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Antipsychotic treatment leading to dopamine supersensitivity persistently alters nucleus accumbens function

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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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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 those 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 2 ML2, 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 via 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).

2.4. Pavlovian conditioning

In operant conditioning chambers (Med Associates, St Albans, Vermont, USA), rats were trained to associate the delivery of 100 μl water (the unconditioned stimulus; UCS) into a receptacle with a light/tone conditioned stimulus (CS), as in Fletcher (1995). We recorded nose-pokes into the receptacle performed both during the presentation of the CS (CS Response: CSR) and during the 5-s period prior to presentation of the CS (Pre-CSR: PCSR). A CSR/PCSR ratio ≥3 over the last 3 training days was used as an index of Pavlovian conditioning. All rats met this learning criterion. Rats were then assigned to the HAL, OLZ or control groups, such that average CSR/PCSR ratios over the last 3 conditioning days were equivalent between groups.

2.5. Implantation of cannulae and osmotic minipumps

Following Pavlovian conditioning, rats were anesthetized with isoflurane (CDMV, Ste-Hyacinthe, Canada) for bilateral intracerebral implantation of 22-gauge stainless steel guide cannulae (HRS Scientific, Anjou, Canada). In Experiment 1, cannulae were implanted to lie 1 mm dorsal to the CPu [A/P, +1.3 mm, M/L, ±3 mm, both from Bregma, and D/V −4.3 mm from the skull surface (Paxinos and Watson, 1986)]. In Experiments 2 to 5, cannulae were implanted to lie 2 mm dorsal to the NAc [A/P, +2.2 mm, M/L, ±2.6 mm, both from Bregma, and D/V, −0.5 mm from the skull surface, at a 10° angle (Paxinos and Watson, 1986)]. The coordinates for the NAc principally target the NAc core and were based on prior findings showing that injecting AMPH into this region of the NAc enhances operant responding for conditioned reward (Taylor and Robbins, 1984, 1986) and locomotor activity (Dougherty and Ellinwood, 1981; Kelly and Iversen, 1976). Cannulae were sealed with stainless steel dummies (HRS Scientific) that lay flush with the tip of the guide cannulae. During the same surgery, rats in the HAL and OLZ groups were implanted with s.c. minipumps in between the scapulae, as described in Samaha et al. (2007). Prior work shows that AMPH-induced locomotion is similar in control rats that had been implanted with a saline-containing minipump (Samaha et al., 2007) compared to control rats that had received a sham surgery without minipump implantation (Samaha et al., 2008). Thus, in the present experiments, control rats received a sham surgery consisting of an incision and sutures. Fifteen to 17 days later, minipumps

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were removed from the antipsychotic-treated rats. Control rats received a second sham surgery.

2.6. Brain microinfusion

Microinfusions were performed using 28-gauge stainless steel injectors (HRS Scientific). Injectors extended 1 or 2 mm past the tips of the guide cannulae for intra-CPu and intra-NAcc injections, respectively. Solutions were administered in a volume of 0.5 μl over 1 min using a microsyringue pump (HARVARD PHD 2000, HARVARD Apparatus, Canada). Injectors were kept in place for an additional minute for diffusion of the solution. Doses of microinjected AMPH (Kelley and Delfs, 1991; Taylor and Robbins, 1986) and muscimol/baclofen (Floresco et al., 2008) are based on prior work.

2.7. EXPERIMENT 1: effects of intra-CPu AMPH on conditioned reward and psychomotor activity

In otherwise naive animals, injecting AMPH into the CPu does not alter psychomotor activity (Kelley et al., 1989) and DA neurotransmission within the CPu also does not play a strong role in conditioned reinforcement (Carr and White, 1983; Robbins and Everitt, 1982; Taylor and Robbins, 1986). However, prior findings show that in rats that have been treated with HAL and that have become DA supersensitive, the ability of AMPH to evoke immediate early gene expression (c-Fos and Nur77) in the CPu is potentiated (Bedard et al., 2011, 2013). This suggests an increased ability of AMPH to engage the CPu in dopamine supersensitive animals. Based on this, we assessed the effects of intra-CPu AMPH on conditioned reward and psychomotor activity. Fig. 1A shows the sequence of experimental events. Following antipsychotic treatment cessation (i.e., minipump removal), rats were given a reminder Pavlovian conditioning session followed by an intra-CPu injection of saline to habituate them to the microinjection procedure. The following day, rats were given a lever-habituation session during which two levers were present. Pressing on the active lever led to the presentation of the CS according to a random ratio 2 schedule. Pressing on the inactive lever was not reinforced. No water was delivered. Sessions ended after 10 active lever presses or 40 min. Starting on the next day the effects of intra-CPu injections of AMPH or saline on lever pressing for the CS (now a CR) were assessed as during the lever habituation sessions, except that active lever presses were not limited. Immediately prior to CR testing, AMPH was injected into the CPu (0, 3, 10 and 20 μg/0.5 μl/side, counterbalanced, one dose/day, every other day). Locomotor activity was measured simultaneously during the CR test sessions using photocell beams in the operant chambers.

2.8. EXPERIMENT 2: effects of intra-NAc AMPH on conditioned reward

The procedures were similar to those described in Experiment 1 except that AMPH was injected into the NAc (0, 2, 6 and 12 μg/0.5 μl/side).

2.9. EXPERIMENT 3: effects of intra-NAc AMPH on psychomotor activity

From this point on, we compared HAL-treated and control rats only. This is because we wished to determine whether the NAc mediates the expression of antipsychotic-induced dopamine supersensitivity, and under the present treatment conditions, HAL produces significant dopamine supersensitivity, while OLZ does not (Bedard et al., 2013; Samaha et al., 2007). Fig. 1B illustrates the sequence of events. Two days following HAL-treatment cessation, rats received an intra-NAc injection of saline to habituate them to the microinjection procedure. Starting two days later, the effects of intra-NAc injections of AMPH on locomotor activity were assessed in Plexiglas cages equipped with photocell beams, as described in Samaha et al. (2007). Immediately prior to locomotor testing, AMPH was injected into the NAc. Locomotor activity was then measured for one hour.

