptions in pre-pulse inhibition and increased locomotor activity (Gerber et al. 2001; Miyakawa et al. 2001). They also exhibit increased sensitivity to amphetamine and striatal dopamine release is increased twofold compared to wild-type mice, suggesting that M1 activation inhibits dopamine release (Gerber et al. 2001). Importantly, M1 deletion does not appear to result in upregulation of other muscarinic receptor subtypes (Miyakawa et al. 2001; Hamilton et al. 1997). In addition, studies showing that mAChR agonists with partial M_4 selectivity, such as BuTAC, PTAC, xanomeline, and sabcomeline, show efficacy in animal models of psychosis; specifically, they are able to inhibit dopamine agonist-induced behaviors such as conditioned avoidance responding, D_1 and D_2 dopamine agonist-induced rotation, and pre-pulse inhibition (Fink-Jensen et al. 1998; Jones et al. 2005; Rasmussen et al. 2001; Shannon et al. 1999; Bymaster et al. 1998). However, the particular contributions of M_1 versus M_4 to cognition and psychosis are still being elucidated.

Xanomeline has been of particular interest because it is a predominantly M_1/M_4 receptor partial agonist which has shown cognition-enhancing and antipsychotic-like properties. Xanomeline has been demonstrated to exhibit functional dopamine antagonism in vitro (Stanhope et al. 2001; Shannon et al. 2000). Xanomeline's particular affinity for M_1/M_4 receptors has made it of relatively greater interest for schizophrenia due to the suggestions that agonism at the M_1 receptor is relevant to cognitive deficits in the disorder, while M_4 agonism may reduce psychotic symptoms (Felder et al. 2000; Bymaster et al. 2003a, b). Consistent with this hypothesis, xanomeline decreases dopamine cell firing in the ventral tegmental area (Shannon et al. 2000) and increases extracellular levels of dopamine in the prefrontal cortex (Perry et al. 2001). In primates, xanomeline inhibits unrest and stereotypies induced by dopamine agonists (Andersen et al. 2003), in spite of having no affinity for dopamine receptors (Bymaster et al. 1994; 1997).

Of the partially selective muscarinic agonists, xanomeline is the only one to progress to a clinical trial in schizophrenia patients. A small study of xanomeline's efficacy in schizophrenia conducted by our group found statistically significant differences between xanomeline and placebo groups in several measures of learning and memory and PANSS total scores, as well as differences between groups in positive and negative symptom subscales and CGI scores in a randomized placebo-controlled, double-blind, 4-week study (Shekhar et al. 2008). Xanomeline demonstrated similar efficacy in an earlier, relatively large ($n = 343$) multisite clinical trial in patients with Alzheimer's-type dementia (Bodick et al. 1997). In that study, in addition to significant differences between groups on cognitive performance measures, individuals on xanomeline fared significantly better on behavioral measures including vocal outbursts, suspiciousness, delusions, agitation, and hallucinations; moreover, these improvements were dose dependent.

While xanomeline's efficacy in improving cognition and reducing psychotic symptoms in schizophrenia (Shekhar et al. 2008) provided an important proof of concept with respect to mAChRs as therapeutic targets in the disorder, its clinical utility could be limited due to adverse side effects elicited by its agonism at other receptor subtypes (Bodick et al. 1997; Bymaster et al. 1998; Sur and Kinney 2005), as is the case with other multiple muscarinic receptor agonists (Schwarz et al. 1999; Wienrich et al. 2001). These adverse side effects are believed to arise due to M_2 and M_3 receptor activation (Bymaster et al. 2003b, c; Bodick et al. 1997). Indeed, most of the available muscarinic agonists display affinity for most of the five receptor subtypes, with varying levels of selectivity for particular subtypes (Heinrich et al. 2009; Bradley et al. 2010) in spite of early reports suggesting better subtype selectivity. Somewhat conflicting results regarding the selectivity of these agonists are believed to have arisen because they were tested in cell lines where receptor reserve was low; but in native tissue studies, selectivity declined and multiple mAChR subtypes were activated, possibly due to higher receptor reserve and systemic differences in the actions of the various compounds (Conn et al. 2009).

4 M_1 and M_4 Allosteric Activators

The difficulty in designing compounds with true subtype specificity at mAChR orthosteric sites, i.e., the binding site of acetylcholine, derives from their highly conserved sequence homology across the five subtypes (Wess 1996), which has inhibited drug discovery efforts (Felder et al. 2000). Recently, an alternative approach targeting allosteric receptor sites has gained momentum. Allosteric activators enhance the actions of endogenous acetylcholine but bind at a poorly conserved site (removed from the orthosteric site). This approach has proven successful for GPCRs in other neurotransmitter systems including at metabotropic glutamate receptors (Rodriguez et al. 2005; Hemstapat et al. 2007). In the muscarinic system, allosteric activators with antipsychotic-like profiles have been reported for the M_1 receptor (Jones et al. 2008; Ma et al. 2009; Langmead et al.

2008b; Vanover et al. 2008; Bradley et al. 2010; Li et al. 2007, 2008) and the M_4 receptor (Shirey et al. 2008; Brady et al. 2008; Chan et al. 2008; Leach et al. 2010), and are now considered highly promising targets for drug discovery efforts (Christopoulos 2002; Conn et al. 2009).

This new drug development strategy focusing on agonists and potentiators for mAChRs, especially at the M_1 and M_4 receptors, may provide new therapeutic compounds capable of true selectivity with fewer side effects (Conn et al. 2009). Moreover, these allosteric agents could be invaluable in dissociating contributions of different muscarinic receptor subtypes. For example, preclinical models suggest that xanomeline's clinical efficacy is due to actions at either the M_1 or the M_4 receptor, or reciprocal interactions between these two receptor subtypes. However, the differential contributions of M_1 versus M_4 mAChRs to xanomeline's antipsychotic and pro-cognitive effects have been an enduring question, but the lack of subtype selective agents has impeded progress in understanding their specific roles (Brady et al. 2008). Below, the recent progress in developing more selective allosteric mAChR agonists and new knowledge derived from studies using these compounds are summarized.

4.1 Selective M_1 Allosteric Activators

Several M_1-selective allosteric agonists and potentiators have been developed recently that have therapeutic relevance for schizophrenia. M_1 is abundantly expressed in forebrain, especially striatum, hippocampus, and cortical regions (Levey et al. 1991; Wall et al. 1991; Levey 1993; Vilaro et al. 1993), all of which are implicated in the pathogenesis of schizophrenia. M_1 agonism has been specifically suggested as a potential treatment for cognitive impairment in schizophrenia (Friedman 2004), and compounds with varying degrees of selectivity for this receptor have shown efficacy in preclinical animal models of cognition (Bodick et al. 1997; Harries et al. 1998; Cui et al. 2008) and in clinical populations in which cognitive deficits are prominent features of the disorder including Alzheimer's disease (Bodick et al. 1997) and schizophrenia (Shekhar et al. 2008).

4.1.1 AC-42 and Analogs

AC-42 and its structural analogs 77-LH-28-01 and AC-260584 are potent and selective M_1 allosteric agonists as determined by calcium mobilization and inositol phosphate accumulation assays (Spalding et al. 2006; Langmead et al. 2008b; Heinrich et al. 2009; Bradley et al. 2010). These compounds have shown vast improvements in subtype selectivity over orthosteric agonists including xanomeline (Heinrich et al. 2009; Bradley et al. 2010) and have some affinity for D2 and 5HT2b receptors (Vanover et al. 2008; Bradley et al. 2010; Heinrich et al. 2009), a profile

that is consistent with atypical antipsychotic drugs and may confer advantages in this regard.

