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Effects of nicotine preexposure on sulpiride-induced dopamine release in the nucleus accumbens

Shafiqur Rahman[a,b,*], Jianhua Zhang[a], William A. Corrigall[a]

[a] *Smoking and Nicotine Dependence Research, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada*
[b] *Department of Psychiatry, University of Toronto, Toronto, ON, Canada*

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Abstract

We examined the effects of nicotine preexposure or saline on dopamine release to sulpiride in the rat nucleus accumbens. Microdialysis was used to locally perfuse the sulpiride into the ventral tegmental area while sampling dopamine levels in the nucleus accumbens. The increase (130% and 165% of basal) in extracellular accumbens dopamine levels observed during ventral tegmental area perfusion for 80 min with 10–100 μM sulpiride in saline-treated animals was reduced (128% and 105% of basal) in nicotine-preexposed animals. The reduction of sulpiride-induced nucleus accumbens dopamine release after nicotine treatment is likely the result of down-regulation of somatodendritic dopamine autoreceptors.

Keywords: Nicotine; Dopamine release; Dopamine autoreceptor; Ventral tegmental area; Nucleus accumbens; In vivo microdialysis

1. Introduction

The nucleus accumbens (accumbens) is one of the main target areas of the mesoaccumbens dopamine system originating in the ventral tegmental area that has been implicated in mediating the rewarding effects of nicotine (Balfour et al., 1998; Corrigall et al., 1994; Di Chiara, 2000). Microdialysis studies indicate that addictive drugs including nicotine typically enhance extracellular levels of dopamine in the accumbens following systemic administration (Nisell et al., 1994; Pontieri et al., 1996). Previous studies indicate that repetitive daily injections of nicotine for 5 days sensitizes the mesoaccumbens dopamine system and increases the accumbens dopamine release to a subsequent systemic or local challenge nicotine (Balfour et al., 1998; Benwell and Balfour, 1992; Marshall et al., 1997). It has been suggested that dopamine autoreceptor down-regulation in the mesoaccumbens dopamine system is associated with the sensitization of dopamine release after subchronic nicotine exposure (Balfour et al., 1998). However, there is no evidence whether down-regulation of somatodendritic or terminal dopamine autoreceptors is involved in the control of dopamine release in the accumbens after nicotine preexposure.

We used reverse microdialysis studies to examine the dopamine autoreceptor function in the ventral tegmental area after nicotine (0.3 mg/kg, s.c.) or saline exposure for 5 days; an approach is comparable to previous studies (Benwell and Balfour, 1992; Balfour et al., 1998). Dual probe microdialysis was used to locally perfuse sulpiride, a dopamine D2 receptor antagonist, into the ventral tegmental area while measuring extracellular levels of dopamine in the ipsilateral accumbens.

2. Materials and methods

2.1. Animals

Adult male Long–Evans rats (275–300g; Charles River, Canada) were used. Rats were singly housed with food and water available ad libitum. All experiments were reviewed

* Corresponding author. Smoking and Nicotine Dependence Research, Centre for Addiction and Mental Health, ARF Division, 33 Russell Street, Toronto, ON, Canada M5S 2S1. Tel.: +1-416-535-8501; fax: 1-416-595-6922.
E-mail address: shafiq_rahman@camh.net (S. Rahman).

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and approved by the Institutional Animal Care Committee, in accordance with the Canadian Council on Animal Care guidelines.

2.2. Surgery

Surgeries for microdialysis were performed as described previously (Corrigall et al., 1994; Rahman and McBride, 2000; Rahman et al., 2003). The guide cannulae (Plastics One) were implanted at a 10° angle from the midline using the following coordinates with the incisor bar set at −3.3 mm: AP +1.7 mm from bregma, L +2.3 mm, and D/V −6.3 mm for the accumbens; AP −5.0 from bregma, L +2.0 and D/V −7.6 mm for the ventral tegmental area.

2.3. Drugs

The following agents were used: [−]-Nicotine hydrogen tartrate and D2 receptor antagonist (−)Sulpiride (all from Sigma-Aldrich, USA). Nicotine was dissolved in sterile saline for injection. Nicotine preexposure groups ($n=6$) received five consecutive daily subcutaneous injections of nicotine (0.3 mg/kg, s.c.), and saline groups ($n=6$) received five consecutive daily injections of saline. Sulpiride was dissolved in microdialysis perfusion fluid for local perfusion (see below). Nicotine doses are expressed as the free base.

