DOES CHOLINERGIC FACILITATION ENHANCE COGNITIVE FUNCTIONS IN SCHIZOPHRENIA?

Veena Kumari, and Tonmoy Sharma

Summary

Individuals with schizophrenia show multifaceted cognitive impairment which is found to predict the functional outcome of this disorder more strongly than its negative or positive symptoms. This has led cognitive impairment now to become a prime target for pharmacological interventions in schizophrenia. Facilitation of central cholinergic activity, which is currently the main therapeutic approach to treat cognitive decline in Alzheimer's disease, has been suggested to form one of the several potential treatment strategies for cognitive improvement in schizophrenia. Exploration of the cognitive effects of acetylcholinesterase inhibitors such as donepezil, rivastigmine and galantamine in schizophrenia has only recently begun. Some but not all studies have shown acetylcholinesterase inhibitors to produce significant improvement in one or more cognitive functions in patients with schizophrenia or schizoaffective disorder. The data available so far on cognitive effects of acetylcholinesterase inhibitors in schizophrenia can be considered promising but unable to conclusively inform about their full potential because most of the published studies are limited by factors such as a lack of blinding of patients and raters, between-subject rather than within-subject designs, poor characterisation of cognitive impairment, limited exploration of cognitive effects and use of a single (and not necessarily effective) dose, all of which can influence study outcome. In addition, actions at nicotinic cholinergic receptions may be required since nicotine has also been found to produce improvements on measures of sensory gating, attention and working memory in schizophrenia patients. We emphasize the need for further empirical studies to determine full therapeutic potential of acetylcholinesterase inhibitors and nicotinic agonists in treating cognitive deficits in schizophrenia with a view to optimize treatment options for individual patients based on their cognitive profile.

Key Words: Schizophrenia – Cognitive impairment – Donezepil – Rivastigmine – Galantamine – Nicotine

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Introduction

Individuals with schizophrenia display multifaceted cognitive deficits including impairments in general intellectual ability (Wiekert and Goldberg 2000, Gold et al. 1994), memory (Saykin et al. 1994, Goldberg and Gold 1995), executive function (Everett et al. 2001), attention (Nestor et al 1990) and information processing (Goldberg et al.1990) (reviews, Rund 1998, Sharma and Antonova 2003). These deficits are found to persist even after noticeable improvements in patients' symptom state (Hughes et al. 2003). Empirical studies have shown that cognitive deficits are more strongly associated than the severity of positive or negative symptoms with functional outcomes in schizophrenia such that patients with severely impaired cognitive functions have much decreased employment prospects and the ability to live independently, and display a greater need for prolonged hospitalisation or residential care and support than those cognitively less impaired (Green 1996, Green et al. 2000, Velligan et al. 1997, Addington and Addington 1999, Evans et al. 2003). Improvement in cognitive functions may help such patients to recover lost skills or learn new ones, and increase their ability to gain from rehabilitation or psychosocial treatment. Cognitive impairment has therefore now become a main target for pharmacological and/or psychological interventions in this population (Sharma and Harvey 2000, Harvey et al. 2004).

Possible Treatment Strategies for Cognitive Enhancement in Schizophrenia

Schizophrenia is believed to involve disturbances of several neurotransmitters including dopaminergic,

serotonergic, cholinergic, adrenergic, and glutamatergic systems, all of which are known to influence functioning of the neural networks that sub-serve a variety of cognitive functions in humans and experimental animals (review, Freidman et al. 1999). The required improvement in cognitive functions in schizophrenia may thus also entail specific actions at one or more of these receptors. Newer atypical antipsychotics, which act on a wider range of neuroreceptors than typical antipsychotics (Arnt and Skarsfeldt 1998, Moller 2000), have shown beneficial effects on a range of cognitive variables and on positive as well as negative symptoms (Keefe et al. 1999, 2004; Meltzer and McGurk 1999; Sharma 1999; Sharma et al. 2003). However, atypical antipsychotics do not appear to improve cognitive functioning to normative standards (Harvey and Keefe 2001, Woodward et al. 2005) so there is still a need for an alternative treatment. One suggested approach to enhance cognitive functioning, especially memory, in schizophrenia has been to use acetylcholinesterase inhibitors (AChE-Is) (Friedman et al. 1999, Friedman 2004).