2.10. EXPERIMENT 4: effects of temporary inhibition of the NAc on the potentiation of conditioned reward evoked by systemic AMPH

Procedures were similar to those described in Experiment 1 with the following exceptions: HAL and control rats received intra-NAc injections of saline or the M/B cocktail (75 ng/0.5 μl/hemisphere) immediately followed by a s.c. injection of saline or AMPH (0.5 mg/kg/ml). CR testing began 10-min later. Each rat received all four combinations of intracerebral/systemic injections in a counterbalanced order, one treatment/day, every other day.

2.11. EXPERIMENT 5: effects of temporary inhibition of the NAc on the potentiation of psychomotor activity evoked by systemic AMPH

Procedures were as described in Experiment 4 except that 10 min following the intracerebral/systemic injections, we measured AMPH-evoked psychomotor activity for one hour in Plexiglas cages equipped with photocell beams, as in Samaha et al. (2007). AMPH was administered subcutaneously at a dose of 1.5 mg/kg/ml.

2.12. Histology

At the end of each experiment, brains were extracted and cut into coronal sections using a cryostat. Rats with injection sites lying outside of the targeted

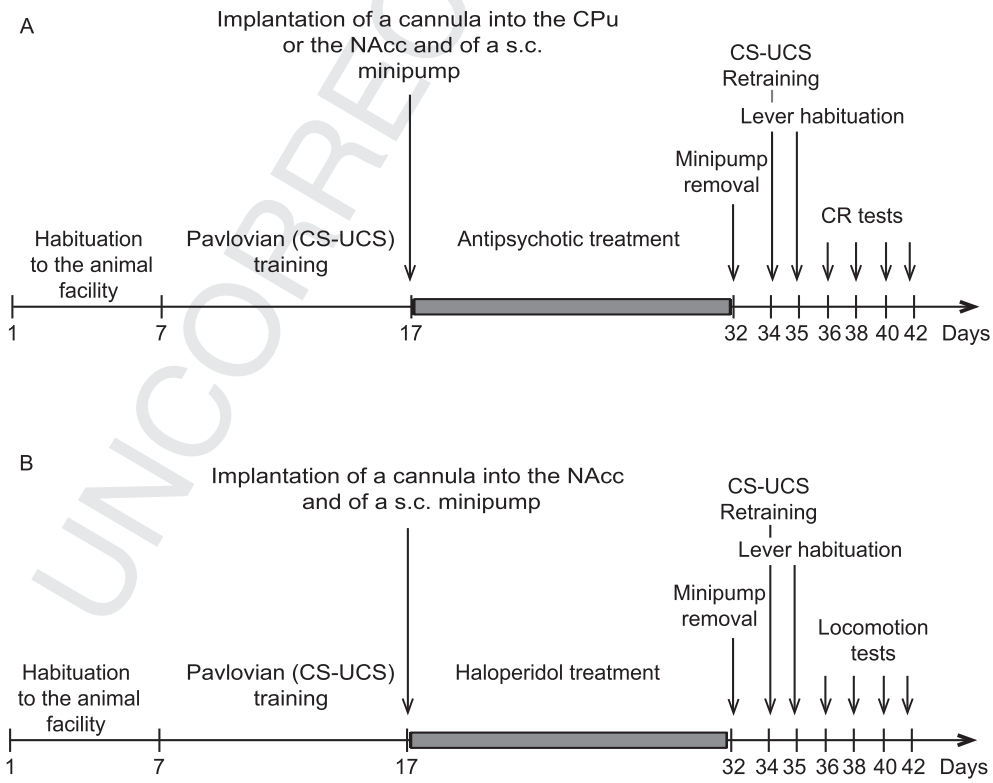

Fig. 1. Timeline of experimental manipulations. (A) illustrates the experimental procedures used in Experiments 1, 2 and 4, where we assessed the respective contributions of the caudate putamen (CPu) and the nucleus accumbens (NAc) to amphetamine-evoked potentiation of conditioned reward (CR) following antipsychotic treatment cessation. (B) illustrates the experimental procedures in Experiments 3 and 5, where we assessed the role of the NAcc in amphetamine-evoked locomotor activity following haloperidol treatment cessation. CS-UCS: conditioned stimulus-unconditioned stimulus.

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regions were excluded from the statistical analyses. This represented 8–13% of rats across experiments (<2 rats/group/experiment).

2.13. Statistical analysis

Average CSR/PCSR ratios were analyzed using a one-way ANOVA in experiments that included three experimental groups, and unpaired t-test in experiments that included two experimental groups. Lever presses were analyzed using three-way ANOVA (Group × Acute Treatment × Lever type). When interaction effects were significant, within group comparisons were analyzed using the Bonferroni test. Within each group, AMPH versus saline effects on lever pressing were analyzed using paired *t*-tests. Locomotor activity was analyzed using two-way ANOVA (Treatment × Time). All values in the figures are expressed as mean ± SEM.

3. Results

3.1. EXPERIMENT 1: effects of intra-CPu AMPH on conditioned reward and psychomotor activity

During the extra Pavlovian conditioning session given after HAL treatment cessation, average CSR/PCSR ratios were >3 in all rats and there were no group differences in this behavior (data not shown; $F(2) = 1.17$; $p = 0.84$). Thus, all groups retained the previously learned CS-UCS association, and did so to a similar extent. Fig. 2 shows that all rats, under all testing conditions, pressed more on the active (A–C) versus inactive (D–F) lever (Main effect of Lever; $F(1, 31) = 31.9$; $p < 0.0001$). Thus, all rats discriminated between the two levers and acquired a new operant response reinforced only by the CR. Intra-CPu AMPH had no effect on lever pressing, in any group (Acute Treatment × Lever type; $F(3, 29) = 1.39$; $p = 0.26$; Group × Acute Treatment × Lever type; $F(6, 60) = 1.08$; $p = 0.38$). In addition, intra-CPu AMPH (3, 10 or 20 μg/hemisphere) did not evoke a greater locomotor response than intra-CPu saline, in either HAL, OLZ or control rats (data not shown; all *P*'s > 0.05), and there were no group differences in either saline or AMPH-induced locomotion (data not shown; all *P*'s > 0.05).

