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REVIEW

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Cholinergic targets for cognitive enhancement in schizophrenia: focus on cholinesterase inhibitors and muscarinic agonists

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Abstract *Rationale:* Alterations in the central cholinergic system of patients with schizophrenia such as reduced numbers of muscarinic and nicotinic receptors in the cortex and hippocampus may contribute to the cognitive impairment of schizophrenia. Therefore, pharmacological treatments that enhance central cholinergic function may be useful as cognitive enhancers in schizophrenia. *Methods:* Searches were conducted for articles which investigated alterations of central cholinergic systems in patients with schizophrenia. Additional searches were conducted for animal and human trials of potential cognitive enhancing compounds that target the cholinergic system and any preliminary trials conducted with schizophrenic patients. *Results:* Currently available treatments which are potentially suitable for this purpose include acetylcholinesterase inhibitors, muscarinic agonists, nicotinic agonists, and allosteric potentiators of nicotinic receptor function. Although some open label studies demonstrate modest cognitive improvements of schizophrenic patients treated with donepezil, data from a blinded, placebo controlled study demonstrate no effect. Data from a controlled trial of galantamine, a combined acetylcholinesterase inhibitor and allosteric potentiator of the nicotinic receptor, indicates that this may be an effective alternative. In addition, some preclinical data indicates that selective M_1 muscarinic agonists under development may have potential as cognitive enhancers and antipsychotic treatments for schizophrenic patients. *Conclusions:* A cholinergic approach to ameliorating the cognitive dysfunction of schizophrenia appears viable. There is some preliminary data to support the efficacy of combined acetylcholinesterase inhibitors and allosteric potentiators of the nicotinic receptor, whereas future trials are awaited for more specific muscarinic agonists currently under development.

Keywords Schizophrenia · Cholinergic · Muscarinic · Nicotinic · Treatment

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Introduction

Central cholinergic dysfunction has been correlated with the cognitive symptoms of various neurological diseases such as dementia of the Alzheimer's type and Parkinson's disease. The cognitive deficits in these patients include disturbances of mnemonic function and language usage. Schizophrenic patients also show impairments of mnemonic function that affect both verbal and episodic long-term memory and language use (Goldberg et al. 1989; Tamlyn et al. 1992; Saykin et al. 1994; Davidson et al. 1996) and therefore may be cholinergically mediated as well. Although the gross neuropathological findings of the central cholinergic system as seen in Alzheimer's disease (e.g. decreased cell density in the nucleus basalis of Meynert) is absent from the brains of schizophrenic patients at post mortem examination nonetheless, observed alterations at the receptor level of cholinergic systems in the brains of schizophrenic patients may contribute to the cognitive impairment of schizophrenia thereby providing a rationale for enhancing central cholinergic neurotransmission to treat the cognitive impairments of schizophrenia. Currently, a number of options are available and these include: acetylcholinesterase inhibitors, muscarinic agonists, nicotinic agonists and, potentiators of nicotinic receptor function (see Table 1 for summary). This review will focus on the rationale for these approaches and review available data that supports their use as potential cognitive enhancers in schizophrenia.

Table 1 Potential cholinergic compounds for cognitive enhancement in schizophrenia

Target	Action	Drug
Acetylcholinesterase	Inhibition of acetylcholinesterase resulting in non-specific increase in synaptic acetylcholine at nicotinic and muscarinic receptors	Tacrine, donepezil, rivastigmine, galantamine
Muscarinic receptor	M_1 agonist	Xanomaline, CDD-0102, CI 1017, YM 796
Nicotinic receptor	Nicotinic receptor agonist	GTS-21
	Nicotinic receptor potentiator	Galantamine

Animal models of cholinergic dysfunction

The basal cholinergic complex sends afferents to the entire non-striatal telencephalon with two projections: the septo-hippocampal and the nucleus basalis of Meynart (NbM)-cortical pathways (Woolf and Butcher 1989). Lesions of the septo-hippocampal pathway decreases performance in the delayed non-match to position paradigm in rats (Aggleton et al. 1992; McAlonan et al. 1995), whereas lesions of the nucleus basalis produces deficits in passive avoidance conditioned responses, radial arm maze and water maze performance (Page et al. 1991; Winkler et al. 1995). These data indicate that the septo-hippocampal pathway is associated with working memory processes through hippocampal storage of intermediate-term memory (Brito et al. 1983; Eichenbaum et al. 1994; Fadda et al. 1996), and that the NbM-cortical pathway is involved in reference memory through long-term information storage in the neocortex (Dunnett 1985; Meek et al. 1987). The memory deficits caused by the above lesions are ameliorated by administration of acetylcholinesterase inhibitors such as physostigmine (Mandel et al. 1989) and the grafting of acetylcholine producing cells into the brains of lesioned rats (Dunnett 1985; Winkler et al. 1995).

Additionally, a role for acetylcholine in the processes of attention has been demonstrated in rats as well monkeys. Performance on the five-choice serial reaction task is impaired following basal forebrain lesions (Robbins et al. 1989). Furthermore, both the systemic administration of physostigmine and the transplant of cholinergic embryonic cells into the brains of rats with basal forebrain lesions improves the visual attentional impairments (Muir et al. 1992). Continuous intraventricular injections of scopolamine into the brains of monkeys during a continuous performance task requiring localization of briefly presented visual stimuli results in a decrease in the number of responses (Callahan et al. 1993). This effect becomes more apparent when the stimulus presentation is shortened and towards the end of the testing session (Callahan et al. 1993).

The notion that alterations of central cholinergic function can contribute significantly to the cognitive impairment of schizophrenia and that this deficit can be effectively treated is convincingly demonstrated in studies involving pharmacological manipulations of central cholinergic function. Indeed, the administration of the anticholinergic drugs scopolamine or atropine produces memory deficits in rats and monkeys (Blozovski et al. 1977; Aigner and Mishkin 1986), whereas the administration of acetylcholinesterase inhibitors such as physostigmine, tacrine and donepezil effectively reverses these pharmacologically induced memory deficits (Bartus and Uehara 1979; Nielsen et al. 1989; Wanibuchi et al. 1994; Rupniak et al. 1997).

