Neuropharmacology 99 (2015) 715–725

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Antipsychotic treatment leading to dopamine supersensitivity persistently alters nucleus accumbens function

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ARTICLE INFO

Article history:
Received 27 December 2014
Received in revised form
13 March 2015
Accepted 14 March 2015
Available online 27 March 2015

Keywords:
Schizophrenia
Haloperidol
Olanzapine
Dopamine supersensitivity
Amphetamine

ABSTRACT

Chronic exposure to some antipsychotic medications can induce supersensitivity to dopamine receptor stimulation. This is linked to a worsening of clinical outcome and to antipsychotic treatment failure. Here we investigated the role of striatal subregions [nucleus accumbens (NAc) and caudate-putamen (CPu)] in the expression of antipsychotic-induced dopamine supersensitivity. We treated rats with haloperidol (HAL) or olanzapine (OLZ), using regimens that achieve clinically relevant kinetics of striatal D2 receptor occupancy. Under these conditions, HAL produces dopamine supersensitivity whereas OLZ does not. We then assessed behaviors evoked by the dopamine agonist amphetamine (AMPH). We either injected AMPH into the striatum or inhibited striatal function with microinjections of GABA receptor agonists prior to injecting AMPH systemically. HAL-treated rats were dopamine supersensitive, as indicated by sensitization to systemic AMPH-induced potentiation of both locomotor activity and operant responding for a conditioned reward (CR). Intra-CPu injections of AMPH had no effect on these behaviors, in any group. Intra-NAc injections of AMPH enhanced operant responding for CR in OLZ-treated and control rats, but not in HAL-treated rats. In HAL-treated rats, inhibition of the NAc also failed to disrupt systemic AMPH-induced potentiation of operant responding for CR. Furthermore, while intra-NAc AMPH enhanced locomotion in both HAL-treated and control animals, inhibition of the NAc disrupted systemic AMPH-induced locomotion only in control rats. Thus, antipsychotic-induced dopamine supersensitivity persistently disrupts NAc function, such that some behaviors that normally depend upon NAc dopamine no longer do so. This has implications for understanding dysfunctions in dopamine-mediated behaviors in patients undergoing chronic antipsychotic treatment.

1. Introduction

Antipsychotic drugs are the mainstay in the current pharmacological treatment of schizophrenia. All currently approved antipsychotic medications occupy D2/D3 receptors and reduce dopamine-mediated neurotransmission, particularly in the striatum. This is thought to be the principal mechanism by which antipsychotics exert their anti-psychotic effects (Farde et al., 1988; Kapur and Remington, 2001).

Chronic exposure to antipsychotic medications can trigger compensatory neurobiological changes that manifest as supersensitivity to dopamine receptor stimulation. Although some atypical antipsychotics can evoke dopamine supersensitivity, it is preferentially triggered by typical antipsychotics (Bedard et al., 2013; Glazer, 2000; Samaha et al., 2007). This supersensitivity to dopamine has tremendous clinical implications because it is linked to augmented behavioral effects of dopamine stimulation on the one hand and diminished anti-dopaminergic effects of antipsychotic drugs on the other. For instance, antipsychotic-induced dopamine supersensitivity is thought to increase the incidence of both psychosis upon treatment cessation (Chouinard et al., 1978; Tollefson et al., 1999) and movement disorders (Casey, 1995). In addition, it increases the ability of dopamine agonists to potentiate both psychomotor activity (Asper et al., 1973; Samaha et al., 2008, 2007;

Abbreviations: CPu, Caudate putamen; NAc, Nucleus accumbens; HAL, Haloperidol; OLZ, Olanzapine; AMPH, Amphetamine; DA, Dopamine; CR, Conditioned reward; M, Muscimol; B, (RS)-baclofen; CS, Conditioned stimulus; UCS, Unconditioned stimulus; CSR, CS Response; PCSR, Pre-CSR.

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http://dx.doi.org/10.1016/j.neuropharm.2015.03.012
0028-3908/

Smith and Davis, 1976) and operant responding for conditioned reward (CR; (Bedard et al., 2011, 2013). Finally, in animal models of antipsychotic-like effects, dopamine supersensitivity following antipsychotic treatment is linked to decreased efficacy of currently used (Samaha et al., 2008, 2007) and experimental (Gill et al., 2014) antipsychotic compounds. This literature has led to proposals that antipsychotic-induced dopamine supersensitivity might contribute to the high rates of drug abuse and addiction in schizophrenia (Samaha, 2014) and to antipsychotic treatment failure over time (Samaha et al., 2007).

The striatum mediates many of the behaviors that are altered in dopamine supersensitive subjects. As such, studies on the neurobiology underlying antipsychotic-induced supersensitivity to dopamine have focused on the striatum. Some studies show an increase in the ability of dopamine agonists to evoke gene regulation in the caudate-putamen [CPu; (Bedard et al., 2011, 2013)]. Others show an increase in the density of striatal D2 receptors (Burt et al., 1977; Ginovart et al., 2009; Muller and Seeman, 1977) and D2 receptors in a high-affinity state for DA (Samaha et al., 2008, 2007). All of these changes remain correlational. Moreover, behavioral supersensitivity to dopamine agonists can be dissociated from changes in striatal D2 receptor number (Pierce et al., 1991; Samaha et al., 2007), and preliminary data suggest that there is no change in D2 high-affinity states in schizophrenia (Graff-Guerrero et al., 2009).