3.2. EXPERIMENT 2: effects of intra-NAc AMPH on conditioned reward

During the extra Pavlovian conditioning session, average CSR/PCSR ratios were >3 in all rats, indicating that all rats retained the previously learned CS-UCS association and there were no group differences in this behavior (data not shown; $F(2) = 1.54$; $p = 0.22$). Fig. 3 shows that all rats, under all testing conditions, pressed more on the active (A-C) versus inactive (D-F) lever (Main effect of Lever; $F(1, 37) = 94.22$; $p < 0.0001$). Visual inspection of Fig. 3 suggested that in control animals, only doses of AMPH less than 12 μg/hemisphere potentiated lever pressing for the CR. Thus, lever-pressing behavior was analyzed separately at each dose with a three-way ANOVA. At the 2-μg dose, there was a significant Group × Acute Treatment × Lever interaction ($F(2, 37) = 3.43$; $p = 0.04$). *Post hoc* analysis of this interaction effect revealed that an intra-NAc injection of 2 μg AMPH potentiated active lever pressing behavior relative to intra-NAc saline only in control rats (Fig. 3A; Paired *t*-test; $t(11) = 2.82$; $p = 0.01$). At the 6-μg dose, there was also a significant Group × Acute Treatment × Lever interaction ($F(2, 37) = 3.18$; $p = 0.05$). *Post hoc* analysis of this interaction effect showed that injecting 6 μg of AMPH into the NAc increased active lever presses to a greater extent in control relative to HAL rats (Fig. 3A and B; Bonferroni test; $p = 0.02$). In addition, an intra-NAc injection of 6 μg AMPH potentiated active lever pressing behavior relative to intra-NAc saline only in control and OLZ rats (Fig. 3A;

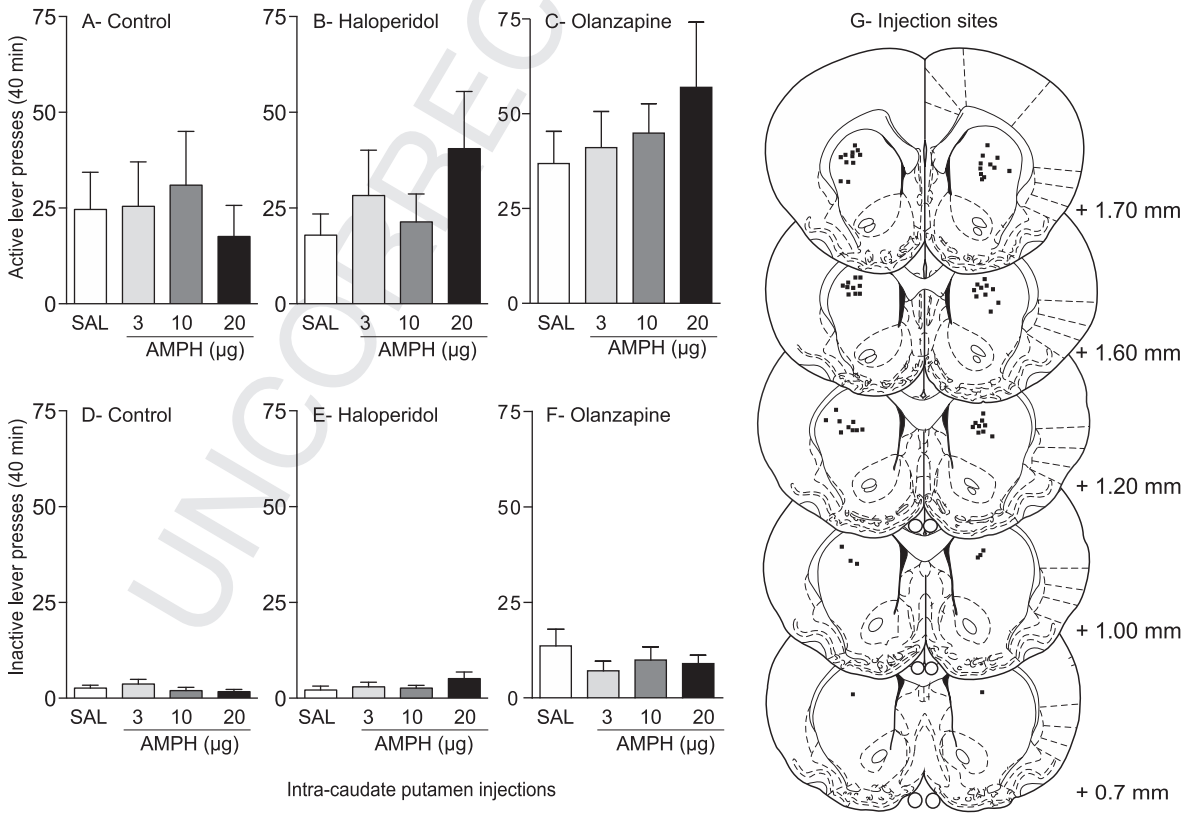

Fig. 2. Intra-caudate putamen injections of amphetamine (AMPH) do not alter the pursuit of conditioned reward in either control, haloperidol-treated or olanzapine-treated rats. (G) shows the estimated location of microinjector tips in coronal brain sections along with the rostrocaudal position from Bregma expressed in millimeters (mm). SAL: saline. N's = 10–13/group.