Cholinergic Facilitation as a Treatment Strategy

Cholinergic systems are well established as important components of the neural substrates of cognitive functions in experimental animals as well as human beings. In animals, lesions to the septohippocampal and nucleus basalis of Meynert cortical pathways produce memory deficits that are reversible by AChE-Is (Page et al. 1991, Aggleton et al. 1992, McAlonan et al. 1995). Similarly, damage to the basal forebrain in humans is associated with memory disturbances (Damasio et al. 1985). Pharmacological studies have also repeatedly shown a relationship between central cholinergic activity and cognitive functions, such as learning, memory, and attention. Both muscarinic and nicotinic cholinergic receptors are important for these areas of cognitive functioning since antimuscarinic agents, such as scopolamine and atropine, as well as nicotinic-cholinergic antagonists, such as mecamylamine, are found to disrupt cognitive functions in both animal and human studies (Decker and McGaugh 1991, Terry et al. 1995, Vitiello et al. 1997, Rezvani and Levin 2001). The administration of anticholinergic drugs has also been linked to disruption of cognitive functions in healthy subjects (Kumari et al. 2001, Zachariah et al. 2002) and with further cognitive deterioration in schizophrenic populations (Strauss et al. 1990, Kumari et al. 2003a, Ettinger et al. 2003).

The use of AChE-Is has been the main therapeutic approach to treat cognitive decline in Alzheimer's disease (AD) for now more than 20 years (reviews, Doody 2003, Giacobini 2003, Terry and Buccafusco 2003). AChE-Is, such as donepezil, tacrine and rivastigmine, are found to improve cognitive functions in AD (reviews, Doody 2003, Giacobini 2003, Terry and Buccafusco 2003). Patients with schizophrenia may also benefit from procholinergic treatment since cholinergic dysfunctions such as abnormal choline acetyltransferase (ChAT) activity and dysfunctional muscarinic-nicotinic cholinergic receptor systems are evident in this disorder (Watanabe et al. 1991, Freedman et al. 1995). The data showing an association between the decreases in ChAT levels at postmortem and the severity of ante mortem cognitive deficits in schizophrenia patients (Powchik et al. 1998), taken together with earlier described relationships between central cholinergic activity and cognitive functions in AD patients as well as in experimental animals (e.g. Mandel et al. 1989), have provided further support for the extension of this approach to treat cognitive deficits in schizophrenia (Friedman et al. 1999). There is also the possibility that patients with schizophrenia may benefit from procholinergic treatment to a greater extent than AD patients, as one major shortfall of procholinergic treatment of AD is that a large proportion of cholinergic neurons are already dead by the time such treatments are initiated. While some amount of upregulated functioning may be produced by treatment with procholinergic treatment, the amount of increased activity in AD would perhaps be less than that expected in schizophrenia where the cholinergic system is known to be relatively more intact (el-Mallack et al. 1991). In the next sections we present the evidence available so far regarding the effects of cholinergic facilitation on cognitive functions in schizophrenia.

Cholinergic Facilitation and Cognitive Functions in Schizophrenia: Current Evidence

Cholinergic facilitation as a treatment option for the cognitive deficits observed in patients with schizophrenia has only recently begun to be explored. Donepezil has received the most attention so far in this context.

Donepezil

Donepezil, a centrally active AChE-I, has been shown to produce predicted beneficial cognitive effects as add-on therapy in schizophrenia or schizoaffective disorder in preliminary studies (Buchanan et al. 2003, Stryjer et al. 2003) and case reports (Risch et al. 2000, MacEwan et al. 2001, Howard et al. 2002). Two randomized, double blind, placebo-controlled studies, however, failed to detect significant effects of this compound in schizophrenia patients though the effects on some tests were in the expected direction (Friedman et al. 2002, Tual et al. 2004). In some studies of schizophrenia patients, a beneficial effect of donepezil was described as improvement in psychotic symptoms (Stryjer et al. 2003), depression (Risch et al. 2001) and tardive dyskinesia (Caraff et al. 2001). The effect of donepezil has also been demonstrated at the neural level in preliminary functional magnetic resonance imaging (fMRI) studies. Donepezil, compared to placebo, has been shown to increase brain activity during cognitive paradigms in the frontal (Risch et al. 2001, Nahas et al. 2003) and basal ganglia regions (Risch et al. 2001) in schizophrenia patients. Taken together, the available data hint that donepezil may have positive cognitive effects perhaps with small effect sizes or in a sub-set of schizophrenia patients.