Results from a study by Langmead et al. (2008) suggest that among the AC-42 family, 77-LH-28-01 may be a better candidate for drug development relative to AC-42 due to its in vitro and in vivo M_1 receptor selectivity. In electrophysiological studies, 77-LH-28-1 showed a full agonist profile, stimulating hippocampal CA1 cell firing in single unit recordings ($pEC_{50} = 6.3$), while AC-42 did not. Carbachol initiated an almost identical response ($pEC_{50} = 5.7$) which was reversed by the M_1 receptor antagonist pirenzepine, suggesting that this effect was mediated by the M_1 receptor. This result also suggests higher potency and efficacy for 77-LH-28-01 relative to AC-42. 77-LH-28-01 also induced gamma oscillatory activity in hippocampus, which studies in knockout mice have demonstrated requires M_1 receptors (Fisahn et al. 2002), and disruptions in gamma oscillations have been linked to schizophrenia (Spencer et al. 2003, 2004) and cognition (Kaiser and Lutzenberger 1999.

Studies of in vitro and in vivo properties of AC-260584 have demonstrated that it has a pharmacological profile similar to that of atypical antipsychotic drugs and orthosteric muscarinic agonists in several important respects. For example, it preferentially increased acetylcholine and dopamine in medial prefrontal cortex compared to that in the nucleus accumbens (Li et al. 2007, 2008). Interestingly, *N*-desmethylclozapine, a metabolite of clozapine, was identified as an M_1 allosteric agonist (Sur et al. 2003), which may account for the pro-cognitive effects of clozapine in schizophrenia (Li et al. 2005; Spalding et al. 2006), and shared the ability of AC-260584 to induce acetylcholine release in the mPFC, an effect that was blocked by the M_1 antagonist telenzepine in the mPFC, but not in the nucleus accumbens (Li et al. 2005). This mPFC finding is consistent with the actions of partial M_1 agonists xanomeline and sabcomeline (Li et al. 2008) and to that of atypical antipsychotics, including clozapine and olanzapine, which increase extracellular dopamine and acetylcholine in the mPFC but not the nucleus accumbens (Kuroki et al. 1999; Ichikawa et al. 2002). Dopamine is believed to modulate critical aspects of prefrontal cortex-mediated working memory function that are compromised in schizophrenia (Braver and Cohen 2000), where dopaminergic hypofunction is believed to contribute to negative and cognitive symptoms of the disorder (Hill et al. 2004; Carter et al. 1998; Perlstein et al. 2001; Riehemann et al 2001; Weinberger et al. 1986; Wolkin et al. 1992; Andreasen et al. 1997). Taken together, these findings add to evidence that atypical antipsychotic drugs and less selective muscarinic agonists could mediate their cognitive effects through M_1 receptor-mediated cholinergic and dopaminergic modulation.

Behaviorally, AC-260584 has demonstrated an antipsychotic-like profile and improved cognitive performance (Vanover et al. 2008; Bradley et al. 2010). An antipsychotic-like profile was demonstrated by AC-260584's ability to reduce amphetamine- and MK-801-induced locomotor hyperactivity as well as reduce apomorphine-induced climbing behavior (Vanover et al. 2008). This finding, along with earlier findings that xanomeline also reduces amphetamine-induced hyperactivity in rodents (Stanhope et al. 2001) and primates (Andersen et al.

2003), suggests that M_1 agonism (versus M_4) may contribute to its antipsychotic effects more than previously believed. However, the activation of D2 and 5HT2b receptors (Vanover et al. 2008; Bradley et al. 2010; Heinrich et al. 2009) by AC-260584 makes it difficult to assess adequately the contribution of M_1 versus M_4 receptors to antipsychotic-like effects observed for compounds like xanomeline (Heinrich et al. 2009).

Preclinical studies have shown cognition-enhancing effects of AC-260584 in two animal models of learning and memory. AC-260584 also improved spatial memory on the Morris water maze (Vanover et al. 2008). Rats treated with AC-260584 demonstrated improved performance on the novel object recognition task, which was reversed by pirenzipene, a muscarinic antagonist (Bradley et al. 2010). $ERK_{1/2}$ phosphorylation, which is associated with important aspects of synaptic plasticity and learning and memory processes (Giovannini 2006), was increased by AC-260584 in hippocampal cells of wild-type but not M_1 knockout mice (Bradley et al. 2010). Moreover, it had low catalepsy rates (Vanover et al. 2008), which is predictive of low EPS in humans (Hoffman and Donovan 1995). Bradley et al. (2010) recently concluded that AC-260584 has high bioavailability, potency, and efficacy, and should serve as a lead compound for drug discovery efforts.

4.1.2 TPBP

Jones and colleagues (2008) recently reported that TPBP is a potent muscarinic allosteric agonist that has shown in vitro M_1 selectivity. TPBP showed robust agonist activity in M_1 transfected cell lines, but not in M_2–M_5 transfected cells. In hippocampal slices, TPBP increased NMDA receptor currents. This is consistent with findings from other studies indicating that this is an M_1-mediated effect. For example, M_1 receptors are co-localized with NMDA receptors in hippocampal neurons, and selective M_1 antagonists block carbachol-induced potentiation of NMDA current (Marino et al. 1998). NMDA-mediated long-term potentiation is enhanced by the muscarinic agonist carbachol in wild-type and M_3 knockout mice, but not in M_1 knockout mice (Shinoe et al. 2005). Potentiation of NMDARs is believed to be critical to synaptic plasticity underlying learning and memory (McBain and Mayer 1994), and is consistent with the finding that the AC-260584 induced $ERK_{1/2}$ phosphorylation in hippocampus (Bradley et al. 2010). Therefore, these effects support a role both for the M_1 receptor in cognition and for the efficacy of TPBP in enhancing cognitive deficits in schizophrenia. Importantly, NMDARs have also been implicated in psychosis, and potentiation of NMDAR current may be a mechanism by which muscarinic agonists mediate their antipsychotic effects (Marino and Conn 2002; Jones et al. 2008). Consistent with this hypothesis, TPBP reversed amphetamine-induced hyperactivity and demonstrated a FOS expression profile similar to both xanomeline and atypical antipsychotics, and these effects were achieved at doses that did not induce catalepsy (Jones et al. 2008).

Indeed, evidence increasingly suggests that in addition to pro-cognitive effects, M_1 receptor activation may also have antipsychotic effects (Vanover et al. 2008;

Mirza et al. 2003; Friedman 2004), consistent with the behavioral effects of TPBP. For example, M_1 knockout mice are hyperactive, most likely due to increased dopamine in the striatum (Wess et al. 2003; Gerber et al. 2001). Striatal hyperdopaminergia has been linked to acute psychotic states in schizophrenia (Schmitt Meisenzahl et al. 2009), striatal neurotransmission in schizophrenia (Gerber et al. 2001), suggesting that M_1 receptor abnormalities may play a role in psychosis.

4.1.3 BQCA

Benzylquinolone carboxylate (BQCA) is a potent and highly selective M_1 positive allosteric modulator that exhibits no agonist properties, but instead greatly enhances the potency of acetylcholine (Ma et al. 2009; Shirey et al. 2009). In wild-type mice but not in $M_1^{-/-}$ mice, oral administration of BQCA induced FOS activation in the cortex, hippocampus, and cerebellum, and significantly increased the ratio of phosophorylated ERK to total ERK (Ma et al. 2008). BQCA ALSO increased contextual fear conditioning in animals that were coadministered scopolamine, but the associative learning was blocked for animals receiving scopolamine only (Ma et al. 2009). The ability of BCQA to counteract the effects of scopolamine in this hippocampus-dependent task suggests that M_1 may enhance learning by reinforcing associative learning; however, M_1 receptors do not appear to be critical for contextual fear conditioning because M_1 knockout mice show no acquisition deficit on this task (Anagnostaras et al. 2003; Miyikawa et al. 2001), and the allosteric selective M_1 antagonist VUO255035 had no effect on contextual fear conditioning (Sheffler et al. 2009). BQCA increased the excitability of mPFC cells in slice preparations from wild-type but not M_1 null mutant mice, and improved impaired PFC-dependent reversal learning in a mouse model of Alzheimer's disease (Shirey et al. 2009).