2.4. Microdialysis

Loop-style probes (Spectra/Por RC) were used (probe tip was 2 mm for the accumbens and 1 mm for the ventral tegmental area). Artificial cerebrospinal fluid (in mM: 145 NaCl, 2.7 KCl, 1.0 $MgCl_2$, 1.2 $CaCl_2$, pH adjusted to 7.3–7.4 with 2 mM sodium phosphate buffer) was perfused through the probe at a flow rate of 1 μl/min for 2 h prior to collection of the baseline samples. Sulpiride was perfused through microdialysis probe for 80 min into the ventral tegmental area to determine the effects on the extracellular levels of dopamine in the accumbens. Samples were immediately frozen on dry ice and stored at −70° C for analysis. Probe placements were evaluated according to the atlas of Paxinos and Watson (1986).

2.5. Sample analysis

Samples were analyzed for dopamine levels using a high performance liquid chromatography with electrochemical detection (HPLC-EC; ESA, MA, USA) as described previously (Rahman et al., 2003). The mobile phase was composed of 75 mM NaH_2PO_4, 1.7 mM 1-octanesulfonic acid, 25 μM EDTA, 100 μl/l triethylamine and 10% acetonitrile; pH 3.0 adjusted with phosphoric acid, and pumped through the system 0.5 ml/min. Samples were loaded into a 20-μl sample loop and injected onto an analytical column (BetaBasic-18 column, 150 × 3 mm, Keystone Scientific, USA). Chromatograms were integrated, compared with the standards run separately on each experimental day, and analyzed using an ESA Chromatography DATA station.

2.6. Data analysis

To minimize the variability between animals, data for individual experiments were normalized and expressed as percent change from baseline values. Percent baseline levels for each experiment were calculated as treatment/control × 100. The average concentration of three stable samples prior to nicotine injection (<10% variation) was considered the control and was defined as 100%. The effects of nicotine on dopamine were compared with control values using two-way analysis of variance (ANOVA) for repeated measures (time × treatment) followed by post hoc Tukey's HSD test for multiple comparisons.

3. Results

3.1. Probe placements

Approximately 80% of the animals that had undergone surgery had both probes correctly implanted and the data from these animals were included in this report. Within the accumbens, almost all of the probes perfused both the core and shell to varying degrees with placements mostly in the core and some in the core and shell. Within the ventral tegmental area, a significant portion of the active membrane was located dorsal to the ventral tegmental area.

3.2. Effects of local sulpiride perfusion on extracellular levels of dopamine in the accumbens

To examine the role of somatodendritic dopamine D2 autoreceptors, sulpiride was perfused for 80 min through the microdialysis probe in the ventral tegmental area. In saline and nicotine preexposure group, local ventral tegmental area perfusion of 10 μM sulpiride increased the extracellular levels of dopamine in the ipsilatearl accumbens to ∼130% and 128% of basal, respectively (Fig. 1, upper panel). Similarly, local ventral tegmental area application of 100 μM sulpiride increased the extracellular levels of dopamine in the ipsilateral accumbens to ∼165% and 105% of basal in saline and nicotine preexposure group, respectively (Fig. 1, lower panel). The enhancement in extracellular levels of dopamine in response to sulpiride 100 μM in nicotine preexposure group was close to the baseline control and significantly different ($P<0.02$) from saline-treated group. The observed difference (128% versus 105%) in dopamine levels in response to low (10 μM) and high (100 μM) doses of sulpiride was not significant ($P=0.1$) in nicotine-pretreated groups. The concentrations of sulpiride used in this study were in the similar range to concentrations used in