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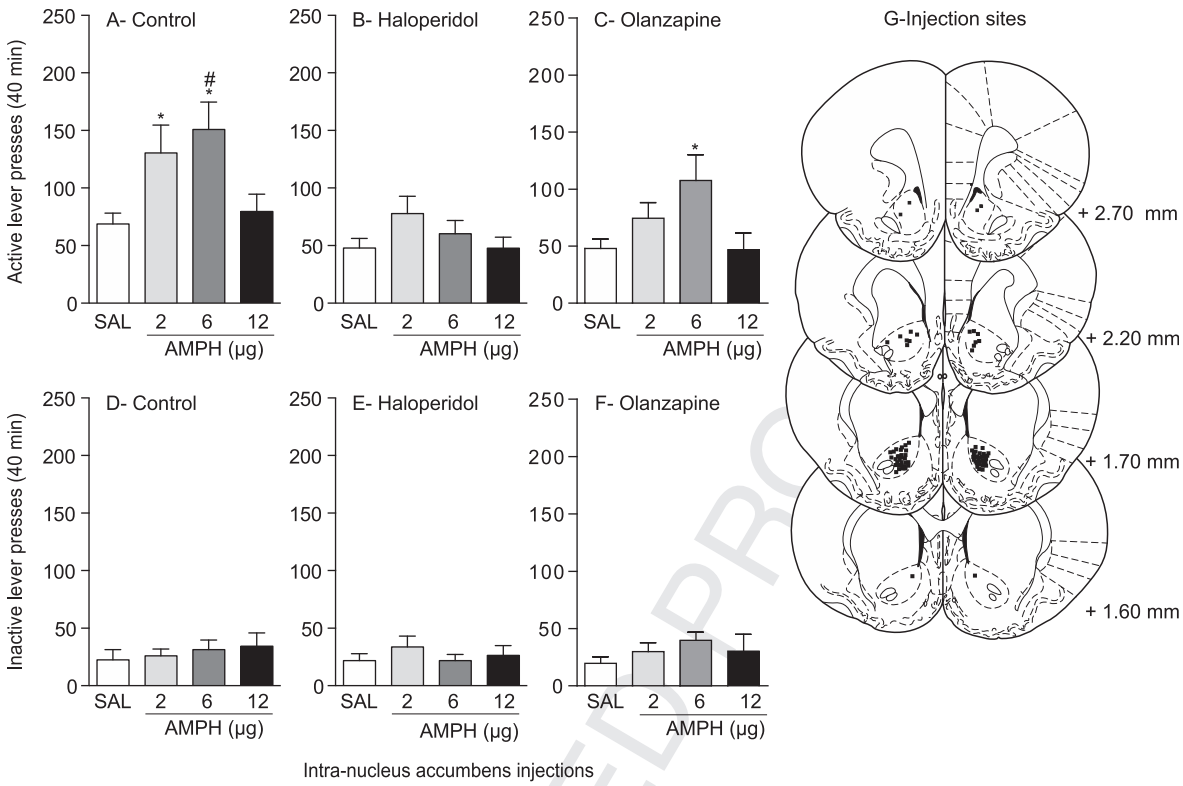

Fig. 3. Intra-nucleus accumbens injections of amphetamine (AMPH) enhance the pursuit of conditioned reward in control and olanzapine-treated rats but not in haloperidol-treated rats. (G) shows the estimated location of microinjector tips in coronal brain sections along with the rostrocaudal position from Bregma expressed in millimeters (mm). $^{*}p < 0.05$ compared to intra-nucleus accumbens saline (SAL) in the same group; $\#p < 0.05$ compared to haloperidol-treated rats injected with the same dose of AMPH. N's = 12–14/group.

Paired *t*-test; t (11) = 2.91; $p = 0.01$; Fig. 3C; Paired *t*-test; t (13) = 3.01; $p = 0.01$). At the 12-µg dose, there was no effect on lever pressing behavior, in any group (Group × Acute treatment × Lever interaction effect (F(2, 37) = 0.92; $p = 0.4$). No other comparisons were significant. Thus, intra-NAc injections AMPH increased operant responding for conditioned reward in control and OLZ rats, but no dose of AMPH altered this behavior in HAL-treated rats.

3.3. EXPERIMENT 3: effects of intra-NAc AMPH on psychomotor activity

Fig. 4 illustrates the effects of an intra-NAc injection of AMPH on psychomotor activity. In both HAL-treated and control rats, there was a significant Acute injection × Time interaction effect (Fig. 4A; Control, F(33, 352) = 6.3; $p < 0.0001$; Fig. 4B; HAL, F(33, 440) = 4.91; $p < 0.0001$). In both groups, all doses of AMPH increased locomotor activity relative to saline (Fig. 4A; Acute injection × Time; SAL vs. 2 µg AMPH, F(11, 176) = 10.44; SAL vs. 6 µg AMPH, F(11, 176) = 12.56; SAL vs. 12 µg AMPH, F(11, 176) = 17.56; Fig. 4B; SAL vs. 2 µg AMPH, F(11, 220) = 2.16; SAL vs. 6 µg AMPH, F(11, 220) = 13.37; SAL vs. 12 µg AMPH, F(11, 220) = 8.07; All *P*'s < 0.05). There were no group differences in AMPH-evoked locomotion (all *P*'s > 0.05).

3.4. EXPERIMENT 4: effects of temporary inhibition of the NAc on the potentiation of conditioned reward evoked by systemic AMPH

During the extra Pavlovian conditioning session, average CSR/PCSR ratios were >3 in both control and HAL rats. In this cohort of rats, average CSR/PCSR ratio was significantly greater in control versus HAL rats (data not shown; t (36) = 1.49; $p = 0.006$). This was due to two control rats having exceptionally high CSR/PCSR ratios (84 and 173, when the group average was 21.33 ± 10.6 SEM). Fig. 5 shows that all rats, under all testing conditions, pressed more on the active (A–B) versus inactive (C–D) lever (Main effect of Lever; F(1, 35) = 59.97; $p < 0.0001$). There was a significant Group × Acute treatment × Lever interaction (F(3, 33) = 4.00; $p = 0.01$). *Post hoc* analysis of this interaction effect showed that a subcutaneous injection of AMPH increased active lever presses to a greater extent in HAL relative to control rats, regardless of whether this systemic injection was preceded by an intra-NAc injection of saline or M/B (Fig. 5B; all *P*'s < 0.05). At this low dose of AMPH (0.5 mg/kg, s.c.), there was no effect on lever pressing behavior in control rats (Fig. 5A; all *P*'s > 0.05). In HAL rats, an intra-NAc injection of M/B decreased active lever presses compared to an intra-NAc injection of saline when the rats were tested following a subcutaneous SAL injection (Fig. 5B; Paired t-test; *t* (20) = 3.36; $p < 0.003$), but not when the rats were tested following subcutaneous AMPH (Fig. 5B; Paired t-test; *t* (19) = 1.05; $p = 0.3$). Moreover, in HAL-treated rats, systemic AMPH evoked greater active lever presses relative to systemic SAL, regardless of whether the systemic injections were combined with intra-NAc SAL or M/B (Fig. 5B; Paired t-test; AMPH s.c. with SAL i.c. vs. SAL s.c. with SAL i.c.; *t* (19) = 5.11; AMPH s.c. with M/B i.c. vs. SAL s.c. with M/B i.c; *t* (20) = 3.07; All *P*'s < 0.007). Thus, HAL rats were sensitized to the ability of systemic AMPH to potentiate operant responding for CR, and NAc inactivation had no effect on the expression of this behavior.