BQCA, TPBP, and AC-42 all reduced amphetamine-induced hyperactivity; however, TBPB and AC-42 did not counteract scopolamine's effects on fear conditioning, which may be due to a different mechanism of action on the part of BQCA, as suggested by the ability of this drug to induce β-arrestin recruitment (Ma et al. 2009). If M_1 activation has both antipsychotic and pro-cognitive properties, it would be a particularly attractive target for schizophrenia-relevant therapies (Vanover et al. 2008). The finding that BQCA can mimic the antipsychotic-like profile of earlier allosteric M_1 activators and also exhibited pro-cognitive effects in contextual fear conditioning, an animal model of cognition suggests that it may have considerable advantages for treatment of schizophrenia.

4.2 Selective M_4 Allosteric Activators

The M_4 receptor is particularly relevant to schizophrenia for several reasons. This receptor is implicated in the regulation of dopamine levels in brain regions important in the pathophysiology of schizophrenia, including the nucleus accumbens

(Tzavara et al. 2004) and the striatum (Zhang et al. 2002a, b; Gomeza et al. 1999), where it is an inhibitory autoreceptor on cholinergic nerve terminals (Zhang et al. 2002a, b). The M_4 receptor is also believed to play a role in the antipsychotic properties of muscarinic agonists such as xanomeline (Mirza et al. 2003) as well as the atypical antipsychotic drug clozapine (Olianas et al. 1999), whose affinity for the M_4 receptor may be one source of its antipsychotic efficacy. Moreover, although the M_1 receptor has been emphasized as a possible mechanism mediating cognitive improvements observed following xanomeline administration (Felder et al. 2000; Bymaster et al. 2003b) and a wealth of evidence supports a role for this receptor in mediating various aspects of cognition, the presynaptic location of M_4 mAChRs excitatory neurons within the hippocampal formation (Rouse et al. 1999) suggests that they may modulate neurocognitive function as well. The finding that M_4 mRNA expression is decreased in schizophrenia but M_1 density being unchanged supports the argument that reductions in M_4 density may play an important role in learning and memory deficits observed in schizophrenia (Scarr et al. 2007).

4.2.1 VU010010 and Analogs

The first M_4 allosteric potentiator was reported by Shirey et al. (2008). VU010010 selectively enhanced the affinity of acetylcholine for the M_4 receptor and enhanced its efficacy. Recordings from hippocampal cells revealed that VU010010 potentiated carbachol's depression of excitatory postsynaptic potentials at schaffer collateral-CA1 synapses in wild-type but not M_4 knockout mice, suggesting a role for the M_4 receptor in mediating NMDA-mediated excitatory neutrotransmission. Further optimization of VU010010 led to the development of two additional potent and selective allosteric modulators of the M_4 receptor, VU0152099 and VU0152100, which have increased bioavailability and superior pharmacokinetic profiles (Brady et al. 2008; Conn et al. 2009). Both have no agonist effects at M_4, but instead potentiate the effects of acetylcholine. These molecules do not bind with other G-protein-coupled receptors, muscarinic or otherwise, and both potentiated M_4 response to acetylcholine as measured by enhanced calcium mobilization. Importantly, acetylcholine was more potent in the presence of these compounds as demonstrated by a dramatic increase in the ability of ACh to displace [3H] NMS. Behaviorally, both compounds reversed amphetamine-induced hyperactivity, demonstrating antipsychotic-like activity. This is consistent with evidence from M_4 knockout mice that M_4 receptors modulate cholinergic and dopaminergic neurotransmission and that loss of M_4 function results in hyperdopaminergia (Tzavara et al. 2004). In the midbrain, cholinergic excitation activates dopamine release, and data from M_4 knockout mice suggest that these mAChRs serve as inhibitory autoreceptors in the midbrain (Tzavara et al. 2004). Therefore, M_4 agonism could reduce acetylcholine release and subsequent overexcitation of midbrain dopamine neurons, which would decrease dopamine release in subcortical structures. This mechanism may provide an explanation for the antipsychotic-like profile of VU0152099 and VU0152100 (Brady et al. 2008) as well as the

antipsychotic properties of agents with partial M_4 selectivity, including clozapine (Olianas et al. 1999), xanomeline (Stanhope et al. 2001; Andersen et al. 2003; Mirza et al. 2003; Shekhar et al. 2008), and the M_2/M_4 preferring partial agonist PTAC (Fink-Jensen et al. 1998).

4.2.2 LY2033298

The Eli Lilly compound LY2033298 was recently identified as a highly potent (>40-fold increase in potency) and selective allosteric potentiator of M_4 receptors that acts primarily by increasing the affinity of acetylcholine for the M_4 receptor as well as demonstrating agonist activity (Chan et al. 2008; Leach et al. 2010). LY2033298 has shown efficacy in two animal models of psychosis; specifically, it attenuated conditioned avoidance responding and reversed apomorphine-induced disruptions of pre-pulse inhibition (Chan et al. 2008). A reduction in conditioned avoidance responding was also observed in M_4 knockout mice, but the effect was significantly smaller compared to that in wild-type mice (Leach et al. 2010). These findings are consistent with the finding that PTAC and BuTAC, which are M_2/M_4 partial agonists with $M_1/M_3/M_5$ antagonist properties, display antipsychotic-like profiles in animal models, including inhibition of conditioned avoidance responding (PTAC; Bymaster et al. 1998), inhibition of apomorphine-induced climbing, and impaired passive avoidance responding (BuTAC; Rasmussen et al. 2001). Taken together with evidence that M_4 modulates dopaminergic neurotransmission in regions implicated in positive symptoms of schizophrenia (Tzavara et al. 2004; Gomeza et al. 1999), the behavioral effects of LY2033298 provide additional evidence that M_4 agonist activity may be a viable novel therapeutic approach for psychotic symptoms of schizophrenia.

5 M_2 and M_5 mAChRs as Potential Therapeutic Targets

The focus on muscarinic receptor-focused therapies for schizophrenia has overwhelmingly focused on M_1 and M_4 receptors. However, there is intriguing, but limited, evidence that the M_2 and M_5 receptors may also be potential therapeutic targets.

5.1 M_2 Receptor

M_2 receptors are found throughout the brain and CNS, including the basal forebrain, where they act primarily as inhibitory autoreceptors, regulating acetylcholine release from forebrain projections including the hippocampus (Zhang et al. 2002a, b; Kitaichi et al. 1999a, b; Rouse et al. 1999, 2000) and cortex (Zhang et al. 2002a, b). The M_2 receptors have been implicated in cognitive and psychotic symptoms of

schizophrenia (Eglen 2005; Fisher 2008), but are especially believed to play a significant role in learning and memory due to their prominence in the hippocampus, where they are found pre- and postsynaptically.

Numerous studies have reported that M_2 receptor antagonists with various levels of selectivity have increased acetylcholine release in vitro in the hippocampus, cortex, and striatum (Billard et al. 1995; Wang et al. 2002; Carey et al. 2001; Quirion et al. 1995; Vannucchi et al. 1997), presumably through inhibition of this negative feedback mechanism. Corticostriatal recordings in rat slice preparations also showed that an antagonist of M_2-like receptors, methoctramine, facilitates striatal long-term potentiation (Calabresi et al. 2000). The finding that the M_2 selective antagonist SCH 55790 enhanced hippocampal, cortical, and striatal acetylcholine release (Carey et al. 2001) is consistent with reports of increased acetylcholine release in hippocampus and cortex in the presence of less selective M_2 antagonists such as BIBN-99 and AF-DX 384 (Quirion et al. 1995; Vannucchi et al. 1997). Interestingly, anatomical evidence of M_2 receptor localization to non-cholinergic neurons indicates that it also acts a presynaptic heteroreceptor (Rouse et al. 2000).

Behaviorally, a number of M_2 antagonists have shown pro-cognitive effects in animal models. For example, bilateral infusion of methoctramine into the dorsolateral striatum of rats improved performance on a memory task (Lazaris et al. 2003). The compound (+)-14 had high oral efficacy, was highly selective for the M_2 receptor, and significantly decreased passive avoidance response latency in young rats (Wang et al. 2002), a result also reported for the highly selective M_2 antagonist SCH 72788 (Lachowicz et al. 2001). Both SCH 57790 and BIBN-99 induced similar improvements in preclinical models of learning and memory (Carey et al. 2001; Rowe et al. 2003).

