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Differential changes in accumbens shell and core dopamine in behavioral sensitization to nicotine

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Abstract

Repeated treatment with nicotine has been shown to sensitize rats to its locomotor stimulant effects and to its properties to stimulate mesolimbic dopamine transmission. We investigated the relationship between sensitization of nicotine induced locomotor stimulation and activation of dopamine transmission in the nucleus accumbens shell and core. Rats were administered daily for 5 days with 0.4 mg/kg s.c. of nicotine or with saline and 24 h later, dopamine was monitored by microdialysis in the shell and in the core of nucleus accumbens and behavioral activity was scored after challenge with nicotine (0.4 mg/kg s.c.). Behavioral sensitization to nicotine was associated with a reduced response of dopamine transmission in the shell and with an increased one in the core of nucleus accumbens.

Keywords: Nicotine sensitization; Nucleus accumben, Shell; Nucleus accumben, Core

Repeated exposure of rats to nicotine induces sensitization to its motor stimulant effects (behavioral sensitization) (Stolerman et al., 1973; Clarke and Kumar, 1983; Nisell et al., 1986; Benwell and Balfour, 1992). However, the relation of this change with the activity of dopamine transmission is debated. While Benwell and Balfour (1992) report a sensitization of the responsiveness of dopamine transmission in the nucleus accumbens, no such change has been observed by Nisell et al. (1986). On the other hand, Benwell and Balfour (1992) failed to observe a stimulation of dopamine release by nicotine in the nucleus accumbens of saline pretreated rats. Recently, we have reported that acute nicotine (Pontieri et al., 1986), like other drugs of abuse, selectively stimulates dopamine transmission in the nucleus accumbens shell as compared to the core. This topographic heterogeneity of nucleus accumbens dopamine responsiveness to nicotine might account for the discrepancies in the literature. In order to test this possibility, we studied the changes in dopamine responsiveness to nicotine in the nucleus accumbens shell and core after a regimen known from previous studies to induce behavioural sensitization to nicotine.

We therefore repeatedly administered nicotine (0.4 mg/kg s.c., calculated as free base), once a day for 5 days, to male Sprague–Dawley rats, weighing 275–300 g at the beginning of the experiments, housed in pair with food and water ad libitum. Control rats were treated with the same schedule with 1 ml/kg s.c. of saline. After 3–4 h from the last injection, rats were implanted with two microdialysis probes (see Cadoni and Di Chiara, 1999), one aimed at the shell (A 2.0 from bregma, L 1.2, V 7.9 from dura) and the other at the core (A 1.6 from bregma, L 1.8, V 7.7 from dura) of the nucleus accumbens, according to the atlas of Paxinos and Watson (1987). After surgery, the animals were individually housed in hemispheric bowls where 24 h later, the microdialysis experiments were performed. The probes were perfused with a Ringer solution (147 mM NaCl, 4 mM KCl and 2.2 mM $CaCl_2$) and dialysates were collected every 20 min and injected in a high performance liquid chromatograph (HPLC) with a coulometric detector (Cadoni and Di Chiara, 1999). When the basal output became stable (three samples differing by no more than 10%), saline and nicotine pretreated rats were challenged with 0.4 mg/kg s.c. of nicotine.

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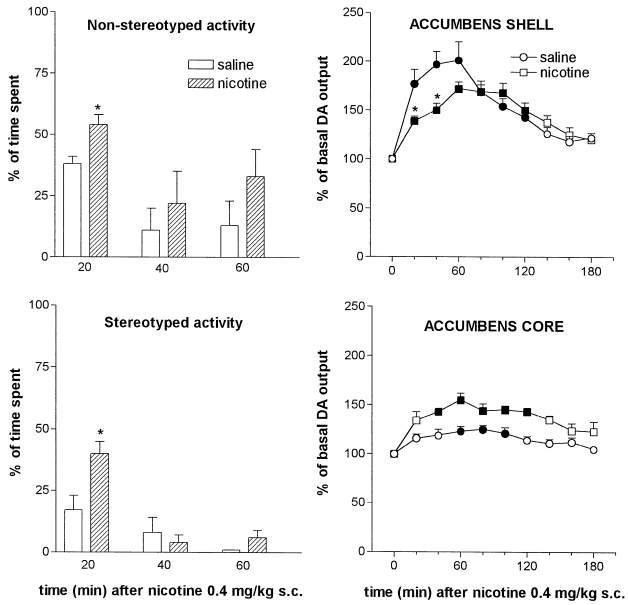