3.5. EXPERIMENT 5: effects of temporary inhibition of the NAc on the potentiation of psychomotor activity evoked by systemic AMPH

Fig. 6 illustrates the effects of functionally inhibiting the NAc on psychomotor activity evoked by a systemic injection of AMPH.

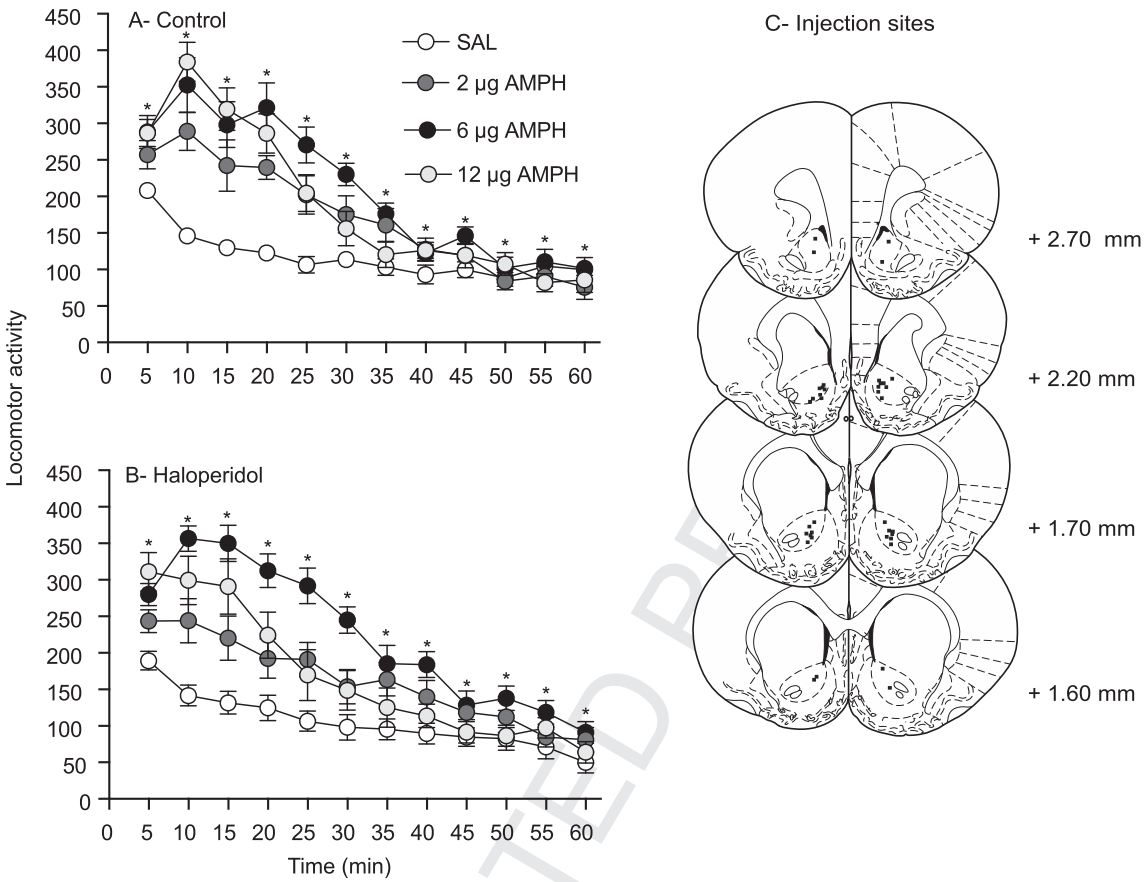

Fig. 4. Intra-nucleus accumbens amphetamine (AMPH) potentiates locomotor activity to a similar extent in control and haloperidol-treated rats. (C) shows the estimated location of microinjector tips in coronal brain sections along with the rostrocaudal position from Bregma expressed in millimeters (mm). *$p < 0.05$, each dose of intra-nucleus accumbens AMPH compared to intra-nucleus accumbens saline (SAL), within each experimental group. N's = 9–11/group.

Following an intra-NAc injection of saline, systemic AMPH increased locomotor activity relative to systemic saline in both control and HAL rats (Main effect of acute injection; Fig. 6A; $F(1, 22) = 73.25$; Fig. 6B; $F(11, 242) = 2.42$; All P's < 0.008). In addition, AMPH-induced locomotor activity was greater in HAL rats compared to controls (Main effect of Group; $F(1, 22) = 43.86$; $p < 0.0001$). This indicates that the HAL rats developed DA supersensitivity. In control rats, temporary inhibition of the NAc with M/B decreased locomotor activity evoked by either s.c. saline (Main effect of acute injection; Fig. 6A; $F(1, 21) = 11.21$; $p < 0.01$) or s.c. AMPH ($F(1, 22) = 7.84$; all P's < 0.05). In HAL rats, inhibition of the NAc had no effect on either saline- or AMPH-evoked locomotion (Fig. 6B; All P's > 0.05).

