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Acquisition of nicotine self-administration in amphetamine and phencyclidine models of schizophrenia: A role for stress?

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ABSTRACT

Nicotine use and dependence is very high in patients with schizophrenia. One possible reason is that altered dopamine or glutamate activity in schizophrenia enhances the reinforcing effectiveness of nicotine. We used animal models to test the hypothesis that a hyperdopaminergic state (induced by repeated intermittent injections of amphetamine) or altered glutamate function (subchronic injection of phencyclidine, PCP) facilitates spontaneous acquisition of nicotine self-administration in rats. In Experiment 1 animals in an amphetamine-induced sensitized state (AISS) did not differ from saline-injected controls in their acquisition and maintenance of nicotine self-administration. This effect was replicated in experiment 2, but it was also found that AISS rats and salineinjected controls showed higher rates of nicotine self-administration compared to uninjected controls. This difference was maintained across several fixed ratio and progressive ratio schedules of reinforcement. In Experiment 3 PCP treated rats and their saline-injected controls did not differ in nicotine self-administration. However, both groups showed consistently increased responding for nicotine on FR and PR schedules compared to an uninjected control group. Injection-stress appeared to influence the outcomes of these experiments in two ways. Firstly, injection stress potentially masked the impact of the AISS and PCP treatment on nicotine self-administration. Secondly, injection stress itself may have been sufficient to induce plastic changes in dopamine and glutamate systems, and these changes enhanced the acquisition and maintenance of nicotine self-administration. Further investigation is needed into the role of stress in the development of nicotine use and dependence, in the aetiology of schizophrenia and in their co-morbidity.

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1. Introduction

The incidence of tobacco use and dependence is extremely high in individuals with schizophrenia (70–85%) compared to the general population (20–30%) (Ziedonis et al., 2008). People with schizophrenia tend to be heavier smokers, and extract more nicotine per cigarette, factors that likely contribute to the fact that they have even more difficulty quitting smoking than non-schizophrenic individuals. The health costs associated with smoking are especially pronounced in people with schizophrenia who have a 20% shorter life-expectancy, in large part due to their higher risk of coronary heart disease (Brown et al., 2000; Hennekens et al., 2005). Understanding the basis of the co-morbidity of smoking and schizophrenia is essential to optimize treatment strategies for nicotine dependence in this large clinical population. Preclinical

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http://dx.doi.org/10.1016/j.schres.2017.02.028 0920-9964/© 2017 Elsevier B.V. All rights reserved. work using animal models of schizophrenia, may be one useful approach to understanding the link between nicotine use and schizophrenia. Relatively little work has investigated this question, but one recent report shows that rats with neonatal ventral hippocampal lesions (NVLH), a neurodevelopmental model of schizophrenia (Lipska and Weinberger, 2002), display enhanced self-administration of nicotine (Berg et al., 2014). The authors suggested that nicotine was "more addictive" in this model.

Neurochemical studies of the causes of schizophrenia suggest that abnormal dopamine (DA) or glutamate function are major contributors to the pathophysiology disorder. A major component of the DA hypothesis is that schizophrenia involves hyperactivity of subcortical DA systems, especially the mesolimbic DA pathway. This is supported by the facts that antipsychotic drugs block DA D2 receptors (Seeman et al., 1976), and that in some individuals chronic use of psychomotor stimulants can induce psychosis (Curran et al., 2004). The binding of radiolabelled DA D2 receptor ligands to D2 receptors is displaced by amphetamine-induced DA release and this effect is enhanced in many

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people with schizophrenia, providing direct evidence of enhanced DA activity in the disease (Abi-Dargham et al., 1998; Abi-Dargham et al., 2000; Laruelle et al., 1999).

2. Methods

2.1. Subjects and housing

The glutamate hypothesis postulates that the disease results from aberrant function of NMDA receptor mediated glutamatergic transmission. Low doses of NMDA receptor antagonists, such as phencyclidine (PCP) or ketamine produce schizophrenia-like symptoms in healthy individuals, while exacerbating symptoms in patients with schizophrenia (Javitt and Zukin, 1991; Lahti et al., 2001). Several candidate genes in schizophrenia (e.g. DAO, GR1A1, GRIN2A, GRM3 and SRR) appear to converge on aspects of glutamate function in general, and NMDA-receptor mediated signalling in particular (Harrison, 2015; Harrison and Weinberger, 2005). Post-mortem studies have identified changes in glutamate receptor binding, transcription, and subunit protein expression in the prefrontal cortex, thalamus, and hippocampus in schizophrenia (Clinton and Meador-Woodruff, 2004). Consistent with these studies, reduced NMDA receptor binding has been found in the hippocampus of medication-free patients (Pilowsky et al., 2006). The glutamate and dopamine hypotheses are not mutually exclusive, and the neurochemical bases of both may be inter-related (Carlsson et al., 2004; Coyle, 2006; Stone et al., 2007). For example, ketamine evokes striatal dopamine release, as measured by displaced ^[11C]raclopride binding, and enhances amphetamine induced striatal DA release in healthy volunteers (Breier et al., 1997; Vollenweider et al., 2000).