Involvement of the human cholinergic system in cognitive functioning

In humans, pharmacologically induced fluctuations of central cholinergic activity can profoundly affect the storage and retrieval of information in memory. Indeed, anticholinergic drugs, like scopolamine, produce learning impairments in healthy subjects similar to that of persons with dementia (Sitaram et al. 1978). Moreover, the administration of cholinomimetic drugs, like physostigmine and arecholine, can significantly enhance the memory functions of healthy individuals (Davis et al. 1978; Sitaram et al. 1978). Interestingly, the degree of enhancement produced by arecholine and the degree of impairment produced by scopolamine is inversely proportional to the subject's baseline performance on tests of learning and memory (Sitaram et al. 1978). In other words, the poorest performers were more susceptible to the memory enhancing effects of the procholinergic drug and to the memory impairing effects of the anticholinergic drug. This is relevant to our discussion of cognitive enhancement in schizophrenia because schizophrenics, in general, are very poor performers on tests of learning and memory. Hence, the memory impairments of schizophrenic patients may be particularly responsive to drugs that enhance central cholinergic activity.

The cholinergic system in schizophrenia

Post mortem investigations have demonstrated that the obvious neuropathology of the cholinergic system in Alzheimer's disease is absent from the brains of schizophrenic patients. Specifically, the size and number of cells in the NbM of schizophrenic patients is not significantly different from that of normal controls (El-Mallack et al. 1991). Moreover, the activity of choline acetyl transferase (ChAT), a marker of cholinergic function, is not significantly reduced in the parietal cortex of schizophrenic patients when compared with normal elderly controls (Powchik et al. 1998). However, when cognitive status

was considered, a relationship was uncovered between cortical levels of ChAT and the cognitive functioning of schizophrenic patients (Powchik et al. 1998). ChAT activity in the parietal cortex of schizophrenic patients was found to be negatively correlated with the severity of cognitive impairment as measured by Clinical Dementia Rating (CDR) scores (therefore, patients with lower ChAT activity had poorer cognitive functioning). These data imply that more modest fluctuations of central cholinergic activity in the schizophrenic brain (than is observed in Alzheimer's disease) can have significant deleterious effects on the cognitive functioning of schizophrenic patients.

At the receptor level, numerous observations implicate the involvement of the muscarinic cholinergic system in schizophrenia. For example, investigations of in vivo muscarinic receptor availability using [^{123}I]IQNB (Idoquinuclidinyl benzilate) SPECT (single photon emission computed tomography) has demonstrated decreased muscarinic receptor binding in the frontal, temporal and occipital cortex and, caudate, putamen and thalamus of un-medicated schizophrenic patients (Raedler et al. 2003). This relatively widespread and regionally non-specific pattern of reduction of muscarinic binding is related to the non-selectivity of IQNB (Bolden et al. 1992) at the five known genetically distinct subtypes of human muscarinic receptors (M_1, M_2, M_3, M_4 and, M_5), and their widespread anatomical distribution in the brain. To address the issue of which muscarinic receptors are altered in the CNS of persons with schizophrenia post mortem brain tissue has been studied with more receptor-specific radioligands. Utilizing the M_1/M_4 selective radioligand [^{3}H]pirenzepine decreased density of M_1 and/or M_4 receptors has been identified in the frontal cortex (Crook et al. 2001), hippocampus (Crook et al. 2000) and caudate-putamen (Dean et al. 1996). Given the different roles for these receptors in the human CNS it is important to determine the changes in M_1 and M_4 receptors that are contributing to the changes in [^{3}H]pirenzepine binding in the CNS of patients with schizophrenia. In order to determine which of the two muscarinic receptors that bind [^{3}H]pirenzepine are altered in schizophrenia levels of M_1 and M_4 receptors have been measured by Western blot with receptor specific antibodies and levels of mRNA determined using in situ hybridization (Dean et al. 2002). The level of M_1 receptor protein has been found to be decreased in Brodmann's area 9, while M_4 receptor protein was not (Dean et al. 2002). Importantly, these differences in M_1 and M_4 receptors in schizophrenics are not due to antipsychotic drug treatment (Wantabe et al. 1983; Crook et al. 2001; Dean et al. 2002).

These data suggest that alterations in central M_1 receptors may have a role in the pathology of schizophrenia, especially in the cognitive dysfunction of schizophrenia. Indeed, the M_1 receptor subtype is the most abundant of the muscarinic receptors in forebrain and hippocampus (Levey et al. 1991; Wei et al. 1994), brain regions crucial to normal cognitive functions. There is substantial evidence to support an important role for M_1 receptors in memory and cognition, including studies of M_1 deficient mice which demonstrate deficits in working memory and remote reference memory indicative of impaired hippocampal-cortical interactions (Anagnostaras et al. 2002).

Alterations in nicotinic cholinergic receptor function may also contribute to the cognitive impairment of schizophrenia. Indeed, schizophrenic patients have been shown to have reduced numbers of low affinity (containing α_7 subunit) nicotinic receptors in the hippocampus (Freedman et al. 1995) and reduced numbers of high affinity (containing $\beta_4\beta_2$ subunits) nicotinic receptors in the hippocampus, cortex, striatum and thalamus (Breese et al. 2000). Involvement of the α_7 receptor in schizophrenia is further supported by genetic linkage to the region containing the α_7 nicotinic receptor subunit gene (Freedman et al. 1997; Riley et al. 2000) and by animal studies showing that antagonists to the α_7 nicotinic receptor induce sensory gating deficits similar to those seen in schizophrenia (Luntz-Leybman et al. 1992).

Impaired sensory motor gating is a hippocampal phenomenon which manifests itself in the schizophrenic symptomatology as an inability to attend appropriately to sensory stimuli (Adler et al. 1993) and therefore may impact greatly on cognitive performance. Nicotinic receptor stimulation via cigarette smoking transiently normalizes these sensory gating deficits (Adler et al. 1993), in addition to abnormal smooth pursuit eye movement (Olincy et al. 1998), suggesting that schizophrenic patients may be self medicating with cigarettes. Therefore, nicotinic receptor stimulation may improve cognitive impairments associated with schizophrenia. Indeed, there is some evidence suggesting that nicotine administration modestly improves some selected aspects of cognitive function in schizophrenia (Smith et al. 2002).