4. Discussion

We show here that key behavioral manifestations of antipsychotic-induced dopamine supersensitivity are not mediated by the striatum (NAc or CPu), and that in parallel, in dopamine supersensitive animals, some behaviors that normally depend upon the NAc are no longer under its control. We treated rats with HAL or OLZ, using regimens that achieve clinically relevant and equivalent kinetics of striatal D2 receptor occupancy. Under these conditions, withdrawal from OLZ treatment does not produce supersensitivity to dopamine agonism, while withdrawal from HAL does (Bedard et al., 2013; Samaha et al., 2007). This supersensitivity is evidenced by sensitization to AMPH-induced potentiation of psychomotor activity and operant responding for CR [(Bedard et al., 2011, 2013; Samaha et al., 2008, 2007); and present findings]. In control animals, both behaviors are tightly regulated by the actions of dopamine within the NAc (Dougherty and Ellinwood, 1981; Kelley and Delfs, 1991; Kelly and Iversen, 1976; Taylor and Robbins, 1984, 1986). By injecting AMPH into the NAc and conversely, by inhibiting NAc function with GABA receptor agonists prior to systemic AMPH injection, we replicated previous work showing that the NAc is both necessary and sufficient for AMPH-induced potentiation of responding for CR and psychomotor activity in control rats (Dougherty and Ellinwood, 1981; Kelley and Delfs, 1991; Kelly and Iversen, 1976; Taylor and Robbins, 1984, 1986). We also showed that following chronic OLZ treatment, the NAc remains sufficient for AMPH-induced potentiation of operant responding for CR. However, while HAL treatment induced sensitization to AMPH-induced potentiation of responding for CR and psychomotor activity, the NAc was neither necessary nor sufficient for the expression of this sensitization. In fact, HAL treatment markedly blunted the ability of the NAc to mediate these AMPH-induced responses.

4.1. Injecting AMPH into the CPu has no effect on either psychomotor activity or conditioned reward

Haloperidol-treated rats developed dopamine supersensitivity, as indicated by an augmented locomotor response to systemic AMPH and by the potentiation of operant responding for CR at a subthreshold dose of systemic AMPH. As shown previously (Mead et al., 2004; Robbins, 1978), the dose of AMPH used here (0.5 mg/

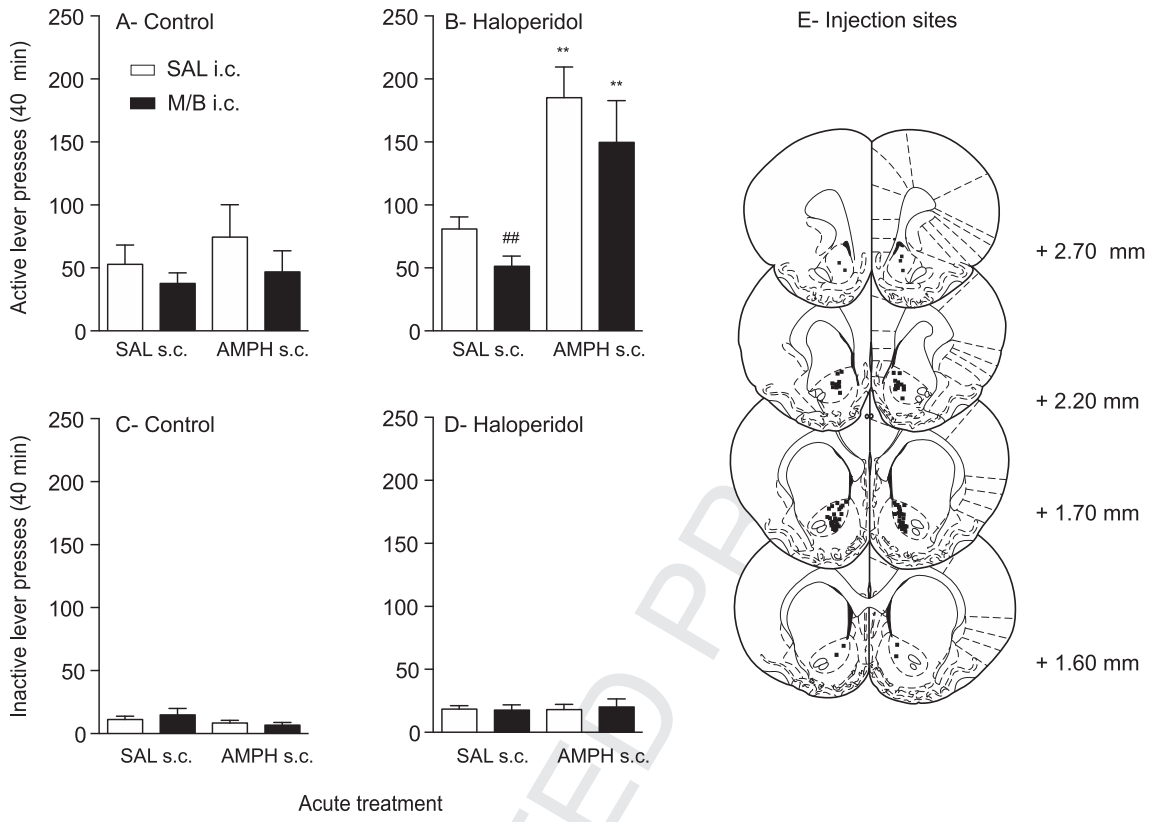

Fig. 5. A subcutaneous injection of AMPH (AMPH s.c.) potentiates conditioned reward in haloperidol-treated rats in spite of inhibition of the nucleus accumbens with muscimol and baclofen (M/B i.c.). (E) shows the estimated location of microinjector tips in coronal brain sections along with the rostrocaudal position from Bregma expressed in millimeters (mm). $^{**}p < 0.01$, compared to the same i.c. injection combined with a subcutaneous saline injection (SAL s.c.) in the same group or compared to the same i.c. injection in the control group; $\#\#p < 0.01$ compared to the same s.c. injection combined with an intra-nucleus accumbens saline injection (SAL i.c.). N's = 18–21/group.