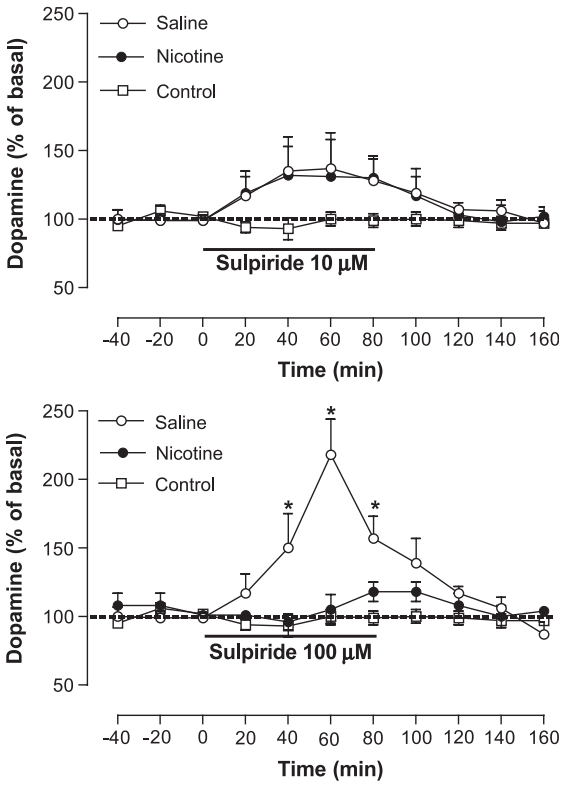

Fig. 1. Effects of local ventral tegmental area perfusion of sulpiride through dialysis probe on extracellular dopamine levels in the accumbens of rats treated with saline or nicotine. On the test day, after establishment of stable baseline, the animals were perfused with 10–100 μM sulpiride through dialysis probe into the ventral tegmental area at the time indicated. Data are the mean ± standard error of mean of four to five animals. A two-way ANOVA (treatment × time) with repeated measures did reveal a significant effect of treatment, $F(2, 10) = 10.75$, $P < 0.01$, $F(2, 10) = 11.31$, $P < 0.01$ with sulpiride 10 and 100 μM and time, $F(10, 1) = 2407.38$, $P < 0.05$ with 100 μM sulpiride. There was significant time by treatment interaction $F(20, 2) = 96.18$, $P < 0.05$ with 100 μM sulpiride. Asterisks indicate that there are significant differences between nicotine vs. saline preexposure group (Tukey's HSD test). The basal extracellular levels of dopamine in the nicotine and saline preexposure groups were 45.12 ± 9.2 and 15.87 ± 2.45 fmol/20 min, respectively.

other microdialysis studies (Rahman and McBride, 2000; Westerink et al., 1996).

4. Discussion

Our results are consistent with local sulpiride-induced enhancement of dopamine release in the ipsilateral accumbens in saline-treated animals with the manipulations of somatodendritic dopamine D2 autoreceptors (Kalivas and Duffy, 1991; Westerink et al., 1996). However, the observation in the study is that the low dose of sulpiride (10 μM) induces similar increase in dopamine release in the accumbens after saline and nicotine-pretreated groups (Fig. 1), suggesting that the dopamine autoreceptors are equally sensitive in both groups. On the other hand, the observed reduction in dopamine release with 100 μM sulpiride is likely the result of a ceiling effect of the drug, which is due to enhancement of basal dopamine levels in the nicotine-pretreated animals (Rahman et al., 2003). Future studies with higher dopamine D2 receptor antagonist and/or uptake inhibitors (Kalivas and Duffy, 1991; Rahman and McBride, 2000) in nicotine and saline pretreated animals may better clarify this issue. Alternatively, the high dose of sulpiride (100 μM) in nicotine-pretreated animals may be less effective owing to the fact that the basal dopamine levels were maximum in nicotine-pretreated rats than in the saline-treated animals (see Fig. 1). Consequently, the dopamine levels are still higher in the nicotine- versus saline-treated animals in absolute terms. Nevertheless, it is plausible to suggest that the down-regulation of somatodendritic dopamine autoreceptors is likely mechanism for the reduction of 100 μM sulpiride-induced dopamine release in the accumbens after nicotine pretreatment. Other studies have shown that the expression of sensitized dopamine responses to psychostimulants (e.g., cocaine and amphetamine) is also associated with the down-regulation of the somatodendritic dopamine D2 autoreceptors (Henry et al., 1989; White and Wang, 1984). It is noteworthy to mention that we used sulpiride perfusion into the ventral tegmental area 18–24 h after last nicotine injection. Therefore, it is unlikely that increased basal dopamine levels in nicotine-pretreated rats are the result of an effect of nicotine other than down-regulation of dopamine D2 autoreceptors (Balfour et al., 1998).

In addition to the mechanism (see above) in the ventral tegmental area, down-regulation of terminal dopamine D2 autoreceptors in the accumbens would be expected after nicotine preexposure. Previous studies have indicated that there is a down-regulation of terminal dopamine D2 autoreceptor function in the dopamine terminals after repeated treatment with nicotine (Harsing et al., 1992). However, we did not observe significant difference in extracellular dopamine levels between saline- and nicotine-exposed animals, suggesting terminal dopamine autoreceptors are not involved in the sensitization of dopamine release at least with the present nicotine regimen (unpublished observation). It is possible that other non-dopamine mechanism is associated with the regulation of dopamine release in the accumbens after nicotine pretreatment (Balfour et al., 1998), which remains to be confirmed. Furthermore, dopamine autoreceptor function in the accumbens core vs. shell region may also account for the differential dopamine regulation after nicotine pretreatment (Di Chiara, 2000), which remains to be determined.

In conclusion, our findings suggest that nicotine preexposure leads to the development of somatodendritic dopamine D2 autoreceptor desensitization in the ventral tegmental area. The down-regulation of these autoreceptors produced by nicotine preexposure might be associated with the sensitization of dopamine release in the ipsilateral accumbens. This type of neuroadaptation that results from repetitive nicotine exposure may enhance and maintain nicotine reinforcement.

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