It should be noted, however, that in contrast to the findings that M_2 antagonism enhanced performance in pharmacological experiments, Seeger et al. (2004) found that M_2-deficient mice showed impaired learning on a hippocampus-dependent spatial learning task and impaired behavioral flexibility. In marked contrast to M_4 (Gerber et al. 2001) null mutant mice, M_2 knockout mice were not different from wild-type mice on locomotor activity, consistent with the hypothesis that of the two inhibitory mAChRs, M_4 has a greater role in regulating dopaminergic neurotransmission (Tzavara et al. 2004).

Antagonism of presynaptic M_2 receptors increases synaptic acetylcholine levels (Meyer and Otero 1985; Billard et al. 1995; Wang et al. 2002), which could lead to increased M_1 receptor activation (Fisher 2008). Thus, it has been hypothesized that M_2 antagonists may be a possible novel therapeutic direction for the improvement of cognitive impairment and psychotic symptoms (Eglen 2005; Clader and Wang 2005; Fisher 2008). However, to date no clinical studies of M_2 selective agonists have been conducted in schizophrenia. More seriously, although they could be efficacious in treating cognitive and psychotic symptoms in schizophrenia, enthusiasm for M_2-targeted therapies is limited due to their high expression in cardiac tissue (Caulfield 1993; Brodde and Michel 1999), which would likely necessitate

more specific CNS targeting than is currently available (Bymaster et al. 2002; Fisher 2008).

5.2 M_5 Receptor

Although the M_5 receptor is found in the cerebral cortex and hippocampus, it is especially predominant in the substantia nigra and ventral tegmental brain regions, where it is localized to dopaminergic neurons (Vilaró et al. 1990; Weiner et al. 1990). Its localization to the so-called "reward pathways" has prompted speculation that it may be an important target for treatment of schizophrenia (Mirza et al. 2003) as well as drug abuse (Raffa 2009; Basile et al. 2002; Fink-Jensen et al. 2003). Dysregulation of motivational drive is a central feature of schizophrenia, implicating M_5 receptors as potential targets for treatment in the disorder.

In addition to its probable role in modulating reward sensitivity, the M_5 receptor has also been implicated in tonic regulation of mesolimbic and striatal dopamine levels (Blaha et al. 1996; Zhang et al. 2002a, b; Basile et al. 2002; Forster and Blaha 2003). In addition, xanomeline's antipsychotic effects may be attributable in part to its partial agonism of the M_5 receptor in striatum, although M_4 is a more likely mechanism (Mirza et al. 2003). M_5-deficient mice retain phasic but not sustained dopamine release into the nucleus accumbens (Forster et al. 2002). M_5 receptors in VTA activate mesolimbic dopamine input to the nucleus accumbens (Yeomans et al. 2001), and M_5 receptor activation may result in sustained activation of dopaminergic neurons (Forster et al 2002). A study by the same group (Wang et al. 2004) reported that compared to control animals, M_5-deficient mice have improved latent inhibition and decreased amphetamine induced locomotor activity, consistent with reduced dopamine release in the nucleus accumbens. Given that earlier studies have reported that inactivation of dopamine terminals in the nucleus accumbens blocks amphetamine induced locomotion (Joyce and Koob 1981), and reduced nucleus accumbens dopamine activity results in increased latent inhibition (Joseph et al 2000; Moser et al 2000; Russig et al 2002; Gray et al 1997), it is probable that decreased dopamine release in the M_5-deficient mice produced these behavioral results. Taken together, these results suggest that antagonism at the M_5 receptor may reduce psychotic symptoms of schizophrenia by decreasing subcortical dopamine release.

To date, no clinical or preclinical studies of M_5 selective compounds have been undertaken. However, two recent reports have described M_5 allosteric modulators. The first such report characterized VU0238429, which displayed high selectivity ($>$30-fold) for the M_5 receptor in comparison to M_1 and M_3, and no potentiator activity in M_2 and M_4 receptor transfected cells (Bridges et al. 2009). The previous study found that VU0238429 increased the potency of acetylcholine, but had poor brain penetration. The second study described the allosteric properties of the antiarrythmia drug amiodarone, which was found to be an allosteric potentiator at

the M_5 receptor, but not M_1 receptors; interestingly, amiodarone enhanced acetylcholine's efficacy at the M_5 receptor, but not its potency (Stahl and Ellis 2010). Discovery of these molecules provides a significant breakthrough and should lead to additional chemical modifications, electrophysiological studies, and in vivo characterizations of M_5 selective modulators in order to gain additional insight into the role of this receptor in psychosis and addictive behavior.

6 Conclusion

As reviewed above, it has become increasingly evident that the muscarinic system is an attractive novel target for treating cognitive and psychotic symptoms of schizophrenia. The major obstacle to exploiting this receptor system's therapeutic promise has been the lack of selectivity for specific receptor subtypes. Therefore, to date, the few muscarinic agonists that have been tested in humans have shown efficacy, but more selective compounds could make this approach highly fruitful in developing new therapies for schizophrenia. New generations of allosteric activators targeting M_1 and M_4 receptors have now demonstrated improved selectivity and some preclinical evidence of antipsychotic-like and pre-cognitive effects. These compounds may offer substantial therapeutic benefit for the treatment of cognitive and psychotic symptoms of schizophrenia and could be entering clinical trials in the next few years.

References

Abood LG, Biel JH (1962) Anticholinergic psychototmimetic agents. Int Rev Neurobiol 4:217–273

Anagnostaras SG, Murphy GG, Hamilton SE et al (2003) Selective cognitive dysfunction in acetylcholine M_1 muscarinic receptor mutant mice. Nat Neurosci 6:51–58

Andersen MB, Fink-Jensen A, Peacock L et al (2003) The muscarinic M_1/M_4 receptor agonist xanomeline exhibits antipsychotic-like activity in *Cebus apella* monkeys. Neuropsychopharmacology 28:1168–1175

Andreasen NC, O'Leary DS, Flaum M et al (1997) Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. Lancet 349:1730–1734

Basile AS, Fedorova I, Zapata A et al (2002) Deletion of the M_5 muscarinic acetylcholine receptor attenuates morphine reinforcement and withdrawal but not morphine analgesia. Proc Natl Acad Sci U S A 99:11452–11457

Bellack AS, Gold JM, Buchanan RW (1999) Cognitive rehabilitation for schizophrenia: problems, prospects, and strategies. Schizophr Bull 25:257–274

Billard W, Binch H 3rd, Crosby G et al (1995) Identification of the primary muscarinic autoreceptor subtype in rat striatum as M_2 through a correlation of in vivo microdialysis and in vitro receptor binding data. J Pharmacol Exp Ther 273:273–279

Blaha CD, Allen LF, Das S et al (1996) Modulation of dopamine efflux in the nucleus accumbens after cholinergic stimulation of the ventral tegmental area in intact, pedunculopontine tegmental nucleus-lesioned, and laterodorsal tegmental nucleus-lesioned rats. J Neurosci 16:714–722

Bodick NC, Offen WW, Levey AI et al (1997) (1997) Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. Arch Neurol 54:465–473

Bolden C, Cusack B, Richelson E (1991) Clozapine is a potent and selective muscarinic antagonist at the five cloned human muscarinic acetylcholine receptors expressed in CHO-K1 cells. Eur J Pharmacol 192:205–206

Bradley SR, Lameh J, Ohrmund L et al (2010) AC-260584, an orally bioavailable M(1) muscarinic receptor allosteric agonist, improves cognitive performance in an animal model. Neuropharmacology 58:365–373

Brady AE, Jones CK, Bridges TM et al (2008) Centrally active allosteric potentiators of the M_4 muscarinic acetylcholine receptor reverse amphetamine-induced hyperlocomotor activity in rats. J Pharmacol Exp Ther 327:941–953

Braver TS, Cohen JD (2000) On the control of control: the role of dopamine in regulating prefrontal function and working memory. In: Monsell S, Driver J (eds) Control of cognitive processes: attention and performance XVIII. MIT Press, Cambridge