kg) had no effect on operant responding for CR in control animals. Prior work in otherwise naïve rats also shows that injecting AMPH into the CPu does not alter the pursuit of CR or psychomotor activity in control animals (Kelley et al., 1989; Robbins and Everitt, 1982; Taylor and Robbins, 1986). There are some reports of enhanced operant responding for CR, but the effect is weak and variable (Kelley and Delfs, 1991; Taylor and Robbins, 1984)]. However, the behavioral effects of intra-CPu injections of AMPH have not been investigated in antipsychotic-treated rats. Relative to either OLZ or vehicle treatment, HAL treatment enhances the ability of AMPH to engage the CPu, as indicated by increased gene regulation in the dorsal CPu (Bedard et al., 2011, 2013). Given this, here we injected AMPH into the same dorsal region of the CPu as in Bedard et al. (Bedard et al., 2011, 2013) and we assessed operant responding for CR and locomotor activity. We found that injecting AMPH into the CPu is not sufficient to potentiate these behaviors, in either control or antipsychotic-treated rats. This supports two conclusions. First, the CPu does not mediate the expression of antipsychotic-induced dopamine supersensitivity. Second, there is no causal link between the ability of AMPH to promote gene regulation in the dorsal CPu and its ability to augment either the pursuit of CR or locomotor activity.

4.2. *Withdrawal from haloperidol treatment disrupts the ability of the NAc to mediate the behavioral effects of AMPH*

Although AMPH influences several neurotransmitter systems, dopamine (but not noradrenaline) neurotransmission in the NAc is both necessary (Cador et al., 1991; Kelly and Iversen, 1976; Taylor and Robbins, 1986) and sufficient (Kelley and Delfs, 1991; Taylor and Robbins, 1986) for AMPH-evoked potentiation of operant responding for CR and locomotor activity. Accordingly, we show that in control animals, injecting AMPH into the NAc is sufficient to increase locomotion and the pursuit of CR, and conversely, inactivating the NAc with muscimol and baclofen attenuates the locomotor response to systemic AMPH. Similar to that seen in control animals, injecting AMPH into the NAc of previously OLZ-treated animals is also sufficient to increase the pursuit of CR. However, we were surprised to find that in previously HAL-treated rats, the NAc becomes neither sufficient nor necessary for AMPH-induced potentiation of responding for CR, and unnecessary for AMPH-induced locomotion. This is not because withdrawal from HAL treatment alters the primary pharmacological effects of AMPH in the NAc. First, AMPH-evoked dopamine overflow in the NAc is similar in previously HAL-treated and control animals (Samaha et al., 2007). Second, in the present study, intra-NAc AMPH enhanced psychomotor activity with similar efficacy in HAL-treated and control rats (also suggesting that the ability of the NAc to mediate AMPH-induced locomotion was partially preserved following HAL treatment).

Thus, the most parsimonious explanation for the effects observed here is that, paradoxically, antipsychotic treatment leading to dopamine supersensitivity evokes neuroplasticity that persistently blunts normal NAc function. This hypothesis is supported by work showing that schizophrenia patients treated with antipsychotic drugs—particularly of the typical class—have blunted activation of the ventral striatum in response to reward cues (Juckel et al., 2006; Kirsch et al., 2007; Schlagenhauf et al., 2008). At present, we do not know how HAL treatment might blunt NAc function. However, we highlight that the apparent blunting of NAc