Within this context, we asked the following question: Does the striatum mediate the behavioral expression of antipsychotic-induced dopamine supersensitivity? To address this question, we first pretreated rats with either the typical antipsychotic haloperidol (HAL), or the atypical antipsychotic olanzapine (OLZ), using doses and a mode of administration that are clinically relevant. Under these conditions, only HAL treatment evokes dopamine supersensitivity, as indicated by sensitization to the behavioral effects of AMPH following cessation of antipsychotic treatment (Bedard et al., 2013; Samaha et al., 2007). Thus, following antipsychotic treatment, we measured changes in two behaviors that depend upon dopamine neurotransmission within the striatum, AMPH-induced potentiation of psychomotor activity and of operant responding for CR. By stimulating striatal subregions (nucleus accumbens and caudate putamen) with microinjections of AMPH and conversely, by functionally inhibiting these subregions with microinjections of GABA receptor agonists prior to injecting AMPH systemically, we found that 1) the striatum does not mediate the expression of augmented AMPH-induced potentiation of psychomotor activity and responding for CR in dopamine supersensitive animals, and 2) an antipsychotic treatment leading to dopamine supersensitivity disrupts the ability of the nucleus accumbens (NAc) to mediate dopamine-dependent behaviors.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (200–225 g upon arrival; Charles River, Montréal, Canada) were housed 1/cage on a reverse light/dark cycle with *ad libitum* access to food. Access to water was restricted to 2 h/day to facilitate subsequent Pavlovian conditioning where water was used as the unconditioned stimulus. Experiments were conducted during the dark phase of the animals' circadian cycle (8 AM–8 PM). Different cohorts of rats were used in each experiment. The number of rats per experimental group ranged between 9 and 21, and n's for each experiment are indicated in the figure legends. All efforts were made to minimize animal suffering and the number of animals used. The Université de Montréal's animal care committee approved all experimental procedures and this was carried out in accordance with the Canadian council on Animal Care.

2.2. Drugs

HAL (Sandoz, Boucherville, Canada) was dissolved in 0.5% glacial acetic acid/water solution (pH adjusted to ~5 with 1 M sodium hydroxide) and administered at a dose of 0.5 mg/kg/day via subcutaneous (s.c.) minipump (Alzet model 2ML2, 15–17 days of drug delivery depending on the batch and according to the manufacturer's specifications; Durect, Cupertino, CA, USA). OLZ (Toronto Research Chemicals, Toronto, Canada) was dissolved in a 2% acetic acid/water solution (pH adjusted to ~5 with 1 M sodium hydroxide) for treatment via minipump. An OLZ/acetic acid formulation delivered via minipump can lead to declining plasma levels of the antipsychotic 14 days into treatment (McCormick et al., 2010; van der Zwaal et al., 2008). However, striatal D2 occupancy remains within the clinical range (74% ± 7% SD) at the 14-day time point (McCormick et al., 2010). D-amphetamine sulfate (AMPH; Sigma–Aldrich, Dorset, UK) was dissolved in 0.9% saline. Muscimol (M) and (RS)-baclofen (B) (GABA type A and B receptor agonists, respectively; Sigma–Aldrich, Oakville, Canada) were dissolved in 0.9% saline such that the concentration of each compound was 125 ng/μl.

2.3. Antipsychotic treatment

Therapeutic efficacy for many antipsychotics is seen with 65–75% D2 receptor occupancy (Farde et al., 1992; Kapur et al., 2000). We used HAL and OLZ doses which produce striatal D2 occupancy levels that lie within this range and that are also equivalent. In rats, 0.5 mg/kg/day HAL via minipump achieves 73% striatal D2 occupancy [±14 SD; unpublished observations; see also (Kapur et al., 2003; Samaha et al., 2007)], a level that falls within the clinically relevant range as well as within the range that produces antipsychotic-like efficacy in animal models (Wadenberg et al., 2000). Note however that if 0.5 mg/kg HAL is given as an acute s.c. injection, it would produce 94% striatal D2 occupancy, a level that well exceeds the clinically relevant range and that also promotes catalepsy in rats (Wadenberg et al., 2001). For OLZ treatment, we used a dose of 10 mg/kg/day OLZ, also administered via minipump. We chose this dose for two reasons. First, a similar dose (7.5 mg/kg/day) produces 74% (±7% SD) striatal D2 receptor occupancy 14 days into treatment (McCormick et al., 2010). Second, we have shown previously that chronic exposure to 10 mg/kg/day OLZ (via minipump, as used here) does not produce supersensitivity to AMPH's behavioral effects (Bedard et al., 2013; Samaha et al., 2007). Thus, although 10 mg/kg/day OLZ might achieve slightly higher striatal D2 receptor blockade than 0.5 mg/kg/day HAL, the OLZ treatment does not produce dopamine supersensitivity. Comparing these two conditions thus enables us to dissociate neuroadaptations that result from chronic antipsychotic drug exposure alone, versus neuroadaptations that result specifically from antipsychotic-induced dopamine supersensitivity. In the current study, both antipsychotics were administered via osmotic minipump. This is because antipsychotic administration through a minipump produces continuously high levels of striatal D2 occupancy over the treatment period (Kapur et al., 2003; McCormick et al., 2010; Samaha et al., 2007). This mimics the kinetics of standard antipsychotic treatment in humans, where striatal D2 occupancy can remain elevated for several days following a single dose (Farde et al., 1989; Tauscher et al., 2002).