Bridges TM, Marlo JE, Niswender CM (2009) Discovery of the first highly M_5-preferring muscarinic acetylcholine receptor ligand, an M_5 positive allosteric modulator derived from a series of 5-trifluoromethoxy N-benzyl isatins. J Med Chem 52:3445–3448

Brodde OE, Michel MC (1999) Adrenergic and muscarinic receptors in the human heart. Pharmacol Rev 51:651–690

Bymaster FP, Wong DT, Mitch CH et al (1994) Neurochemical effects of the M_1 muscarinic agonist xanomeline (LY246708/NNC11-0232). J Pharmacol Exp Ther 269:282–289

Bymaster FP, Whitesitt CA, Shannon HE et al (1997) Xanomeline: a selective muscarinic agonist for the treatment of Alzheimers disease. Drug Dev Res 40:158–177

Bymaster FP, Shannon HE, Rasmussen K et al (1998) Unexpected antipsychotic-like activity with the muscarinic receptor ligand (5R,6R)6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo [3.2.1]octane. Eur J Pharmacol 356:109–119

Bymaster FP, Felder C, Ahmed S et al (2002) Muscarinic receptors as a target for drugs treating schizophrenia. Curr Drug Targets CNS Neurol Disord 1:163–181

Bymaster FP, Felder CC, Tzavara E (2003a) Muscarinic mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 27:1125–1143

Bymaster FP, McKinzie DL, Felder CC et al (2003b) Use of M_1-M_5 muscarinic receptor knockout mice as novel tools to delineate the physiological roles of the muscarinic cholinergic system. Neurochem Res 28:437–442

Bymaster FP, Carter PA, Yamada M et al (2003c) Role of specific muscarinic receptor subtypes in cholinergic parasympathomimetic responses, in vivo phosphoinositide hydrolysis, and pilocarpine-induced seizure activity. Eur J Neurosci 17:1403–1410

Calabresi P, Centonze D, Gubellini P et al (2000) Acetylcholine-mediated modulation of striatal function. Trends Neurosci 23:120–126

Carey GJ, Billard W, Binch H 3rd et al (2001) SCH 57790, a selective muscarinic M(2) receptor antagonist, releases acetylcholine and produces cognitive enhancement in laboratory animals. Eur J Pharmacol 431:189–200

Carter CS, Perlstein P, Ganguli R et al (1998) Functional hypofrontality and working memory dysfunction in schizophrenia. Am J Psychiatry 155:1285–1287

Caulfield MP (1993) Muscarinic receptors – characterization, coupling and function. Pharmacol Ther 58:319–379

Chan WY, McKinzie DL, Bose S, Mitchell SN, Witkin JM, Thompson RC, Christopoulos A, Lazareno S, Birdsall NJ, Bymaster FP, Felder CC. Allosteric modulation of the muscarinic M4 receptor as an approach to treating schizophrenia. Proc Natl Acad Sci USA. 2008 Aug 5;105 (31):10978–10983. Epub 2008 Aug 4. PubMed PMID: 18678919; PubMed Central PMCID: PMC2495016

Christie JE, Shering A, Ferguson J et al (1981) Physostigmine and arecoline: effects of intravenous infusions in Alzheimer presenile dementia. Br J Psychiatry 138:46–50

Christopoulos A (2002) Allosteric binding sites on cell-surface receptors: novel targets for drug discovery. Nat Rev Drug Discov 1:198–210

Clader JW, Wang Y (2005) Muscarinic receptor agonists and antagonists in the treatment of Alzheimer's disease. Curr Pharm Des 11:3353–3361

Clarke LA, Cassidy CW, Catalano G et al (2004) Psychosis induced by smoking cessation clinic administered anticholinergic overload. Ann Clin Psychiatry 16:171–175

Conn PJ, Jones CK, Lindsley CW (2009) Subtype-selective allosteric modulators of muscarinic receptors for the treatment of CNS disorders. Trends Pharmacol Sci 30:148–155

Crook JM, Tomaskovic-Crook E, Copolov DL et al (2000) Decreased muscarinic receptor binding in subjects with schizophrenia: a study of the human hippocampal formation. Biol Psychiatry 48:381–388

Crook JM, Tomaskovic-Crook E, Copolov DL et al (2001) Low muscarinic receptor binding in prefrontal cortex from subjects with schizophrenia: a study of Brodmann's areas 8, 9, 10, and 46 and the effects of neuroleptic drug treatment. Am J Psychiatry 158:918–925

Cui YH, Si W, Yin L et al (2008) A novel derivative of xanomeline improved memory function in aged mice. Neurosci Bull 24:251–257

Dean B, Crook JM, Opeskin K et al (1996) The density of muscarinic M_1 receptors is decreased in the caudate-putamen of subjects with schizophrenia. Mol Psychiatry 1:54–58

Dean B, Crook JM, Pavey G et al (2000) Muscarinic$_1$ and $_2$ receptor mRNA in the human caudate-putamen: no change in m1 mRNA in schizophrenia. Mol Psychiatry 5:203–207

Dean B, McLeod M, Keriakous D et al (2002) Decreased muscarinic1 receptors in the dorsolateral prefrontal cortex of subjects with schizophrenia. Mol Psychiatry 7:1083–1091

Dean B, Bymaster FP, Scarr E (2003) Muscarinic receptors in schizophrenia. Curr Mol Med 3:419–426

Deng C, Huang XF. Decreased density of muscarinic receptors in the superior temporal gyrusin schizophrenia. J Neurosci Res 2005 Sep 15;81(6):883–890. PubMed PMID: 16041805

Dickinson D, Coursey RD (2002) Independence and overlap among neurocognitive correlates of community functioning in schizophrenia. Schizophr Res 56:161–170

Doods HN, Mathy MJ, Davidesko D et al (1987) Selectivity of muscarinic antagonists in radioligand and in vivo experiments for the putative M_1, M_2 and M_3 receptors. J Pharmacol Exp Ther 242:257–262

Eglen RM (2005) Muscarinic receptor subtype pharmacology and physiology. Prog Med Chem 43:105–136

Felder CC, Bymaster FP, Ward J et al (2000) Therapeutic opportunities for muscarinic receptors in the central nervous system. J Med Chem 43:4333–4353

Fink-Jensen A, Kristensen P, Shannon HE et al (1998) Muscarinic agonists exhibit functional dopamine antagonism in unilaterally 6-OHDA lesioned rats. Neuroreport 9:3481–3486

Fink-Jensen A, Fedorova I, Wortwein G (2003) Role for M_5 muscarinic acetylcholine receptors in cocaine addiction. J Neurosci Res 74:91–96

Fisher CM (1991) Visual hallucinations on eye closure associated with atropine toxicity. A neurological analysis and comparison with other visual hallucinations. Can J Neurol Sci 18:18–27

Fisher A (2008) Cholinergic treatments with emphasis on M_1 muscarinic agonists as potential disease-modifying agents for Alzheimer's disease. Neurotherapeutics 5:433–442

Fisahn A, Yamada M, Duttaroy A, Gan JW, Deng CX, McBain CJ, Wess J. Muscarinic induction of hippocampal gamma oscillations requires coupling of the M1 receptor to two mixed cation currents. Neuron 2002 Feb 14;33(4):615–624. PubMed PMID:11856534

Forster GL, Blaha CD (2003) Pedunculopontine tegmental stimulation evokes striatal dopamine efflux by activation of acetylcholine and glutamate receptors in the midbrain and pons of the rat. Eur J Neurosci 17:751–762

Forster GL, Yeomans JS, Takeuchi J et al (2002) M_5 muscarinic receptors are required for prolonged accumbal dopamine release after electrical stimulation of the pons in mice. J Neurosci 22:RC190

Fredrickson A, Snyder PJ, Cromer J (2008) The use of effect sizes to characterize the nature of cognitive change in psychopharmacological studies: an example with scopolamine. Hum Psychopharmacol 23:425–436

Friedman JI (2004) Cholinergic targets for cognitive enhancement in schizophrenia: focus on cholinesterase inhibitors and muscarinic agonists. Psychopharmacology (Berl) 174:45–53