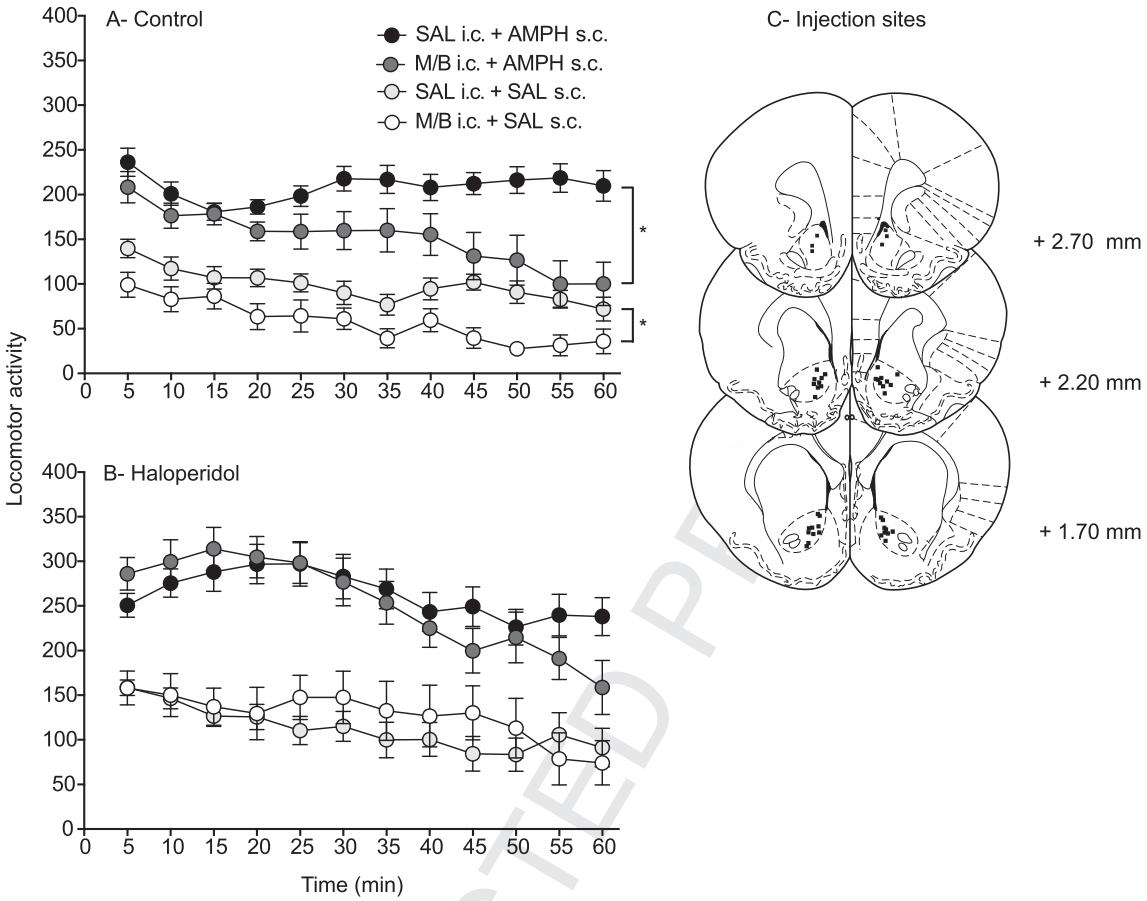

Fig. 6. Inhibition of the nucleus accumbens with muscimol/baclofen (M/B i.c.) decreases the locomotor response evoked by either subcutaneous amphetamine (AMPH s.c.) or subcutaneous saline (SAL s.c.) in control but not in haloperidol-treated rats. (C) shows the estimated location of microinjector tips in coronal brain sections along with the rostrocaudal position relative to Bregma expressed in millimeters (mm). $^{*}p < 0.05$. SAL i.c.: intra-nucleus accumbens injection of saline. N's = 12/group.

function occurred in parallel to the development of behavioral sensitization to AMPH. The implication is that following withdrawal from HAL treatment, some NAc functions are blunted, and in parallel, an extrastriatal circuit undergoes plasticity enabling it to mediate the behavioral manifestations of dopamine supersensitivity. In this context, it is notable that in another pharmacological model of dopamine supersensitivity (repeated exposure to AMPH), there is enhanced AMPH-induced dopamine overflow in the amygdala (Harmer et al., 1997). This could be relevant here because an inverse relationship exists between dopamine neurotransmission in the amygdala and in the NAc (Louilot et al., 1985). Moreover, the amygdala mediates AMPH-induced potentiation of both locomotor activity (O'Dell et al., 1999) and operant responding for CR (Ledford et al., 2003). Thus, an antipsychotic treatment that induces dopamine supersensitivity could evoke neuroadaptations within the amygdala that would both blunt the ability of the NAc to mediate dopamine-dependent behaviors and promote the expression of dopamine supersensitivity. Consistent with this, medicated schizophrenic patients have decreased levels of dopamine transporters (Markota et al., 2014) and increased concentrations of dopamine in the amygdala (Reynolds, 1983). Future studies can determine how antipsychotic treatment might influence dopamine function in the amygdala.

We have shown previously that using the same exposure regimen as used here, withdrawal from HAL, but not OLZ treatment produces dopamine supersensitivity (Bedard et al., 2013; Samaha et al., 2007). The present findings show that HAL, but not OLZ treatment also markedly diminishes the ability of the NAc to mediate dopamine-dependent behaviors. At present, we do not know why the two antipsychotic drugs produce different outcomes. However, several pharmacological properties distinguish typical and atypical antipsychotic mediations. Compared with typical antipsychotics, atypical antipsychotics are more loosely bound to D2/3 receptors, such that atypical compounds might allow a greater degree of endogenous dopamine to gain access to its receptors (Seeman et al., 1997). This could reduce the likelihood of developing dopamine supersensitivity and functional changes within dopamine-rich areas such as the NAc. Atypical antipsychotics also have higher affinities at several serotonin receptor types (Meltzer et al., 1989). For example, olanzapine (but not haloperidol) has inverse agonist/antagonist effects at the 5-HT_{2C} receptor (Rauser et al., 2001; Zhang et al., 2006). 5-HT_{2C} receptors play a prominent role in regulating terminal dopamine function and they could also play a role in the different effects produced by OLZ versus HAL treatment. Finally, glutamate modulates dopamine function, and chronic exposure to typical versus atypical antipsychotics can evoke different neuroadaptations within the glutamate system. Chronic exposure to HAL but not to the atypical antipsychotic clozapine enhances basal extracellular glutamate levels in the striatum (See and Chapman, 1994; Yamamoto and Cooperman, 1994). In addition, chronic exposure to HAL versus to OLZ or clozapine has differential effects on the density of the NR1 subunit of the NMDA receptor in the striatum (Fitzgerald et al., 1995), and on the density of type II metabotropic glutamate receptors in the frontal cortex (Tascedda et al., 2001). Future studies can determine whether

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these different pharmacological profiles contribute to the behavioral effects observed here.

5. Elements to consider when interpreting the present results

We used neurologically unaltered animals. This allowed us to assess cause-and-effect relationships between chronic antipsychotic exposure and striatal dopamine function in an otherwise intact brain. However, it is important to extend this work to animal models of schizophrenia-like symptoms. The present study did not dissect the contributions of the core versus shell subgerions of the NAc. The coordinates used resulted in microinjections principally targeting the core. This was based on work showing that injecting AMPH into the NAc core robustly enhances operant responding for conditioned reward and locomotor activity (Dougherty and Ellinwood, 1981; Kelly and Iversen, 1976; Taylor and Robbins, 1984, 1986). All animals we tested had restricted access to water in order to facilitate subsequent Pavlovian conditioning, where water was used as the unconditioned stimulus. Water restriction could have neurobiological effects that might interact with the behavioral measures studied here. However, water restriction was held constant across experimental groups, making it unlikely to act as a significant confounding factor. Finally, we assessed outcome following antipsychotic treatment cessation. We do not know whether the changes observed here would be manifest during ongoing antipsychotic treatment. However, understanding striatal dopamine function during periods of antipsychotic treatment cessation is important because patients with schizophrenia frequently interrupt their antipsychotic treatment (Lieberman et al., 2005; Perkins, 1999).

6. Conclusions

Some antipsychotic treatment regimens can evoke a state of supersensitivity to dopamine receptor stimulation and this has a significant impact on clinical outcome. Although the NAc plays a central role in the expression of dopamine-mediated behaviors, antipsychotic-induced dopamine supersensitivity appears to be linked to a persistent blunting of NAc function. Investigating the neurobiological changes underlying this effect could provide new insights into dopamine-mediated dysfunctions in patients undergoing antipsychotic treatment. Thus, building upon the present findings could have implications for both the treatment of schizophrenia and the design of new antipsychotic drugs.

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