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Physostigmine and cognition in schizotypal personality disorder

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Abstract

There is evidence that reduced cholinergic activity may play a role in the pathophysiology of cognitive impairment in the schizophrenia spectrum. We tested the effects of physostigmine, an anticholinesterase inhibitor, on visuospatial working memory as evaluated by the Dot test, and on verbal learning and recall as measured by a serial learning task in patients with schizotypal personality disorder. Physostigmine tended to improve the Dot test, but not serial verbal learning performance in these patients. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Cognitive impairment; Physostigmine; Schizotypal personality disorder

1. Introduction

Reduced cholinergic activity may play a role in the pathophysiology of schizophrenia. Decreased choline acetyltransferase has been noted in post-mortem brains of schizophrenic patients (Karson et al., 1993), as have decreased numbers of nicotine receptors in the hippocampi of schizophrenic patients post-mortem. Specifically, in seven of eight schizophrenic brains there was less alpha-bungarotoxin labelling than in the comparison non-schizophrenic brains (alpha-bungarotoxin binds to a subset of nicotine receptors). Thus a possible mechanism for cholinergic dysfunction in schizophrenia is a deficit in nicotinic post-synaptic receptors for acetylcholine (Freedman et al., 1995).

Reduced cholinergic activity may also play a role in the cognitive impairment of schizophrenia. An overwhelming amount of evidence favoring the importance of central cholinergic systems in learning and memory exists. In animals, a variety of cholinergic drugs have been shown to enhance retention of learned responses (Haroutunian et al., 1985). Specifically, physostigmine in rats enhanced both memory consolidation and memory retrieval processes (Santucci et al., 1989). In a study of the effects of four cholinomimetics on cognition in rats following disruption by scopolamine or by lists of objects, physostigmine was clearly the most efficacious and best tolerated agent examined (Rupniak et al., 1989). Physostigmine has also improved memory processes in normal humans (Davis et al., 1978).

While there is a well-documented association between cognitive impairment and decreased cholinergic activity in Alzheimer's disease (Perry et al., 1978), there is also evidence to support the role of reduced cholinergic activity in the cognitive impairment of schizophrenia, including a significant correlation between the reduced choline acetyltransferase

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concentration (Karson et al., 1993) and two domains of cognitive performance in schizophrenia (Karson et al., 1996). Further evidence comes from studies of the alpha-7 nicotine receptor, showing that dysfunction of this receptor may be responsible for the abnormal sensory gating found in schizophrenia, and may also predispose patients to difficulty with learning efficiency and accuracy (Adler et al., 1998). Nicotine administration, via a patch, has improved attentiveness during a continuous performance task and has reversed some of the haloperidol dose-related impairments in a variety of cognitive tests that assess memory performance in patients with schizophrenia (Levin, 1996).

Schizotypal personality disorder (SPD) is a disorder of the schizophrenia spectrum, similar to schizophrenia in its biology, genetics, and treatment (Siever et al., 1993). Cognitive impairment exists in both disorders (Weinberger et al., 1986; Siever et al., 1993) and includes abnormalities in verbal learning, attention, and working memory (Lees Roitman et al., 2000; Trestman et al., 1995; Bergman et al., 1998). The cognitive impairment in SPD is hypothesized to be associated with frontal cortical hypodopaminergia; administration of the dopamine releasing agent amphetamine improves cognitive performance in SPD patients (Kirrane et al., 2000; Siegel et al., 1996). There is also evidence that nicotine modulates dopaminergic neurotransmission, and there are significant differences in nicotinic regulation of cortical and subcortical dopaminergic activity; for example, chronic nicotine treatment changes dopamine metabolism in the prefrontal cortex but not in the dorsal striatum (Dalack et al., 1998). Preclinical studies suggest that chronic nicotine treatment affects cortical sensitivity to nicotine challenges to a greater extent than it does subcortical nicotinic receptor sensitivity, consistent with the hypothesis of cortical/subcortical dissociation in schizophrenia (Dalack et al., 1998; Davis et al., 1991). A complex interaction between the cholinergic and dopaminergic systems may thus play a role in the pathophysiology of cognitive impairment in the schizophrenia spectrum. SPD patients may be a suitable population in which to study the basis of this cognitive impairment, as they are less affected by confounding factors such as chronic psychosis and long-term antipsychotic administration.

We hypothesized that physostigmine, an indirectly-acting cholinomimetic which works by inhibiting anticholinesterase, would ameliorate the cognitive impairment found in SPD. We studied its effects on visuospatial working memory and verbal learning in SPD patients.

2. Methods

We administered physostigmine in a double-blind placebo-controlled manner in a total of 10 patients who met criteria for SPD. Signed informed consent was obtained according to IRB guidelines. Subjects were diagnosed according to DSM-III-R by experienced raters using the Schedule for Affective Disorders and Schizophrenia (SADS) and the Structured Interview for DSM-III-R Personality (SIDP-R). Inter-rater reliability in our laboratory for SPD is $k = 0.73$. Patients with Axis I schizophrenia-related psychotic disorders or bipolar disorder were excluded. Patients were medically healthy, and had no past substance dependence, and no substance abuse in the previous six months. Patients were free of psychoactive medication for at least one month prior to the first study day.

Patients fasted from midnight. At 8 a.m. an IV line was inserted and normal saline infused. At 9.30 a.m. glycopyrrolate 0.2 mg in 9 ccs normal saline was injected; glycopyrrolate is an anticholinergic drug which decreases the cardiac side effects of physostigmine. Beginning at 10 a.m., physostigmine 0.014 mg/kg or placebo was infused either over 20 min (short infusion) or over 60 min (long infusion). While physostigmine administered over a shorter period of time would be the best way to test its effect on cognitive performance (more drug 'on board' in a shorter period of time), we have previously reported that the short infusion produces significant side effects (nausea, vomiting) in some personality disorder patients (Steinberg et al., 1997), which could conceivably interfere with the cognitive testing/performance. Administration of physostigmine over a longer period of time would allow us to test for drug effects while minimizing the side effects, although that dose would result in lower drug concentrations. Side effects were rated on a scale of 0–3 (0 = none, 1 = dry mouth, 2 = nausea, 3 = vomiting).

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