Frommann I, Pukrop R, Brinkmeyer J et al (2011) Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the early – and additional memory dysfunction in the late – prodromal state. Schizophr Bull 37(4):861–873

Gerber DJ, Sotnikova TD, Gainetdinov RR et al (2001) Hyperactivity, elevated dopaminergic transmission, and response to amphetamine in M_1 muscarinic acetylcholine receptor-deficient mice. Proc Natl Acad Sci U S A 98:15312–15317

Gershon S, Olariu J (1960) JB 329 degrees—a new spychotomimetic, its antagonism by tetrahydroaminacrin and its comparison with LSD, mescaline and sernyl. J Neuropsychiatr 1:283–292

Giovannini MG (2006) The role of the extracellular signal-regulated kinase pathway in memory encoding. Rev Neurosci 17:619–634

Gold JM, Goldberg RW, McNary SW et al (2002) Cognitive correlates of job tenure among patients with severe mental illness. Am J Psychiatry 159:1395–1402

Gomeza J, Zhang L, Kostenis E et al (1999) Enhancement of D1 dopamine receptor-mediated locomotor stimulation in M_4 muscarinic acetylcholine receptor knockout mice. Proc Natl Acad Sci U S A 96:10483–10488

Granacher RP, Baldessarini RJ (1975) Physostigmine. Its use in acute anticholinergic syndrome with antidepressant and antiparkinson drugs. Arch Gen Psychiatry 32:375–380

Gray JA, Moran PM, Grigoryan G (1997) Latent inhibition: the nucleus accumbens connection revisited. Behav Brain Res 88:27–34

Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–330

Hamilton SE, Loose MD, Qi M et al (1997) Disruption of the M_1 receptor gene ablates muscarinic receptor-dependent M current regulation and seizure activity in mice. Proc Natl Acad Sci U S A 94:13311–13316

Han M, Newell K, Zavitsanou K et al (2008) Effects of antipsychotic medication on muscarinic M_1 receptor mRNA expression in the rat brain. J Neurosci Res 86:457–464

Harries MH, Samson NA, Cilia J et al (1998) The profile of sabcomeline (SB-202026), a functionally selective M_1 receptor partial agonist, in the marmoset. Br J Pharmacol 124:409–415

Heinrich JN, Butera JA, Carrick T et al (2009) Pharmacological comparison of muscarinic ligands: historical versus more recent muscarinic M_1-preferring receptor agonists. Eur J Pharmacol 605:53–56

Hemstapat K, Da Costa H, Nong Y et al (2007) A novel family of potent negative allosteric modulators of group II metabotropic glutamate receptors. J Pharmacol Exp Ther 322:254–264

Hill K, Mann L, Laws KR et al (2004) Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. Acta Psychiatr Scand 110:243–256

Hirsch S, Barnes TRE (1995) The clinical treatment of schizophrenia with antipsychotic medication. In: Hirsch SR, Weinberger DR (eds) Schizophrenia. Blackwell Science, Oxford

Hoffman DC, Donovan H (1995) Catalepsy as a rodent model for detecting antipsychotic drugs with extrapyramidal side effect liability. Psychopharmacology 120:128–133

Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III – the final common pathway. Schizophr Bull 35:549–562

Hulme EC, Birdsall NJ, Buckley NJ (1990) Muscarinic receptor subtypes. Annu Rev Pharmacol Toxicol 30:633–673

Ichikawa J, Dai J, O'Laughlin IA et al (2002) Atypical, but not typical, antipsychotic drugs increase cortical acetylcholine release without an effect in the nucleus accumbens or striatum. Neuropsychopharmacology 26:325–339

Jones CK, Eberle EL, Shaw DB et al (2005) Pharmacologic interactions between the muscarinic cholinergic and dopaminergic systems in the modulation of prepulse inhibition in rats. J Pharmacol Exp Ther 312:1055–1063

Jones CK, Brady AE, Davis AA et al (2008) Novel selective allosteric activator of the M_1 muscarinic acetylcholine receptor regulates amyloid processing and produces antipsychotic-like activity in rats. J Neurosci 28:10422–10433

Joseph MH, Peters SL, Moran PM et al (2000) Modulation of latent inhibition in the rat by altered dopamine transmission in the nucleus accumbens at the time of conditioning. Neuroscience 101:921–930

Joyce EM, Koob GF (1981) Amphetamine-, scopolamine- and caffeine-induced locomotor activity following 6-hydroxydopamine lesions of the mesolimbic dopamine system. Psychopharmacology (Berl) 73:311–313

Kaiser J, Lutzenberger W (2005) Cortical oscillatory activity and the dynamics of auditory memory processing. Rev Neurosci 16:239–254

Kitaichi K, Hori T, Srivastava LK et al (1999a) Antisense oligodeoxynucleotides against the muscarinic M_2, but not M_4, receptor supports its role as autoreceptors in the rat hippocampus. Brain Res Mol Brain Res 67:98–106

Kitaichi K, Day JC et al (1999b) A novel muscarinic M(4) receptor antagonist provides further evidence of an autoreceptor role for the muscarinic M(2) receptor sub-type. Eur J Pharmacol 383:53–56

Kuroki T, Meltzer HY, Icikawa J (1999) Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. J Pharmacol Exp Ther 288:774–781

Lachowicz JE, Duffy RA, Ruperto V, Kozlowski J, Zhou G, Clader J, Billard W, Binch H 3rd, Crosby G, Cohen-Williams M, Strader CD, Coffin V. Facilitation of acetylcholine release and improvement in cognition by a selective M2 muscarinic antagonist, SCH 72788. Life Sci 2001 Apr 27;68(22–23):2585–2592. PubMed PMID: 11392630

Lazaris A, Bertrand F, Lazarus C, Galani R, Stemmelin J, Poirier R, Kelche C, Cassel JC. Baseline and 8-OH-DPAT-induced release of acetylcholine in the hippocampus of aged rats with different levels of cognitive dysfunction. Brain Res 2003 Mar 28;967(1–2):181–190. PubMed PMID: 12650979

Langmead CJ, Austin NE, Branch CL (2008a) Characterization of a CNS penetrant, selective M_1 muscarinic receptor agonist, 77-LH-28-1. Br J Pharmacol 154:1104–1115

Langmead CJ, Watson J, Reavill C (2008b) Muscarinic acetylcholine receptors as CNS drug targets. Pharmacol Ther 117:232–243

Leach K, Loiacono RE, Felder CC, McKinzie DL, Mogg A, Shaw DB, Sexton PM, Christopoulos A. Molecular mechanisms of action and in vivo validation of an M_4 muscarinic acetylcholine receptor allosteric modulator with potential antipsychotic properties. Neuropsychopharmacology. 2010 Mar; 35(4):855–869. Epub 2009 Nov 25. PubMed PMID: 19940843; PubMed Central PMCID: PMC3055367

Levey AI (1993) Immunological localization of M1–M5 muscarinic acetylcholine receptors in peripheral tissues and brain. Life Sci 52:441–448

Levey AI, Kitt CA, Simonds WF et al (1991) Identification and localization of muscarinic acetylcholine receptor proteins in brain with subtype-specific antibodies. J Neurosci 11:3218–3226

Li Z, Huang M, Ichikawa J et al (2005) N-desmethylclozapine, a major metabolite of clozapine, increases cortical acetylcholine and dopamine release in vivo via stimulation of M_1 muscarinic receptors. Neuropsychopharmacology 30:1986–1995

Li Z, Bonhaus DW, Huang M et al (2007) AC260584 (4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one), a selective muscarinic M_1 receptor agonist, increases acetylcholine and dopamine release in rat medial prefrontal cortex and hippocampus. Eur J Pharmacol 572:129–137

Li Z, Snigdha S, Roseman AS et al (2008) Effect of muscarinic receptor agonists xanomeline and sabcomeline on acetylcholine and dopamine efflux in the rat brain; comparison with effects of 4-[3-(4-butylpiperidin-1-yl)-propyl]-7-fluoro-4H-benzo[1,4]oxazin-3-one (AC260584) and N-desmethylclozapine. Eur J Pharmacol 596:89–97