Specific pharmacological treatments

Atypical antipsychotics

Given the above data, drugs which enhance central cholinergic activity may therefore be effective in treating some of the cognitive impairments seen in schizophrenia. In fact, this may be an important mechanism governing the ability of atypical antipsychotics to improve some of the aspects of cognitive dysfunction in schizophrenia given that no particular pharmacological property of atypical antipsychotics has been definitively attributed to its cognitive enhancing ability. While it is commonly known that atypical antipsychotics are more potent antagonists at serotonin $5HT_{2a}$ compared with dopamine D_2 receptors (Meltzer et al. 1989; Schotte et al. 1996), less well known is that atypical antipsychotic drugs such as clozapine, olanzapine, risperidone and ziprasidone significantly increase acetylcholine release in the medial prefrontal cortex (Ichikawa et al. 2002). In comparison, typical antipsychotics have no effect on acetylcholine release in the prefrontal cortex (Ichikawa et al. 2002).

Table 2 Comparison of cholinesterase inhibitor augmentation trials in schizophrenia

Study	AChE inhibitor	Dose	Study design	*n*	Treatment duration	Antipsychotic
Stryjer et al. (2003)	Donepezil	5 mg	Open label	6	4 weeks	Risperidone, olanzapine, haloperidol
Buchanan et al. (2002)	Donepezil	10 mg	Open label	15	6 weeks	Olanzapine
Friedman et al. (2002)	Donepezil	5 mg 10 mg	Double blind, placebo controlled	36	12 weeks	Risperidone
McEvoy et al. (2003)	Galantamine	16 mg, 24 mg, 32 mg	Double blind, placebo controlled	24	4 weeks	Risperidone

Given these data, it is reasonable to speculate that increasing cholinergic activity at muscarinic and/or nicotinic receptors may alleviate some of the cognitive impairment associated with schizophrenia.

Acetylcholinesterase inhibitors

The effects of atypical antipsychotics on cognition are modest at best as they fail to completely restore the cognitive functions of schizophrenic patients to normative levels (Harvey and Keefe 2001). If one considers adjunctive pharmacological strategies to improve upon these treatments, then there are data to support the possibility for further augmenting central cholinergic function in the face of treatment with atypical antipsychotics. Following the administration of atypical antipsychotic treatment, cholinesterase inhibitors can further increase the concentration of acetylcholine in the medial prefrontal cortex by 2- to 3-fold (Ichikawa et al. 2002). Indeed, the addition of an acetylcholinesterase inhibitor to atypical antipsychotic treatment produces some functional normalization of brain activity during verbal fluency task performance of schizophrenic patients characterized by a significant increase in frontal lobe and cingulate activity on fMRI (Nahas et al. 2003).

Several acetylcholinesterase inhibitors currently available for clinical trials targeting cognitive symptoms in schizophrenia include tacrine, donepezil, rivastigmine and galantamine, all of which have proven effective in treating the core cognitive symptoms of Alzheimer's disease (Knapp et al. 1994; Rogers et al. 1998a, 1998b; Rosler et al. 1999; Tariot et al. 2000). Although tacrine was the first available cholinesterase inhibitor for clinical use, it is limited by its short duration of action, narrow dosing range, and liver toxicity (Watkins et al. 1994). The newer acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine are free of these limitations. However, unlike donepezil and galantamine, rivastigmine inhibits butylcholinesterase (Polinsky 1998), which explains the higher incidence of gastrointestinal (GI) side effects upon initiation of therapy (Rosler et al. 1999). These facts may explain why donepezil and galantamine have been the acetylcholinesterase inhibitors of choice in cognitive enhancement trials with schizophrenic patients. To date, data is available from two open label studies with donepezil, one double blind study with donepezil and one double blind study with galantamine (see Table 2 for summary).

The open label trial conducted by Stryjer and colleagues (2003) examined the effects of donepezil given as adjunctive treatment to both typical and atypical antipsychotics to treat co-morbid dementia in elderly schizophrenic subjects (mean age=65, range: 54–76). Dementia was defined by a Mini Mental State Examination (MMSE) score at entry $\leq$24. A total of six subjects received 5 mg per day of donepezil for a period of 4 weeks. Unfortunately, a number of the subjects were also receiving anticholinergic medication, which may have significantly confounded these results. Moreover, the methodology of this study is unclear if subjects were excluded on the basis of cognitive impairment possibly related to alternative neurological factors such as Alzheimer's disease and cerebrovascular accident, for example, especially given the age of the study population. This study demonstrated modest effects of donepezil on improving scores for the MMSE and the Alzheimer's Disease Assessment Scale cognitive subscale. However, these results lost their significance when the change in negative subscale scores from the Positive and Negative Syndrome Scale was co-varied. The other open label trial of donepezil in schizophrenia, which was conducted by Buchanan and colleagues (2003) was a 6-week study evaluating the effects of donepezil given as adjunctive treatment to olanzapine. A total of 15 non-geriatric schizophrenic patients were treated with adjunctive donepezil, which was increased to a maximum dose of 10 mg per day for the final 2 weeks of the study. As with the Stryjer et al. study (2003), concomitant psychotropic use, which included benzodiazepines, valproate and antidepressants, was a possible confound of the results. Over the course of 6 weeks, donepezil was associated with only a modest effect on P50 suppression in addition to its very modest effects on neuropsychological testing, except for a more robust effect on the Grooved Pegboard test, suggesting a possible enhancement of motor speed. Currently, the only published double blind study of donepezil in schizophrenia is a 12-week placebo controlled, parallel designed trial of donepezil adjunctive treatment of non-geriatric schizophrenia patients receiving risperidone monotherapy (Friedman et al. 2002). In this study, subjects were excluded on the basis of alternative neurological factors that may have contributed to their cognitive impairment and concomitant psycho-

