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Cortical cholinergic deficiency enhances amphetamine-induced dopamine release in the accumbens but not striatum

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Abstract

Cholinergic dysfunction has been implicated as a putative contributing factor in the pathogenesis of schizophrenia. Recently, we showed that cholinergic denervation of the neocortex in adult rats leads to a marked increase in the behavioral response to amphetamine. The main objective of this study was to investigate if the enhanced locomotor response to amphetamine seen after cortical cholinergic denervation was paralleled by an increased amphetamine-induced release of dopamine in the nucleus accumbens and/or striatum. The corticopetal cholinergic projections were lesioned by intraparenchymal infusion of 192 IgG-saporin into the nucleus basalis magnocellularis of adult rats. Amphetamine-induced dopamine release in the nucleus accumbens or striatum was monitored by in vivo microdialysis 2 to 3 weeks after lesioning. We found that cholinergic denervation of the rat neocortex leads to a significantly increased amphetamine-induced dopamine release in the nucleus accumbens. Interestingly, the cholinergic lesion did not affect amphetamine-induced release of dopamine in the striatum. The enhanced amphetamine-induced dopamine release in the nucleus accumbens in the cholinergically denervated rats could be reversed by administration of the muscarinic agonist oxotremorine, but not nicotine, prior to the amphetamine challenge, suggesting that loss of muscarinic receptor stimulation is likely to have caused the observed effect. The results suggest that abnormal responsiveness of dopamine neurons can be secondary to cortical cholinergic deficiency. This, in turn, might be of relevance for the pathophysiology of schizophrenia and provides a possible link between cholinergic disturbances and alteration of dopamine transmission.
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Keywords: Cholinergic; Saporin; Accumbens; Muscarinic; Schizophrenia; Nucleus basalis magnocellularis; Cortex

Introduction

Schizophrenia is a chronic mental illness characterized by positive and negative symptoms as well as cognitive impairments. Although etiologies remain unknown, a predominant pathophysiologic hypothesis of schizophrenia for the past decades, the dopamine hypothesis, postulates that enhanced activity in the mesolimbic dopamine system is associated with psychotic episodes. Thus, dopamine D2 receptor antagonists can alleviate positive symptoms of the disease (Carlsson, 1988), although other mechanisms may contribute to this effect (Svensson, 2003), while dopamine-releasing compounds, such as amphetamine, can induce schizophrenia-like symptoms in healthy volunteers and exacerbate the psychotic symptoms in schizophrenics (Angrist et al., 1974). Further, amphetamine-induced dopamine release is increased in the striatum in psychotic schizophrenic patients (Abi-Dargham et al., 1998; Breier et al., 1997; Laruelle et al., 1996). However, the cause of this purported dopamine hyperactivity remains unclear.

A number of recent studies have provided evidence that altered cholinergic function may contribute to schizophrenic symptoms, suggesting that cholinergic disturbances may be involved in the etiology of schizophrenia. For instance, mutations in the α7 nicotinic acetylcholine receptor gene have been linked to auditory sensory gating deficits characteristic of a considerable number of schizophrenic patients and their relatives (Adler et al., 1985; Freedman et al., 1997). Postmortem studies of schizophrenic brains provide evidence for decreased muscarinic and nicotinic receptor binding in the frontal cortex (Crook et al., 2001; Guan et al., 1999), the hippocampus (Crook et al., 2000; Freedman et al., 1995), the reticular thalamic

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nucleus (Court et al., 1999), and the caudate–putamen (Dean et al., 1996). Decreased muscarinic receptor availability *in vivo* in the cortex, basal ganglia, and thalamus in patients with schizophrenia have also been reported (Raedler et al., 2003). Furthermore, pharmacological studies indicate that muscarinic M1/M4 receptor agonists may have antipsychotic properties (Andersen et al., 2003; Shannon et al., 2000).

It has been hypothesized that specific dysfunction in cortical regions might be involved in the failure to regulate subcortical dopamine neurotransmission (Grace, 1991). Recently, we showed that loss of cortical cholinergic innervation results in an enhanced behavioral response to D-amphetamine in the form of increased locomotor activity (Mattsson et al., 2004). Hence, cortical acetylcholine appears to influence the regulation of dopaminergic activity important for the motor stimulatory effect of D-amphetamine. This appears to be due to an altered functional state of the dopamine neurons since activation of postsynaptic dopamine receptors did not cause the same increase in locomotor activity as dopamine-releasing compounds in cholinergically denervated rats (Mattsson et al., 2002). Therefore, the present experiment was designed to determine if the increased sensitivity to D-amphetamine seen after cholinergic denervation is mediated via the dopamine system. Understanding the interactions between basalocortical cholinergic systems and dopaminergic systems in response to D-amphetamine might help elucidate possible etiological pathways in schizophrenia.