Ma L, Seager MA, Wittmann M, Jacobson M, Bickel D, Burno M, Jones K, Graufelds VK, Xu G, Pearson M, McCampbell A, Gaspar R, Shughrue P, Danziger A, Regan C, Flick R, Pascarella D, Garson S, Doran S, Kreatsoulas C, Veng L, Lindsley CW, Shipe W, Kuduk S, Sur C, Kinney G, Seabrook GR, Ray WJ. Selective activation of the M_1 muscarinic acetylcholine receptor achieved by allosteric potentiation. Proc Natl Acad Sci USA 2009 Sep 15;106 (37):15950–15955. Epub 2009 Aug 26. Erratum in: Proc Natl Acad Sci USA 2009 Oct 20;106(42):18040. Seager, Matthew [corrected to Seager, Matthew A]. PubMed PMID: 19717450; PubMed Central PMCID:PMC2732705

Mancama D, Arranz MJ, Landau S et al (2003) Reduced expression of the muscarinic 1 receptor cortical subtype in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 119B:2–6

Marino MJ, Conn PJ (2002) Direct and indirect modulation of the N-methyl D-aspartate receptor. Curr Drug Target CNS Neurol Disord 1:1–16

Marino MJ, Rouse ST, Levey AI et al (1998) Activation of the genetically defined M_1 muscarinic receptor potentiates N-methyl-D-aspartate (NMDA) receptor currents in hippocampal pyramidal cells. Proc Natl Acad Sci U S A 95:11465–11470

McBain CJ, Mayer ML (1994) N-methyl-D-aspartic acid receptor structure and function. Physiol Rev 74:723–760

Mego DM, Omori JM, Hanley JF (1988) Transdermal scopolamine as a cause of transient psychosis in two elderly patients. South Med J 81:394–395

Meyer EM, Otero DH (1985) Pharmacological and ionic characterizations of the muscarinic receptors modulating [3H]acetylcholine release from rat cortical synaptosomes. J Neurosci 5:1202–1207

Minzenberg MJ, Poole JH, Benton C et al (2004) Association of anticholinergic load with impairment of complex attention and memory in schizophrenia. Am J Psychiatry 161:116–124

Mirza N, Peters D, Sparks RG (2003) Xanomeline and the antipsychotic potential of muscarinic receptor subtype selective agonists. CNS Drug Rev 9:159–186

Miyakawa T, Yamada M, Duttaroy A, Wess J. Hyperactivity and intact hippocampus-dependent learning in mice lacking the M1 muscarinic acetylcholine receptor. J Neurosci 2001 Jul 15;21 (14):5239–5250. PubMed PMID: 11438599

Moser PC, Hitchcock JM, Lister SD et al (2000) The pharmacology of latent inhibition as an animal model of schizophrenia. Brain Res Rev 33:275–307

Neubauer H, Gershon S, Sundland DM (1966) Differential responses to an anticholinergic psychotomimetic (Ditran) in a mixed psychiatric population. Psychiatr Neurol (Basel) 151:65–80

Newell KA, Zavitsanou K, Jew SK et al (2007) Alterations of muscarinic and GABA receptor binding in the posterior cingulate cortex in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 31:225–233

Olianas MC, Maullu C, Onali P (1999) Mixed agonist-antagonist properties of clozapine at different human cloned muscarinic receptor subtypes expressed in Chinese hamster ovary cells. Neuropsychopharmacology 20:263–270

Perlstein WM, Carter CS, Noll DC et al (2001) Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. Am J Psychiatry 158:1105–1113

Perry EK, Perry RH (1995) Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. Brain Cogn 28:240–258

Perry KW, Nisenbaum LK, George CA et al (2001) The muscarinic agonist xanomeline increases monoamine release and immediate early gene expression in the rat prefrontal cortex. Biol Psychiatry 49:716–725

Quirion R, Wilson A, Rowe W et al (1995) Facilitation of acetylcholine release and cognitive performance by an M(2)-muscarinic receptor antagonist in aged memory-impaired. J Neurosci 15:1455–1462

Raedler TJ, Knable MB, Jones DW et al (2003) In vivo determination of muscarinic acetylcholine receptor availability in schizophrenia. Am J Psychiatry 160:118–127

Raedler TJ, Bymaster FP, Tandon R et al (2007) Towards a muscarinic hypothesis of schizophrenia. Mol Psychiatry 12:232–246

Raffa RB (2009) The M_5 muscarinic receptor as possible target for treatment of drug abuse. J Clin Pharm Ther 34:623–629

Rasmussen T, Fink-Jensen A, Sauerberg P et al (2001) The muscarinic receptor agonist BuTAC, a novel potential antipsychotic, does not impair learning and memory in mouse passive avoidance. Schizophr Res 49:193–201

Reichenberg A, Caspi A, Harrington H et al (2010) Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: a 30-year study. Am J Psychiatry 167:160–169

Riehemann S, Volz HP, Stützer P (2001) Hypofrontality in neuroleptic-naive schizophrenic patients during the Wisconsin card sorting test – a fMRI study. Eur Arch Psychiatry Clin Neurosci 251(2):66–71

Rodriguez AL, Nong Y, Sekaran NK (2005) A close structural analog of 2-methyl-6-(phenylethynyl)-pyridine acts as a neutral allosteric site ligand on metabotropic glutamate receptor subtype 5 and blocks the effects of multiple allosteric modulators. Mol Pharmacol 68:1793–1802

Rouse ST, Marino MJ, Potter LT et al (1999) Muscarinic receptor subtypes involved in hippocampal circuits. Life Sci 64:501–509

Rouse ST, Edmunds SM, Yi H (2000) Localization of M(2) muscarinic acetylcholine receptor protein in cholinergic and non-cholinergic terminals in rat hippocampus. Neurosci Lett 284:182–186

Rowe WB, O'Donnell JP, Pearson D et al (2003) Long-term effects of BIBN-99, a selective muscarinic M_2 receptor antagonist, on improving spatial memory performance in aged cognitively impaired rats. Behav Brain Res 145:171–178

Russig H, Murphy CA, Feldon J (2002) Clozapine and haloperidol reinstate latent inhibition following its disruption during amphetamine withdrawal. Neuropsychopharmacology 26:765–777

Scarr E, Sundram S, Keriakous D (2007) Altered hippocampal muscarinic M_4, but not M_1, receptor expression from subjects with schizophrenia. Biol Psychiatr 61:1161–1170

Schwarz RD, Callahan MJ, Coughenour LL et al (1999) Milameline (CI-979/RU35926): a muscarinic receptor agonist with cognition-activating properties: biochemical and in vivo characterization. J Pharmacol Exp Ther 291:812–822

Seeger T, Fedorova I, Zheng F et al (2004) M_2 muscarinic acetylcholine receptor knock-out mice show deficits in behavioral flexibility, working memory, and hippocampal plasticity. J Neurosci 24:10117–10127

Sellin AK, Shad M, Tamminga C (2008) Muscarinic agonists for the treatment of cognition in schizophrenia. CNS Spectr 13:985–996

Senda T, Matsuno K, Kobayashi T et al (1997) Reduction of scopolamine-induced impairment of passive-avoidance performance by s-receptor agonist in mice. Physiol Behav 61:257–264

Shannon HE, Hart JC, Bymaster FP et al (1999) Muscarinic receptor agonists, like dopamine receptor antagonist antipsychotics, inhibit conditioned avoidance response in rats. J Pharmacol Exp Ther 290:901–907

Shannon HE, Rasmussen K, Bymaster FP et al (2000) Xanomeline, an M(1)/M(4) preferring muscarinic cholinergic receptor agonist, produces antipsychotic-like activity in rats and mice. Schizophr Res 42:249–259

Shekhar A, Potter WZ, Lightfoot J et al (2008) Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. Am J Psychiatry 165:1033–1039

Sheffler DJ, Williams R, Bridges TM, Xiang Z, Kane AS, Byun NE, Jadhav S, Mock MM, Zheng F, Lewis LM, Jones CK, Niswender CM, Weaver CD, Lindsley CW, Conn PJ. A novel selective muscarinic acetylcholine receptor subtype 1 antagonist reduces seizures without impairing hippocampus-dependent learning. Mol Pharmacol 2009 Aug;76(2):356–368. Epub 2009 Apr 30. PubMed PMID: 19407080; PubMed Central PMCID: PMC2713127