tropic medications were disallowed for the duration of the study. The efficacy of donepezil for enhancing cognitive functions was assessed at a 5 mg and 10 mg per day dose. Neither dose produced a significant improvement in the any of the primary cognitive outcome measures. It is possible that the dose of donepezil was inadequate to produce muscarinic and/or nicotinic stimulation necessary to enhance the cognitive abilities of the schizophrenic patients treated in this study. However, simply increasing the level of cholinesterase inhibition would significantly increase the likelihood of side effects associated with muscarinic receptor over-stimulation. Furthermore, the heavy cigarette smoking of these schizophrenic patients, which has been associated with normalization of the sensory motor gating and eye tracking abnormalities in schizophrenia (Adler et al. 1993; Freedman et al. 1997; Olincy et al. 1998) and desensitization of the $\alpha 7$ nicotinic receptor (Benwell et al. 1995; Fenster et al. 1999; Reitsletter et al. 1999) may have rendered the nicotinic receptors of the patients treated in this study insensitive to the effects of increased acetylcholine produced by donepezil. This could be problematic for our attempts at cognitive enhancement given that $\alpha 7$ nicotinic receptors mediate the predominant nicotinic current in the hippocampus (Frazier et al. 1998; Zarei et al. 1999) and the vast majority of schizophrenics are regular smokers (Hughes et al. 1986). Since the smoking status of the schizophrenic subjects treated in the Stryjer et al. (2003) and Buchanan et al. (2003) studies was not reported the possible confounds of nicotine in these studies cannot be discussed.

An alternative to pure cholinesterase inhibitors are drugs like galantamine with a dual mechanism of action including selective competitive inhibition of acetylcholinesterase (Thomsen et al. 1991) and allosteric potentiation of nicotinic receptor response (Maelicke et al. 1995; Maelicke and Albuquerque 1996; Schrattenholz et al. 1996; Samochocki et al. 2003). Galantamine interacts with the nicotinic receptor at sites that are different from those for acetylcholine and nicotine where it modulates ion channel activity and potentiates the actions of the nicotinic receptors in the presence of acetylcholine. Therefore, drugs like galantamine provide the requisite cholinergic stimulation without problematic desensitization. The effectiveness of galantamine in enhancing the cognitive functioning of schizophrenic patients was tested in a 4-week double blind placebo controlled trial of galantamine given as adjunctive treatment to risperidone (Allen et al. 2003). Similar to the double blind trial of donepezil in schizophrenia (Friedman et al. 2002), concomitant psychotropic use in this study was limited to lorazepam and subjects were excluded on the basis of alternative neurological factors which may have explained their cognitive impairment. Twenty-four subjects were equally randomized to four different treatment groups: placebo, galantamine 16, 24 and 32 mg per day. Higher doses of galanatamine were associated with significantly greater improvements on continuous performance task (CPT) errors of commission and verbal fluency test performance. The results of this controlled trial suggest that galantamine improves cognitive deficits in schizophrenia and that further study is warranted with combined acetylcholinesterase inhibitors and allosteric potentiators of the nicotinic receptor in schizophrenia. Moreover, the supposition that nicotinic receptor desensitization may be blocking any cognitive enhancing effect of donepezil in schizophrenic patients (Friedman et al. 2002) is supported by the observation that galantamine produced cognitive enhancement in schizophrenic patients despite all patients smoking at least 10 cigarettes per day (Allen et al. 2003).

Nicotinic agonists

An alternative approach to a combined acetylcholinesterase inhibitor and nicotinic receptor potentiator are direct acting nicotinic agonists, especially in light of data suggesting a cognitive enhancing effect of nicotine in schizophrenic patients (Smith et al. 2002). GTS-21, a selective partial agonist for the α_7 receptor (Briggs et al. 1997) is currently under investigation for the treatment of memory impairment in Alzheimer's disease. GTS-21 improves cognition (Arendash et al. 1995) and improves schizophrenic like deficits in sensory inhibition (Stevens et al. 1998) in rodent models. However, a complete discussion of nicotinic compounds is beyond the scope of this essay.

Muscarinic agonists

Given the non-selective activation of muscarinic and nicotinic receptor subtypes produced by acetylcholinesterase inhibitors, selective muscarinic and nicotinic agonists agonists should theoretically have distinct advantages by producing fewer unwanted side effects associated with activation of M_3 receptors localized to smooth muscle and exocrine glands (Caulfield 1993) such as nausea, vomiting and diarrhea. Drug development efforts in this area have focused on M_1 agonists given that the M_1 receptor is the most abundant subtype in the hippocampus and cortex (Levey et al. 1991; Flynn et al. 1995), regions crucial for cognitive function and their involvement in cognitive functions. The involvement of M_1 activity in cognitive functions has been demonstrated through the administration of selective antagonists (Hagan et al. 1987) and genetically engineered M_1 deletions (Anagnostaras et al. 2003) that produce significant cognitive impairments.

The first generation of M_1 agonists included compounds such as cevimeline, sabcomeline, and milameline which were all associated with side effects stemming from significant M_3 activity and which limited their therapeutic utility in cognitive disorders (Iga et al. 1998; Schwarz et al. 1999; Wienrich et al. 2001). Following the failure of these earlier compounds, progress was made with the introduction of xanomeline, a potent muscarinic agonist with high M_1 activity and subtype specificity in