Fig. 1. Behavioral and biochemical effects of nicotine challenge (0.4 mg/kg s.c.) in rats pretreated with saline or nicotine. Left panels show the effect of nicotine on behavior of saline (unfilled bars) and nicotine (hatched bars) pretreated rats. Results are expressed as means ± SEM of the percentage of time spent in each behavioral item. $^{*}P < 0.05$ versus the correspondent value of the control (Student *t*-test). Right panels show the effect of nicotine on basal dopamine output in dialysates from the nucleus accumbens shell and core of saline (circles) and nicotine (squares) pretreated rats. The results (means ± SEM) are expressed as percent of basal values. Filled symbols represent points significant different ($P < 0.05$) from respective basal values by two way ANOVA followed by Tukey's test. $^{*}P < 0.05$ versus the corresponding time point of the control group by two way ANOVA followed by Tukey's test.

During the microdialysis experiments, the behavior of the animals was videotaped and analysed by an observer unaware of the treatment the animals received. The following behavioral categories were distinguished: *non-stereotyped activity*, including locomotion, sniffing upward and grooming, and *stereotyped activity*, including confined sniffing and gnawing. The percentage of time spent by the rat performing each behavior was quantified throughout the test session and recorded for 1 h. As shown in Fig. 1, nicotine pretreatment potentiated the behavioral stimulation induced by 0.4 mg/kg s.c. of nicotine. Non-stereotyped and stereotyped activities (confined sniffing and gnawing) were significantly increased at 20 min compared to control animals [$t(12) = 2.96$, $P < 0.05$ and $t(12) = 3.00$, $P < 0.05$ by Student's *t*-test].

Basal values of controls ($n = 6$) and sensitized rats ($n = 8$) were as follows: *nucleus accumbens shell* 54 ± 7 and 69 ± 12 fmol/sample ($F(1,9) = 0.97$, $P > 0.05$) and *nucleus accumbens core* 105 ± 16 and 96 ± 14 fmol/sample ($F(1,9) = 0.17$, $P > 0.05$). Challenge with 0.4 mg/kg s.c. of nicotine elicited a significant increase of extracellular dopamine in the shell [controls $F(9,50) = 9.12$, $P < 0.001$, sensitized $F(9,70) = 9.48$, $P < 0.001$] and in the core of saline [$F(9,50) = 2.72$, $P < 0.05$] and nicotine [$F(9,30) = 8.29$, $P < 0.001$] pretreated rats (Fig. 1). Statistical analysis of the data showed a significant effect of nicotine pretreatment in the nucleus accumbens core [two way analysis of variance (ANOVA) for repeated measure $F_{\text{treatment}}(1,8) = 8.99$, $P < 0.001$]. Post hoc analysis revealed an increased stimulation in the core of sensitized animals (Tukey's post hoc $P < 0.01$). In the nucleus accumbens shell, analysis revealed a significant time × treatment interaction [$F_{\text{time} \times \text{treatment}}(9,108) = 4.31$, $P < 0.0001$] with a significant decrease at 20 and 40 min in the sensitized group compared to controls. Therefore, nicotine sensitization is associated with an increased stimulation of dopamine transmission in the nucleus accumbens core but not in the nucleus accumbens shell, where the response of dopamine transmission to nicotine challenge appears reduced. These data are in agreement with our previous reports on opiate and psychostimulants sensitized rats (Cadoni and Di Chiara, 1999; Cadoni et al., 1999), and they suggest that behavioral sensitization differentially affects dopamine responsiveness to drugs of abuse in the shell and in the core of the nucleus accumbens. The present findings might also provide an explanation of the discrepancies in the literature. Thus, depending on the fact that the microdialysis probes are located in the nucleus accumbens core or shell, respectively, no change in the nucleus accumbens dopamine in nicotine naive and sensitization in nicotine pre-exposed rats, as in the case of Benwell and Balfour (1992), or stimulation in nicotine naive and no sensitization in nicotine pre-exposed rats, as in the case of Nisell et al. (1986), would be obtained.

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