Rivastigmine

More recently, studies have addressed the effects of rivastigmine, a pseudo-irreversible, central nervous system-selective, AChE-I (Polinsky 1998). Rivastigmine carries with it the theoretical advantage of inhibiting butyrylcholinesterase (BuChE) as well as AChE, both of which are known to be involved in cognition (Mesulam et al. 2002). It is classified as an intermediate-acting or pseudo-irreversible agent due to its long inhibition of AChE (up to 10 hours), compared to donepezil which is classified as short-acting or reversible agent (binding to AChE hydrolysed within minutes). In AD, it has been found to produce improvements in global scales of behaviour, daily activities, cognition and psychopathology, with benefits occurring as early as 12 weeks post-treatment (reviews, Jann 2000, Birks et al. 2002, Williams et al. 2003), and to enhance brain activity in the frontal, parietal (Potkin et al. 2001, Vennerica et al. 2002) and temporal regions (Vennerica et al. 2002) across a range of cognitive tasks.

A preliminary study has shown beneficial cognitive effects on several cognitive domains with rivastigmine in schizophrenia (Lenzi et al. 2003). We have recently examined cognitive and neural effects of adjunctive rivastigmine treatment (at doses known to be effective for cognitive symptoms in AD) to antipsychotics in schizophrenia patients using a randomised, placebo-controlled, double blind, parallel group design and have observed improvements in spatial working memory (with no effects of some other cognitive domains; Sharma et al. 2004) and significant changes in brain activity assessed with fMRI (Assen et al. in press; Kumari et al. 2004). One major problem that we encountered while investigating cognitive effects using standard neuropsychological tests was that most measures showed considerable practice effects and thus improved also in the placebo group. The brain areas influenced by the drug were consistent with those identified in previous studies of cholinergic augmentation in association with enhanced perceptual processing during working memory encoding and enhanced visual attention in normal subjects. At this point we believe that the behavioural effects of rivastigmine noted in our investigation may get strengthened with relatively higher doses of rivastigmine (none of the patients reported serious adverse effects with the highest, 12mg/daily, dose used in our study) and await future studies of schizophrenia patients with this drug.

Galantamine

Galantamine, a reversible AChE-I, has shown cognitive efficacy relative to placebo and better tolerability relative to tacrine in patients with AD (Krall et al. 1999, Tariot et al. 2000). It also acts on nicotinic receptors and nicotine itself is known to improve attention and information processing measures in normal subjects (Warburton 1990) and clinical populations including AD and schizophrenia (Levin and Rezvani 2002). As described in the next section (*Nicotine*), cigarette smoking is very common and is considered to desensitise nicotine receptors in patients with schizophrenia who do not show the normal upregulation following chronic nicotine use (Breese et al. 1997). This might prevent the AChE-Is, such as rivastigmine, reaching their full therapeutic potential in this population. The use of allosterically potentiating ligands, such as galantamine (Maelicke et al. 2001), which inhibit cholinesterase and, at the same time, enhance nicotinic receptor sensitivity in the presence of ACh by binding to the nicotinic receptor (Schrattenholz et al. 1996) could be considered a more effective treatment of cognitive deficits in schizophrenia (Friedman 2004). There are no published data to our knowledge testing cognitive effects of this drug in schizophrenia patients.

Nicotine

The pharmacological actions of nicotine are complex and involve a wide diversity of transmitter pathways, including the cholinergic system itself, by both post- and pre-synaptic mechanisms, and dopamine, serotonin, norepinephrine, glutamate, γ-aminobutyric acid, opioid, and histaminergic systems (Gay et al. 1994). Nicotinic acetylcholine receptors (nAChRs), the main sites via which nicotine exerts its behavioural effects, are found in many areas of the brain (Levin and Simon 1998) implicated in working memory, attention and motivation (Sawaguchi and Goldman-Rakic 1995). Accordingly, nicotine/nicotine ligands influence a broad range of behaviours including improvements in a variety of cognitive functions (review, Rezvani and Levin 2001). Animal studies suggest that the effects of nicotinic on cognition performance most often involve the cholinergic projections to neocortex and hippocampus (Gray et al. 1994).