Table 3 Comparison of muscarinic agonists

Drug	M_1 selectivity	Dose reversing memory deficits in rats	Dose producing M_3 mediated side effects	Reference
Xanomeline	No	1 mg/kg IP	1 mg/kg IP	Messer (2001)
CDD-0102	Yes	1 mg/kg IP	10 mg/kg IP	Messer (2001)
CI 1017	Yes	0.3 mg/kg PO	178 mg/kg PO	Tecle et al. (2000)
YM 796	Yes	0.5 mg/kg PO	22 mg/kg PO	Wanibuchi et al. (1994)

vitro (Shannon et al. 1994). In phase III clinical trials with Alzheimer's patients, xanomeline produced significant improvements in ADAS-Cog, CIBIC plus and simple reaction time; however, these improvements were seen only with the highest dose of xanomeline used in that study (225 mg/day) (Bodick et al. 1997). Unfortunately, this dose was associated with a 59% discontinuation rate during the double blind phase of the study (Bodick et al. 1997). Moreover, M_3 mediated side effects occurred very frequently in the high dose group and included nausea, vomiting, dyspepsia, diaphoresis and salivation. These side effects are consistent with more recent pharmacological models using microphysiometry which demonstrate markedly less functional selectivity of xanomeline for M_1 compared to M_3 receptors than previously thought (Wood et al. 1999). Despite additional clinical trials with a patch formulation, the propensity of xanomeline to produce side effects still outweighs its cognitive enhancing benefits. However, xanomeline has demonstrated antipsychotic properties that have been further investigated. Even though xanomeline demonstrates little or no binding affinity for dopamine receptors or transporters (Bymaster et al. 1994), it shows functional dopamine antagonism (therefore inhibits firing of dopamine A10 neurons) and an antipsychotic like profile (therefore inhibits conditioned avoidance responding and dopamine agonist induced climbing) in rodents (Perry et al. 2001; Stanhope et al. 2001) and monkeys (Andersen et al. 2003). This has indeed translated into antipsychotic like effects in patients with Alzheimer's disease (Bodick et al. 1997). Interestingly, M_1 deficient mice have significantly elevated dopamine neurotransmission in the striatum (Gerber et al. 2001), significantly increased locomotor activity and increased response to the stimulatory effects of amphetamine which demonstrates a regulatory effect of the M_1 receptor on dopamine transmission and is consistent with the antipsychotic effects of M_1 agonists. Therefore, should more selective M_1 agonists become available they may serve a dual role in schizophrenia as cognitive enhancers and antipsychotics.

Over the past few years, considerable progress has been made in producing selective muscarinic agonists. Several new compounds that demonstrate in vitro and vivo M1 receptor potency and very low activity at M_3 receptors include CDD-0102, CI-1017, and YM-706. All three compounds, at doses comparable to or less than xanomeline, effectively reverse the cognitive impairment induced by nucleus basalis lesions in rodents (Wanibuchi et al. 1994; Messer et al. 2000; Tecle et al. 2000) (see Table 3 for comparisons). Moreover, these drugs appear superior to xanomeline in that effects on M_3 mediated processes such as salivation and GI motility occur at doses much higher than the doses required to reverse memory deficits (Wanibuchi et al. 1994; Messer et al. 2000; Tecle et al. 2000) (see Table 3 for comparisons). Although early in their development these compounds seem to have promising cognitive enhancing and antipsychotic potential in the treatment of schizophrenia. Therefore, controlled clinical trials with human subjects are needed to determine if this preclinical superiority to xanomeline translates into real benefit in humans.

Dosing consideration

When planning future trials with cholinergic drugs for the purposes of enhancing the cognitive functions of schizophrenic patients careful attention must be paid to the dosing used in such studies. Although the data from the double trial of galantamine (Allen et al. 2003) suggested that higher doses produced greater improvements in cognitive test performance a number of other studies have demonstrated an inverted-U response to be typical of the cognitive effects of increasing doses of cholinomimetic drugs in animal models (Santucci et al. 1991), even when more selective M_1 receptor agonists are used (Wanibuchi et al. 1994). This is important to keep in mind because higher doses of cholinergic drugs may be sub-optimal for the purposes of cognitive enhancement in schizophrenia.

Conclusion

In sum, these data suggest that pharmacological approaches directed at cholinergic targets to enhance the cognitive abilities of schizophrenic patients is a viable option that should be actively investigated. To date, compounds that appear to hold promise include those which are dual cholinesterase inhibitors and allosteric potentiators of the nicotinic receptor and selective M_1 receptor agonists. Moreover, while investigating these compounds it is important to be mindful of a potentially narrow optimal dosing range for the purposes of cognitive enhancement in schizophrenic patients.

References

Adler LE, Hoffer LD, Wiser A, Freedman R (1993) Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 150:1856–1861

Aggleton J, Keith A, Rawlins J, Hunt P, Sahgal A (1992) Removal of the hippocampus and transection of the fornix produce comparable deficits on delyed non-match to position by rats. Behav Brain Res 52:61–71

Aigner T, Mishkin M (1986) The effects of physostigmine and scopolamine on recognition memory in monkeys. Behav Neural Biol 45:81–87

Allen T, McEvoy JP, Keefe R, Levin E, Wilson W (2003) Galantamine as an adjunctive therapy in the treatment of schizophrenia. Presented at 11th Congress of the International Psychogeriatric Association (IPA), Chicago, Ill., August 17–22

Anagnostaras SG, Murphy GG, Hamilton SE, Mitchell SL, Rahnama NP, Nathanson NM, Silva AJ (2003) Selective cognitive dysfunction in acetylcholine M_1 muscarinic receptor mutant mice. Nat Neurosci 6:51–58

Andersen MB, Fink-Jensen A, Peacock L, Gerlach J, Bymaster F, Lundbaek JA, Werge T (2003) The muscarinic M_1/M_4 receptor agonist xanomeline exhibits antipsychotic-like activity in *Cebus apell*a monkeys. Neuropsychopharmacology 28:1168–1175

Arendash GW, Sengstock GJ, Sanberg PR, Kem WR (1995) Improved learning and memory in aged rats with chronic administration of the nicotinic receptor agonist GTS-21. Brain Res 674:252–259

Bartus R, Uehara Y (1979) Physostigmine and recent memory: effects in young and aged nonhuman primates. Science 206:1085–1087

Benwell ME, Balfour DJ, Birrell CE (1995) Desensitization of the nicotine-induced mesolimbic dopamine responses during constant infusion with nicotine. Br J Pharmacol 114:454–460

Blozovski D, Cudennec A, Garrigou D (1977) Deficits in passive avoidance learning following atropine in the developing rat. Psychopharmacology 54:139–144