The basalocortical cholinergic projections were lesioned by local injections of the immunotoxin 192 IgG-saporin, selective for cholinergic neurons expressing the low-affinity p75 NGF receptor (Heckers et al., 1994; Wiley et al., 1991), into nucleus basalis magnocellularis (nbm) of adult rats. Two to three weeks after lesioning, D-amphetamine-induced dopamine release in the nucleus accumbens or striatum was measured by *in vivo* microdialysis in awake rats. We also examined the effect of oxotremorine, a muscarinic agonist, and nicotine on the amphetamine-induced release of dopamine in rats with cortical cholinergic denervation.

Methods and materials

A total of 28 male Sprague–Dawley rats (B&K, Sollentuna, Sweden), weighing 200 g at the time of surgery, were used. The animals were housed under standard laboratory conditions with food and water ad lib. All experimental procedures conformed to the Swedish Animal Welfare Act SFS 1988:534, as approved by the local Animal Research Committee of Stockholm. All efforts were made to minimize the number of animals used and their suffering.

Cholinergic lesioning

The basalocortical cholinergic projections were lesioned by local infusion of 192 IgG-saporin into nbm as follows: Rats were anesthetized by a cocktail containing Hypnorm® (Fentanyl 0.315 mg/ml + Fluanison 10 mg/ml, Janssen-Cilag) and Dormicum® (Midazolam 5 mg/ml, Roche) diluted in distilled water (1:1:2; 5 ml/kg i.p.) and positioned in a stereotaxic frame. The skull was exposed, drillholes were made above nbm, and 0.067 μg 192 IgG-saporin (Advanced Targeting System, San Diego, CA, USA; dissolved in 1 μl PBS) was injected bilaterally with a 5-μl Hamilton syringe connected to a pump (Micro 4 Micro Syringe Pump Controller; World Precision Instruments) (infusion rate 0.2 μl) at the following coordinates relative to the Bregma: AP +1.0, ML ±3.2, DV −7.5, with the incisor bar set at +5.0 (total dose 192 IgG-saporin/rat: 0.134 μg). The needle was left in place for 3 min before being slowly withdrawn. Sham-lesioned animals received equal volumes of vehicle.

Microdialysis

Microdialysis was performed 2 to 3 weeks after cholinergic lesioning. Rats were anesthetized as above and positioned in a stereotaxic frame. The skull was exposed and a hole was drilled above the nucleus accumbens or striatum. Two shallow holes were also drilled for insertion of anchor screws. Concentric dialysis probes were constructed in-house using the principles described by Nomikos et al. (1991). The length of active membrane was approximately 2.25 mm. The probe was slowly lowered into position at the following coordinates relative to the Bregma: for the nucleus accumbens (N=22) AP +1.6, ML ±1.4, and DV −8.2 mm; for the striatum (N=6) AP +0.7, ML ±3.5, and DV −6.2 mm. The incisor bar was set at −3.2. The probe was fixed to the skull with stainless steel screws and dental cement (Dentalon, AgnTho's AB, Lidingö, Sweden). After surgery, rats were housed individually and left to recover for approximately 48 h. Microdialysis was performed in freely moving rats. Food and water were not available during experiment. The probe was perfused with a modified Ringer's solution (Apoteksbolaget, Stockholm, Sweden) delivered via a polyethylene tubing from an infusion pump (Harvard Apparatus, Holliston, MA, USA) at a rate of 2.5 μl/min. Dialysate was collected over 15-min intervals (37.5 μl) and automatically injected into a high-performance liquid chromatography system. Separation of dopamine, dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) was achieved by reversed-phase liquid chromatography using a 55-mM sodium acetate buffer (pH 4.0, 10% methanol) with 0.1 mM octanesulfonic acid and 0.01 mM Na_2EDTA. The mobile phase was delivered by an HPLC pump (Model 2150, Pharmacia LKB, Uppsala, Sweden) through a C-18 column (Nucleocil 150×4.6 mm, 5 mm) at a rate of 0.8 ml/min. Following separation, the analysate was first passed through a guard cell with an applied oxidizing potential of 50 mV to reduce baseline noise from other electroactive compounds. Samples were then quantified by sequential oxidation and reduction in a high-sensitivity analytical cell (5011 ESA, Chelmsford, MA, USA) controlled by a potentiostat (Coulochem II, model 5200, ESA) with applied potentials of 400 mV and −200 mV for detection of metabolites and dopamine, respectively. Detection limits for dopamine and DOPAC is about 1 fmol/sample and for HVA about 3 fmol/sample. After stable baseline values in the dialysates were obtained (following 3 to 4 h of dialysis), nicotine (0.5 mg/kg s.c., Sigma), oxotremorine (0.1 mg/kg s.c., Sigma), or vehicle was administered to the rats. Amphetamine

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