Shirey JK, Xiang Z, Orton D et al (2008) An allosteric potentiator of M_4 mAChR modulates hippocampal synaptic transmission. Nat Chem Biol 4:42–50

Shirey JK, Brady AE, Jones PJ et al (2009) A selective allosteric potentiator of the M_1 muscarinic acetylcholine receptor increases activity of medial prefrontal cortical neurons and restores impairments in reversal learning. J Neurosci 29:14271–14286

Shinoe T, Matsui M, Taketo MM, Manabe T. Modulation of synaptic plasticity by physiological activation of M1 muscarinic acetylcholine receptors in the mouse hippocampus. J Neurosci 2005 Nov 30;25(48):11194–11200. PubMed PMID: 16319319

Schmitt GJ, Meisenzahl EM, Dresel S, Tatsch K, Rossmuller B, Frodl T, Preuss UW, Hahn K, Moller HJ. Striatal dopamine D2 receptor binding of risperidone in schizophrenic patients as assessed by 123I-iodobenzamide SPECT: a comparative study with olanzapine. J Psychopharmacol 2002 Sep;16(3):200–206. PubMed PMID: 12236625

Spalding TA, Ma J-N, Ott TR et al (2006) Structural requirements of transmembrane domain 3 for activation by the M_1 muscarinic receptor agonists AC-42, AC-260584, clozapine, and N-desmethylclozapine: evidence for three distinct modes of receptor activation. Mol Pharmacol 70:1974–1983

Spencer KM, Nestor PG, Niznikiewicz MA et al (2003) Abnormal neural synchrony in schizophrenia. J Neurosci 23:7407–7411

Spencer KM, Nestor PG, Perlmutter R et al (2004) Neural synchrony indexes disordered perception and cognition in schizophrenia. Proc Natl Acad Sci U S A 101:17288–17293

Stanhope KJ, Mirza NR, Bickerdike MJ et al (2001) The muscarinic receptor agonist xanomeline has an antipsychotic-like profile in the rat. J Pharmacol Exp Ther 299:782–792

Stoll C, Schwarzwälder U, Johann S et al (2003) Characterization of muscarinic autoreceptors in the rabbit hippocampus and caudate nucleus. Neurochem Res 28:413–417

Stahl E, Ellis J. Novel allosteric effects of amiodarone at the muscarinic M5 receptor. J Pharmacol Exp Ther 2010 Jul;334(1):214–222. Epub 2010 Mar 26. PubMed PMID: 20348203; PubMed Central PMCID: PMC2912050

Sur C, Kinney GG (2005) Selective Targeting of Muscarinic Receptors: Novel Therapeutic Approaches for Psychotic Disorders. Current Neuropharmacology 3:63–71

Sur C, Mallorga PJ, Wittmann M et al (2003) N-desmethylclozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. Proc Natl Acad Sci USA 100:13674–13679

Tzavara ET, Bymaster FP, Davis RJ et al (2004) M_4 muscarinic receptors regulate the dynamics of cholinergic and dopaminergic neurotransmission: relevance to the pathophysiology and treatment of related CNS pathologies. FASEB J 18:1410–1412

Vannucchi MG, Pepeu G. Muscarinic receptor modulation of acetylcholine release from rat cerebral cortex and hippocampus. Neurosci Lett 1995 Apr 28;190(1):53–56. PubMed PMID: 7624055

Vannucchi MG, Scali C, Kopf SR et al (1997) Selective muscarinic antagonists differentially affect in vivo acetylcholine release and memory performances of young and aged rats. Neuroscience 79:837–846

Vanover KE, Veinbergs I, Davis RE (2008) Antipsychotic-like behavioral effects and cognitive enhancement by a potent and selective muscarinic M-sub-1 receptor agonist, AC-260584. Behav Neurosci 122:570–575

Vilaro MT, Palacios JM, Mengod G (1994) Multiplicity of muscarinic autoreceptor subtypes? Comparison of the distribution of cholinergic cells and cells containing mRNA for five subtypes of muscarinic receptors in the rat brain. Brain Res Mol Brain Res 21:30–46

Vilaró MT, Palacios JM, Mengod G (1990) Localization of M_5 muscarinic receptor mRNA in rat brain examined by in situ hybridization histochemistry. Neurosci Lett 114:154–159

Wall SJ, Yasuda RP, Hory F (1991) Production of antisera selective for M_1 muscarinic receptors using fusion proteins: distribution of M_1 receptors in rat brain. Mol Pharmacol 39:643–649

Wang Y, Chackalamannil S, Hu Z et al (2002) Improving the oral efficacy of CNS drug candidates: discovery of highly orally efficacious piperidinyl piperidine M_2 muscarinic receptor antagonists. J Med Chem 45:5415–5418

Wang H, Ng K, Hayes D et al (2004) Decreased amphetamine-induced locomotion and improved latent inhibition in mice mutant for the M_5 muscarinic receptor gene found in the human 15q schizophrenia region. Neuropsychopharmacology 29:2126–2139

Weinberger DR, Berman KF, Zec RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 43:114–124

Weiner DM, Levey AI, Brann MR (1990) Expression of muscarinic acetylcholine and dopamine receptor mRNAs in rat basal ganglia. Proc Natl Acad Sci U S A 87:7050–7054

Weiner DM, Meltzer HY, Veinbergs I et al (2004) The role of M_1 muscarinic receptor agonism of N-desmethylclozapine in the unique clinical effects of clozapine. Psychopharmacol 177:207–216

Wess J (1996) Molecular biology of muscarinic acetylcholine receptors. Crit Rev Neurobiol 10:69–99

Wess J, Duttaroy A, Zhang W et al (2003) M_1-M_5 muscarinic receptor knockout mice as novel tools to study the physiological roles of the muscarinic cholinergic system. Receptors Channels 9:279–290

Wienrich M, Ceci A, Ensinger HA et al (2002) Talsaclidine (WAL 2014 FU): a muscarinic M_1 receptor agonist for the treatment of Alzheimer's disease. Drug Develop Res 56:321–334

Williams LM, Whitford TJ, Flynn G et al (2008) General and social cognition in first episode schizophrenia: identification of separable factors and prediction of functional outcome using the IntegNeuro test battery. Schizophr Res 99:182–191

Winkler J, Thal LJ, Gage FH et al (1998) Cholinergic strategies for Alzheimer's disease. J Mol Med 76:555–567

Wolkin A, Sanfilipo M, Wolf AP et al (1992) Negative symptoms and hypofrontality in chronic schizophrenia. Arch Gen Psychiatry 49:959–965

Yeomans JS (1995) Role of tegmental cholinergic neurons in dopaminergic activation, antimuscarinic psychosis and schizophrenia. Neuropsychopharmacology 12:3–16

Yeomans JS, Forster G, Blaha C (2001) M_5 muscarinic receptors are needed for slow activation of dopamine neurons and for rewarding brain stimulation. Life Sci 68:2449–2456

Zavitsanou K, Katsifis A, Mattner F et al (2004) Investigation of M_1/M_4 muscarinic receptors in the anterior cingulate cortex in schizophrenia, bipolar disorder, and major depression disorder. Neuropsychopharmacology 29:619–625

Zavitsanou K, Katsifis A, Yu Y et al (2005) M_2/M_4 muscarinic receptor binding in the anterior cingulate cortex in schizophrenia and mood disorders. Brain Res Bull 65:397–403

Zhang W, Yamada M, Gomeza J et al (2002a) Multiple muscarinic acetylcholine receptor subtypes modulate striatal dopamine release, as studied with M_1-M_5 muscarinic receptor knockout mice. J Neurosci 22:6347–6352

Zhang W, Basile AS, Gomeza J et al (2002b) Characterization of central inhibitory muscarinic autoreceptors by the use of muscarinic acetylcholine receptor knock-out mice. J Neurosci 22:1709–1717