Bodick NC, Offen WW, Levey AI, Cutler NR, Gauthier SG, Satlin A, Shannon HE, Tollefson GD, Rasmussen K, Bymaster FP, Hurley DJ, Potter WZ, Paul SM (1997) Effects of xanomaline, 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. (1992) Antagonism by antimuscarinic and neuroleptic compounds at the five cloned human muscarinic cholinergic receptors expressed in Chinese hamster ovary cells. J Pharmacol Exp Ther 260:576–580

Breese CR, Lee MJ, Adams CE, Sullivan B, Logel J, Gillen KM, Marks MJ, Collins AC, Leonard S (2000) Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 23:351–364

Briggs CA, Anderson DJ, Brioni JD, Buccafusco JJ, Buckley MJ, Campbell JE, Decker MW, Donnelly-Roberts D, Elliott RL, Gopalakrishnan M, Holladay MW, Hui YH, Jackson WJ, Kim DJ, Marsh KC, O'Neill A, Prendergast MA, Ryther KB, Sullivan JP, Arneric SP (1997) Functional characterization of the novel neuronal nicotinic acetylcholine receptor ligand GTS-21 in vitro and in vivo. Pharmacol Biochem Behav 57:231–241

Brito G, Davis B, Stopp L, Stanton M (1983) Memory and the septohippocampal cholinergic system in the rat. Psychopharmacology 81:315–320

Buchanan RW, Summerfelt A, Tek C, Gold J (2003) An open-labeled trial of adjunctive donepezil for cognitive impairments in patients with schizophrenia. Schizophr Res 59:29–33

Bymaster FP, Wong DT, Mitch CH, Ward JS, Calligaro DO, Schoepp DD, Shannon HE, Sheardown MJ, Olesen PH, Suzdak PD, et al. (1994). Neurochemical effects of the M_I muscarinic agonist xanomeline. J Pharmacol Exp Ther 269:282–289

Callahan M, Kinsora J, Harbaugh R, Reeder T, Davis R (1993) Continuous icv infusion of scopolamine impairs sustained attention of rhesus monkeys. Neurobiol Aging 14:147–151

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

Crook JM, Tomaskovic-Crook E, Copolov DL, Dean B (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, Dean B (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

Davidson M, Harvey PD, Welsh KA, Powchik P, Putnam KM<Mohs RC (1996) Cognitive functioning in late-life schizophrenia: A comparison of elderly schizophrenic patients with Alzheimer's disease. Am J Psychiatry 153:1274–1279

Davis KL, Mohs R, Tinklenberg J, Pfefferbaum A, Hollister L, Kopell B (1978) Physostigmine: improvement of long-term memory in normal humans. Science 201:272–274

Dean B, Crook JM, Opeskin K, Hill C, Keks N, Copolov DL (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, McLeod M, Keriakous D, McKenzie J, Scarr E (2002) Decreased muscarinic$_1$ receptors in the dorsolateral prefrontal cortex of subjects with schizophrenia. Mol Psychiatry 7:1083–1091

Dunnett S (1985) Comparative effects of cholinergic drugs and lesions of the nucleus basalis or fimbria-fornix on delayed-matching in rats. Psychopharmacology 87:357–363

Eichenbaum H, Otto T, Cohen N (1994) Two functional components of the hippocampal memory system. Behav Brain Sci 17:449–518

El-Mallack R, Kirch D, Shelton R, Fan K, Pezeshkpour G, Kanhouwa S et al. (1991) The nucleus basalis of Meynert, senile plaques, and intellectual impairment in schizophrenia. J Neuropsychiatr Clin Neurosci 3:383–386

Fadda F, Melis F, Stancampiano R (1996) Increased hippocampal acetylcholine release during a working memory task. Eur J Pharmacol 307:R1–R2

Fenster CP, Whitworth TL, Sheffield EB, Quick MW, Lester RA (1999) Upregulation of Surgace alpha$_4$beta$_2$ nicotine receptors in initiated by receptor desensitization after chronic exposure to nicotine. J Neurosci 19:4804–4818

Flynn DD, Ferrari-DiLeo G, Mash DC, Levey AI (1995) Differential regulation of molecular subtypes of muscarinic receptors in Alzheimer's disease. J Neurochem 64:1888–1891

Frazier CJ, Rollins YD, Breese CR, Leonard S, Freedman R, Dunwiddie TV (1998) Acetylcholine activates an α-bungarotoxin-sensitive nicotinic current in rat hippocampal interneurons, but not pyramidal cells. J Neurosci 18:1187–1195

Freedman R, Hall M, Adler LE, Leonard S (1995) Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 38:22–33

Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, Polymeropoulos M, Holik J, Hopkins J, Hoff M, Rosenthal J, Waldo MC, Reimherr F, Wender P, Yaw J, Young DA, Breese CR, Adams C, Patterson D, Adler LE, Kruglyak L, Leonard S, Byerley W (1997) Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci 94:587–592

Friedman JI, Adler DN, Howanitz E, Harvey PD, Brenner G, Temporini H, White L, Parrella M, Davis KL (2002) A double blind placebo controlled trial of donepezil adjunctive treatment to risperidone for the cognitive impairment of schizophrenia. Biol Psychiatry 51:349–357

Gerber DJ, Sotnikova TD, Gainetdinov RR, Huang SY, Caron MG, Tonegawa S (2001) Hyperactivity, elevated dopaminergic transmission, and response to amphetamine in M_1 muscarinic acetylcholine receptor-deficient mice. Proc Natl Acad Sci USA 98:15312–15317

Goldberg T, Weinberger D, Pliskin N, berman K, Podd M (1989) Recall memory deficit in schizophrenia: a possible manifestation of prefrontal dysfunction. Schizophr Res 2:251–257

Hagan JJ, Jansen JH, Broekkamp CL (1987) Blockade of spatial learning by the M_1 muscarinic antagonist pirenzepine. Psychopharmacology 93:470–476

Harvey PD, Keefe RS (2001) Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. Am J Psychiatry 158:176–184

Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA (1986) Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 143:993–997