Nicotine is the primary psychoactive substance in tobacco. Its stimulant, reinforcing and subjective effects are mediated in large part by increased mesolimbic dopamine (DA) activity (Balfour, 2004; Markou, 2008). Given the role of dopamine in the reinforcing effects of nicotine it is possible that the striatal hyperdopaminergic state of schizophrenia may increase vulnerability to the reinforcing and subjective effects of nicotine, and that this promotes the initiation and maintenance of nicotine dependence in schizophrenia. Indeed, smoking may have stronger reinforcing effects in people with schizophrenia (Lo et al., 2011), with one study finding that schizophrenia patients reported a stronger motivation to smoke for "reasons related to pleasure from the act of smoking" and for psychomotor stimulation (Barr et al., 2008). The fact that use of other drugs, especially psychomotor stimulants, is increased in schizophrenia supports the notion that schizophrenia may be associated with an "addiction vulnerability" (Green and Brown, 2006).

Repeated treatment with psychomotor stimulants, such as amphetamine, sensitizes the DA system, and enhances acquisition of self-administration of those, or similar drugs (Horger et al., 1992; Vezina, 2004; Vezina et al., 2002) implying that a hyperdopaminergic state may predispose individuals to drug self-administration. Therefore, the amphetamine-induced sensitized state (AISS) can be a useful model for inducing an functional hyperdopaminergic state (Featherstone et al., 2007). One aim of the experiments reported here was to test the hypothesis that nicotine self-administration would be increased in rats with a sensitized DA system, similar to that thought to underlie schizophrenia. A second aim was to examine the impact of altered glutamate function on nicotine self-administration, induced by a sub-chronic regimen of phencyclidine (PCP) treatment. The AISS (Featherstone et al., 2007) and sub-chronic PCP treatment models (Morris et al., 2005; Neill et al., 2011) produce overlapping but separable behavioural and neurochemical phenotypes that model aspects of schizophrenia, as reviewed extensively elsewhere. We examined the impact of these treatments on spontaneous acquisition of responding for low doses of intravenous nicotine infusions (Shram et al., 2008b). We predicted that self-administration of nicotine would be enhanced in amphetamine-sensitized and PCP treated animals compared to saline-injected controls. Due to an unexpected outcome in the first experiment subsequent experiments included an additional control group consisting of animals that were not handled, or injected during the drug sensitization period.

Male Sprague-Dawley rats (initially 175–200 g for Experiment 1, and 275–300 g for Experiments 2 and 3; Charles River, Quebec), were individually housed in hanging clear plastic cages on a 12 h light-dark cycle (lights off at 7:00 am) in a temperature controlled room (22 °C). Training and testing occurred during the dark phase of the cycle. During training and testing, food was restricted to 18–20 g per day. Water was available ad-libitum in the home cages.

2.1.1. Drug treatment regimens

In Experiment 1 rats were assigned to four groups; two groups received IP injections of d-amphetamine sulphate (Sigma-RBI, Oakville, Ontario), and two groups received injections of 0.9% saline (Sal; 1 ml/kg) on 3 days each week for 5 weeks. One injection per day was administered on Monday, Wednesday and Friday. The amphetamine dose increased from 1 to 5 mg/kg over the 5 weeks. In Experiment 2 a similar procedure was used except that amphetamine was administered 5 times per week, daily Monday to Friday, for 3 weeks, with the dose escalating from 1 to 3 mg/kg. A shorter time schedule was preferable in this experiment, which also included an additional control group that received no injections and was minimally-handled (see Section 2.3). We have previously found that these two regimens of amphetamine administration induce a reliable AISS (Fletcher et al., 2007; Tenn et al., 2003). The saline control group was injected with 0.9% saline. In Experiment 3 rats were injected SC with 3 mg/kg phencyclidine HCl twice a day (approx. 9 am and 4 pm) for 7 days; a control group was treated similarly except 0.9% saline was injected.

2.1.2. Locomotor activity testing

Horizontal locomotor activity was measured in stainless-steel chambers with wire mesh floors (40 cm L, 25 cm D, 20 cm H). Each chamber contained two infrared photocells mounted 3 cm above the floor that divided it into three equal-size compartments. Locomotor activity was inferred from the number of photobeam interruptions recorded by computer in 10-min intervals.

2.1.3. Surgery

At the time of surgery rats weighed 380–430 g. Rats were anaesthetised with isoflurane to implant a Silastic® catheter into the right jugular vein. The external end of the catheter was mounted between the scapulae (see, Corrigall and Coen, 1989; Le et al., 2006). During surgery the analgesic agent Ketoprofen (5 mg/kg SC), and the antibiotic Penlong (1 ml/kg) were given. Catheters were flushed daily with 0.1 ml of sterile 0.9% saline solution containing 50 U/ml heparin.

2.1.4. Nicotine self-administration

Testing was conducted in operant conditioning chambers $(28 \times 21 \times 21 \text{ cm}; \text{Med. Associates Inc., St Albans, VT, USA})$. Each chamber contained two response levers, a Sonalert and a stimulus light located above each lever. A syringe mounted on a motor driven pump (PHM-100VS, Med Associates) delivered nicotine infusions to the catheter via Tygon tubing, protected by a stainless steel spring, attached to a swivel located above the test chamber. Each chamber was illuminated by a house light and housed in a sound-attenuating box equipped with a ventilating fan. All boxes were controlled by a computer running Med-PC-IV. A variety of schedules of reinforcement and nicotine infusion doses were used in these experiments and specific details are provided below for each experimental description. Each infusion was accompanied by a 1 s tone (2900 Hz) and followed by a 20s time-out period during which responses were recorded but not reinforced. On fixed ratio (FR) schedules, infusions were earned by completing the required ratio (1, 2 or 5 responses). A progressive ratio (PR) schedule was also used. The first three ratios were fixed at 3, 6 and 10; thereafter response

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