The cognitive effects of nicotine in schizophrenia have been of much interest in recent years following the observation that the rate of cigarette smoking in this population is two-to-four fold the rate seen in the general population (review, Kumari and Postma in press). While over two thousand different compounds have been identified in cigarette smoke, nicotine is generally acknowledged as the substance accountable for continued smoking behaviour (Jaffe 1985). The strongest evidence for a role for nicotine in schizophrenia comes from studies showing sensory gating improvement with smoking/nicotine on two experimental paradigms, namely prepulse inihibition (PPI) of the startle response and gating of the acoustically elicited P50 wave, both of which reliably show deficient performance in this patient group (review, Kumari and Postma in press). The neural substrates of PPI, mainly the hippocampus, amygdala, thalamus and basal ganglia (Swerdlow et al. 2001, Kumari et al. 2003b, in press), are also implicated in the neuroanotomy of nicotine (Clarke 1993).

Nicotine is found to enhance PPI in experimental animals (Acri et al. 1994, Curzan et al. 1994) though this effect is found to be strain dependent in some studies (Faraday et al. 1999). In humans, nicotine administered via cigarette smoking increases PPI in healthy smokers (Kumari et al. 1996, Dela Casa et al. 1998, Duncan et al. 2004); a similar effect of nicotine administered subcutaneously is seen in non-smokers (Kumari et al. 1997). Nicotine intake via cigarette smoking also has a positive, though most likely transient, effect on PPI in people with schizophrenia (Kumari et al. 2001,

George et al. 2003). Animal studies suggest that the modulatory effect of nicotine in PPI may involve an interaction between the low affinity (i.e. α7 subunit containing) nicotinic receptors and glutamatergic transmission (Spielewoy and Markou 2004). A role for nicotine in the improvement of sensory gating deficits in schizophrenia is also suggested by observations of normalization of reduced P50 gating by nicotine in patients with schizophrenia (Adler et al. 1992, 1993; Griffith et al. 1998). Both schizophrenia and P50 gating deficit have been linked to the á7-nicotinic cholinergic receptor subunit gene locus (Freedman et al. 1997, 2001). In addition, nicotine seems to improve performance on two eye movement tasks, namely the smooth pursuit eye movement and antisaccade tasks (review, Ettinger and Kumari 2003) and on some higher order cognitive measures, most reliably those indexing attention and working memory, that reveal deficient performance in this patient population (review, Kumari and Postma in press). It is interesting to note that the cognitive effects of nicotine/nicotine ligands in experimental animals have also been demonstrated most reliably in terms of improved attention and working memory performance after both acute and chronic administrations (Levin and Rezvani 2002, Levin and Simon 1998).

Conclusions and Future Developments

Several studies of cognitive enhancement with donezepil in schizophrenia have revealed promising data and indicate that it has positive cognitive effects at least with a small effect size or in a sub-set of patients. Most of the positive studies with this compound however suffer from a number of potential issues, for example, a lack of blinding of patients and raters, between-subject rather than within-subject designs, poor characterisation of cognitive impairment, limited exploration of cognitive effects, use of a single (and not necessarily effective) dose, all of which can influence study outcome. The evidence for the effects of rivastigmine is also promising but very limited at present and suggests a small and selective effect on visual and spatial attention systems. The effects observed so far need to be further explored using higher doses than used in previous studies and the cognitive assessments need to include cognitive variables, in particular memory, that are found to be most affected by this drug in AD patients. Attention is also required to potential practice effects in studies involving repeated measurement while designing the study and selecting the battery of cognitive tests. There are currently no empirical data with galantamine but this drug, given its pharmacology and smoking habits of the schizophrenia patients, in theory should produce better effects that those seen with donepezil and rivastigmine. The beneficial effects of nicotine have been noted on sensory gating (early information processing), working memory and attention measures in schizophrenia patients and stress the importance of pursuing the development of nicotinic agonist treatments (Levin and Rezvani 2002, Martin et al. 2004) at least for the subgroup of schizophrenia patients who tend to be heavy smokers and may suffer more severe deficits in these cognitive domains. Over the last decade attempts have been made to develop promising α7 selective agonists such as they are yet to be formally tested for their cognitive efficacy in schizophrenia (Martin et al. 2004). Potentially such a treatment strategy would not only represent a useful advancement in treatment of cognitive impairment in schizophrenia but also, by providing an alternative to smoking, reduce the harmful effects of excessive chronic smoking in this population.

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