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

Iga Y, Arisawa H, Ogane N, Saito Y, Tomizuka T, Nakagawa-Yagi Y, Masunaga H, Yasuda H, Miyata N (1998) (±)-cis-2-methylspiro[1,3-oxathiolane-5,3'-quinuclidine] hydrochloride, hemihydrate (SNI-2011, cevimeline hydrochloride) induces saliva and tear secretions in rats and mice: the role of muscarinic acetylcholine receptors. Jpn J Pharmacol 78:373–380

Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI (1994) A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA 271:985–991

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

Luntz-Leybman V, Bickford PC, Freedman R (1992) Cholinergic gating of response to auditory stimuli in rat hippocampus. Brain Res 587:130–136

Maelicke A, Albuquerque EX (1996) New approach to drug therapy in Alzheimer's disease. Drug Discovery Today 1:53–59

Maelicke A, Schrattenholz A, Storch A, Schroder B, Gutrod O, Methfessel C, Weber KH, Pereira EE, Alkondon M, Albuquerque EX (1995) Noncompetitive agonism at nicotinic acetylcholine receptors; functional significance for CNS signal transduction. J Recept Signal Transduct Res 15:333–353

Mandel R, Chen A, Connor D, Thal L (1989) Continuous physostigmine infusion in rats with excitotoxic lesions of the nucleus basalis magnocellularis: effects on performance in the water maze task and cortical cholinergic markers. J Pharmacol Exp Ther 251:612–619

McAlonan G, Wilkinson L, Robbins T, Everitt B (1995) The effects of AMPA-induced lesions of the septohippocampal cholinergic projection on aversive conditioning to explicit and contextual cues and spatial learning in the water maze. Eur J Neurosci 7:281–292

McEvoy et al. (2003)

Meek W, Chuch R, Wenk G, Olton D (1987) Nucleus basalis magnocellularis and medial septal area lesions differentially impair temporal memory. J Neurosci 7:3505–3511

Meltzer HY, Matsubara S, Lee JC (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin$_2$ pKi values. J Pharmacol Exp Ther 251:238–246

Messer WS Jr, Rajeswaran WG, Cao Y, Zhang HJ, el-Assadi AA, Dockery C, Liske J, O'Brien J, Williams FE, Huang XP, Wroblewski ME, Nagy PI, Peseckis SM (2000) Design and development of selective muscarinic agonists for the treatment of Alzheimer's disease: characterization of tetrahydropyrimidine derivatives and development of new approaches for improved affinity and selectivity for M_1 receptors. Pharm Acta Helv 74:135–140

Muir J, Dunnett S, Robbins T, Everitt B (1992) Attentional functions of the forebrain cholinergic systems: effects of intraventricular hemicholinium, physostigmine, basal cortical lesions and intracortical grafts on a multiple choice serial reaction time task. Exp Brain Res 89:611–622

Nahas Z, George MS, Horner MD, Markowitz JS, Li X, Lorberbaum JP, Owens SD, McGurk S, DeVane L, Risch SC (2003) Augmenting atypical antipsychotics with a cognitive enhancer (donepezil) improves regional brain activity in schizophrenia patients: a pilot double-blind placebo controlled BOLD fMRI study. Neurocase 9:274–282

Nielsen J, Mena A, Williams I, Nocerini M, Liston D (1989) Correlation of brain levels of 9-amino-1,2,3,4-tetrahydroacridine (THA) with neurochemical and behavioral changes. Eur J Pharmacol 173:53–64

Olincy A, Ross RG, Young DA, Roath M, Freedman R (1998) Improvement in smooth pursuit eye movements after cigarette smoking in schizophrenic patients. Neuropsychopharmacology 18:175–185

Page K, Everitt B, Robbins T, Marston H, Wilkinson L (1991) Dissociable effects on spatial maze and passive avoidance acquisition and retention following AMPA- and ibotenic acid-induced excitotoxic lesions of the basal forebrain in rats: diffrential dependence on cholinergic neuronal loss. Neuroscience 43:457–472

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

Polinsky RJ (1998) Clinical pharmacology of rivastigmine: a new-generation acetylcholinesterase inhibitor for the treatment of Alzheimer's disease. Clin Ther 20:634–647

Powchik P, Davidson M, Haroutunian V, Gabriel SM, Purohit DP, Perl DP, Harvey PD, Davis KL (1998) Postmortem studies in schizophrenia. Schizophr Bull 24:325–341

Raedler TJ, Knable MB, Jones DW, Urbina RA, Gorey JG, Lee KS, Egan MF, Coppola R, Weinberger DR (2003) In vivo determination of muscarinic acetylcholine receptor availability in schizophrenia. Am J Psychiatry 160:118–127

Reitstetter R, Lukas RJ, Gruener R (1999) Dependence of nicotinic acetylcholine receptor recovery from desensitization on the duration of agonist exposure. J Pharmacol Exp Ther 289:656–660

Riley BP, Makoff AM, Mogudi-Carter M, Jenkins TJ, Williamson R, Collier DA, Murray RM (2000) High marker-density analyses of the α_7-nicotine cholinergic receptor subunit (CHRNA7) gene region on chromosome 15q13-q14 and 5' RACE cloning of fragments specific to CHRNA7 or its partial duplication. Schizophr Res 41:93

Robbins T, Everitt B, Marston H, Wilkinson J, Jones G, Page K (1989) Comparative effects of ibotenic acid and quisqualic acid-induced lesions of the substantia innominata on attentional function in the rat: further implications for the role of the cholinergic neurons of the nucleus basalis in cognitive processes. Behav Brain Res 35:221–240

Rogers SL, Doody RS, Mohs RC, Friedhoff LT (1998a) Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Int Med 158:1021–1031

Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT (1998b) A 24-week, double blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease: Donepezil Study Group. Neurology 50:136–145

Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stahelin HB, Hartman R, Gharabawi M (1999) Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 318:633–638

Rupniak N, Spencer T, Field M (1997) Enhanced performance of spatial and visual memory tasks by the selective acetylcholinesterase inhibitor E2020 in rhesus monkeys. Psychopharmacology 131:406–410

Samochocki M, Hoffle A, Fehrenbacher A, Jostock R, Ludwig J, Christner C, Radina M, Zerlin M, Ullmer C, Pereira EF, Lubbert H, Albuquerque EX, Maelicke A (2003) Galantamine is an allosterically potentiating ligand of neuronal nicotinic but

not of muscarinic acetylcholine receptors. J Pharmacol Exp Ther 305:1024–1036
Santucci AC, Haroutunian V, Davis KL (1991) Pharmacological alleviation of combined cholinergic/noradrenergic lesion-induced memory deficits in rats. Clin Neuropharmacol 14:S1–8
Saykin A, Shtasel D, Gur R, Kester D, Mozley L, Stafiniak P et al. (1994) Neuropsycholoigcal deficits in neuroleptic naïve patients with first-episode schizophrenia. Arch Gen Psychiatry 51:124–131
Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, De Loore K, Leysen JE (1996) Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology 124:57–73
Schrattenholz A, Pereira EFR, Roth U, Weber KH, Albuquerque EX, Maelicke A (1996) Agonist responses of neuronal nicotinic are potentiated by a novel class of allosterically acting ligands. Mol Pharmacol 49:1–6
Schwarz RD, Callahan MJ, Coughenour LL, Dickerson MR, Kinsora JJ, Lipinski WJ, Raby CA, Spencer CJ, Tecle H (1999) Milameline (CI-979/RU35926): a muscarinic receptor agonist with cognition-activating properties: biochemical and in vivo characterization. J Pharmacol Exp Ther 291:812–22
Shannon HE, Bymaster FP, Calligaro DO, Greenwood B, Mitch CH, Sawyer BD, Ward JS, Wong DT, Olesen PH, Sheardown MJ et al. (1994) Xanomeline: a novel muscarinic receptor agonist with functional selectivity for M_1 receptors. J Pharmacol Exp Ther 269:271–281
Sitaram N, Weingarten H, Gillin J (1978) Human serial learning: enhancement with arecholine and choline and impairment with scopolamine. Science 201:274–276
Smith RC, Singh A, Infante M, Khandat A, Kloos A (2002) Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. Neuropsychopharmacology 27:479–497
Stanhope KJ, Mirza NR, Bickerdike MJ, Bright JL, Harrington NR, Hesselink MB, Kennett GA, Lightowler S, Sheardown MJ, Syed R, Upton RL, Wadsworth G, Weiss SM, Wyatt A (2001) The muscarinic receptor agonist xanomeline has an antipsychotic-like profile in the rat. J Pharmacol Exp Ther 299:782–792
Stevens KE, Kem WR, Mahnir VM, Freedman R (1998) Selective alpha$_7$-nicotinic agonists normalize inhibition of auditory response in DBA mice. Psychopharmacology 136:320–327
Stryjer R, Strous RD, Bar F, Werber E, Shaked G, Buhiri Y, Kotler M, Weizman A, Rabey JM (2003) Beneficial effect of donepezil augmentation for the management of comorbid schizophrenia and dementia. Clin Neuropharmacol 26:12–17
Tamlyn D, McKenna PJ, Mortimer A, Lund C, Hammond S, Beddeley A (1992) Memory impairment in schizophrenia: its extent, affiliations and neuropsychological character. Psychol Med 12:564–571
Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C (2000) A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 54:2269–2276
Tecle H, Schwarz RD, Barrett SD, Callahan MJ, Caprathe BW, Davis RE, Doyle P, Emmerling M, Lauffer DJ, Mirzadegan T, Moreland DW, Lipiniski W, Nelson C, Raby C, Spencer C, Spiegel K, Thomas AJ, Jaen JC (2000) CI-1017, a functionally M1-selective muscarinic agonist: design, synthesis, and preclinical pharmacology. Pharm Acta Helv 74:141–148
Thomsen T, Kaden B, Fischer JP, Bickel U, Barz H, Gusztony G, Cervos-Navarro J, Kewitz H (1991) Inhibition of acetylcholinesterase activity in human brain tissue and erythrocytes by galanthamine, physostigmine and tacrine. Eur J Clin Chem Clin Biochem 29:487–492
Wanibuchi F, Nishida T, Yamashita H, Hidaka K, Koshiya K, Tsukamoto S, Usuda S (1994) Characterization of a novel muscarinic receptor agonist, YM796: comparison with cholinesterase inhibitors in in vivo pharmacological studies. Eur J Pharmacol 265:151–158
Watanabe S, Nishikawa T, Takashima M, Toru M (1983) Increased muscarinic cholinergic receptors in prefrontal cortices of medicated schizophrenics. Life Sci 33:2187–2196
Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW (1994) Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA 271:992–998
Wei J, Walton EA, Milici A, Buccafusco JJ (1994) m1-m5 muscarinic receptor distribution in rat CNS by RT-PCR and HPLC. J Neurochem 63:815–821
Wienrich M, Meier D, Ensinger HA, Gaida W, Raschig A, Walland A, Hammer R (2001) Pharmacodynamic profile of the M_1 agonist talsaclidine in animals and man. Life Sci 68:2593–2600
Winkler J, Suhr S, Gage F, Thal L, Fisher L (1995) Essential role of neocortical acetylcholine in spatial memory. Nature 375:484–487
Wood MD, Murkitt KL, Ho M, Watson JM, Brown F, Hunter AJ, Middlemiss DN (1999) Functional comparison of muscarinic partial agonists at muscarinic receptor subtypes hM_1, hM_2, hM_3, hM_4 and hM_5 using microphysiometry. Br J Pharmacol 126:1620–1624
Woolf N, Butcher L (1989) Cholinergic systems: synopsis of anatomy and overview of physiology and pathology. In: The biological substrates of Alzheimer's disease. Academic Press, New York, pp 73–86
Zarei M, Radcliffe KA, Chen D, Patrick JW, Dani JA (1999) Distribution of nicotinic acetylcholine receptor α_7 and β_2 submits on cultured hippocampal neurons. Neuroscience 88:755–764