Short communication

Nicotine-induced locomotor activity is increased by preexposure of rats to prenatal stress

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Abstract

Genetic factors are believed to play a predominant role in the individual differences observed in behavioral and pharmacological responses to drugs of abuse. An increasing literature indicates, however, that epigenetic factors can be involved as well. In this report we examined whether developmental changes induced by prenatal stress could alter the way animals respond to the psychostimulant effect of nicotine when adults. The results show that nicotine induces a dose-dependent increase of locomotor activity in both groups, and that prenatally-stressed animals exhibit a higher behavioral response at all doses. This study emphasizes the importance of early environment in the later development of drug-related behavior.

Theme: Neural basis of behavior

Topic: Drugs of abuse: amphetamine and other stimulants

Keywords: Nicotine; Locomotor activity; Rat; Development; Prenatal stress

Although research in recent decades has resulted in increased knowledge about the neurobiological substrates of reinforcing drugs, the psychobiological determinants of drug addiction are still largely unknown. Clinical and experimental studies indicate that one of the main factors underlying the development of addiction is a particular sensitivity of some individuals to the reinforcing effects of drugs of abuse. The understanding of the origins of such differences should, therefore, throw light on the etiology of addiction.

Nicotine is one of the most universally abused drugs and has a wide range of behavioral effects. Individual differences in the susceptibility to develop nicotine addiction are well recognized, but their basis is still unknown [3]. Variability in the acute response to nicotine is generally attributed to stable characteristics such as genetic factors [20]. In humans, studies consistently indicate that multiple aspects of smoking behavior, such as initiation, dependence and cessation, depend on genetic influences [25,30]. In animals, inbred strains of mice differ with respect to the effects of nicotine on many behavioral and physiological parameters [7,15,29], and inbred strains of rats exhibit differences in the locomotor effects of the drug [18] or in the acquisition of nicotine self-administration [27].

What is often overlooked, however, is that such variability may also be due to early environmental influences. Indeed, although the development of the central nervous system and behavioral patterns is governed by a genetic component, epigenetic factors can strongly influence them. Extensive research shows that events occurring as early as during the intra-uterine life act to organize behavioral and neurophysiological processes. For example, clinical studies have shown a highly significant correlation between infant morbidity and maternal stress during gestation [10]. Animal studies have revealed that prenatally-stressed rats exhibit modifications in behavioral and physiological systems that are particularly relevant for the study of
nicotine susceptibility. Thus, prenatal stress augments anxiety [31,32,34] and has been proposed as a model of depression [34] and these neurotic traits have been strongly linked in humans to cigarette smoking [9]. Prenatally-stressed rats also show an increased sensitivity to amphetamine [8,11]. Given that a cross-sensitization between nicotine and amphetamine has been reported [2,4], it may be expected that these two drugs share common neuronal substrates that could be affected by prenatal stress.

Hence, in the present study, we tested the effect of stress applied to pregnant rats on the sensitivity of the adult offspring to the locomotor effects of nicotine.

Adult virgin Sprague–Dawley female rats (Ifa-Credo, France), which were housed individually for a whole estrous cycle in the presence of a sexually-experienced Sprague–Dawley male rat. Pregnant rats were then individually housed in breeding cages and randomly assigned to prenatal stress and control groups. Animals were allowed ad libitum access to food and water and maintained on a constant light/dark cycle (lights on 08:00–20:00). Prenatal stress was performed as previously described [12]. The offspring were weaned 21 days after birth, group-housed, and tested at 3 months of age.

Horizontal locomotor activity was tested in response to novelty (first exposure to the test cage) and to different doses of nicotine during the light phase. This activity was monitored in Plexiglas cages (41×26×28 cm) equipped with infrared beams. Photocell beam interruptions cumulated over 10-min intervals were monitored and recorded via a computer system located outside the testing room.

Rats were first exposed to novelty for 2 h. Two days later, they received different doses of nicotine (0.0, 0.1, 0.2, and 0.4 mg/kg) following a 1-h period of habituation to the activity cages. Nicotine free base was purchased from Sigma, diluted in NaCl 0.9% and injected subcutaneously. The different doses of nicotine were injected according to a latin square design in both control (N=8) and prenatally-stressed (PreS) rats (N=12).

Locomotor activity in response to novelty was analyzed by a two-way analysis of variance (ANOVA) with one between factor: the prenatal treatment (two levels, control and PreS), and one within factor: the time course of locomotor activity (12 levels corresponding to the 12 time-bins of 10 min). Locomotor activity data in response to nicotine were submitted to a three-way ANOVA with one between factor: the prenatal treatment and two within factors: (1) the dose of nicotine injected (four levels for the four doses), and (2) the time course (12 levels). Whenever interactions were found, two-way ANOVAs restricted to the dose or treatment effects followed by post-hoc tests (Newman–Keul’s, NK or t-test when appropriate) were performed.

Experiments have been carried out in accordance with the European Communities Council Directive (86/609/EEC).

Prenatal stress did not modify either the total activity (546±58 activity counts over 2 h for control animals vs. 571±44 for PreS animals; treatment effect, F(1,18)=0.11, P=ns), or the time-course of activity (treatment×time interaction, F(11,198)=0.43, P=ns) in response to novelty.

Analysis of locomotor responses to nicotine revealed a significant effect of prenatal treatment (F(1,18)=17.394, P<0.001), doses of nicotine (F(3,54)=28.526, P<0.0001), and time (F(11,198)=130.799, P<0.0001). All the interactions between the main factors were found significant [treatment×doses (F(3,54)=3.059), treatment×time (F(11,198)=3.434), doses×time (F(33,594)=2.710) and treatment×doses×time (F(33,594)=1.439); P<0.05 for each].

Fig. 1 shows that nicotine induced a dose-dependent increase in locomotor activity in both control (dose effect: F(3,21)=27.323, P<0.0001) and PreS rats (F(3,33)=20.466, P<0.0001). In control rats, post-hoc Newman-keul’s tests indicated that differences between the locomotor response to saline and nicotine emerged at 0.2 mg/kg of nicotine [saline=0.1 mg/kg, 0.1 mg/kg<0.2 mg/kg (NK, P<0.01) and 0.2 mg/kg<0.4 mg/kg (NK, P<0.001). In PreS rats, differences between the response to saline and nicotine appeared at 0.1 mg/kg, indicating an increased sensitivity to the lowest dose in this group of animals [saline<0.1 mg/kg (NK, P<0.02); 0.1 mg/kg=0.2 mg/kg<0.4 mg/kg (NK, P<0.001)].

Furthermore, as shown in Figs. 1 and 2, whereas control

![Fig. 1. Effects of acute injections of different doses of nicotine in control and prenatally-stressed (PreS) rats. Nicotine induces a dose-dependent increase in locomotor activity in both groups (*, different from the previous dose, P<0.05). Furthermore, the locomotor response to each dose of the drug tested is enhanced in the prenatally stressed group (#, different from control animals, P<0.05). Results are expressed as mean±S.E.M.](image-url)
and PreS rats exhibited the same locomotor response to saline injection (treatment effect: $F(1,18)=0.06$, $P>0.8$), prenatally-stressed animals showed a greater behavioral response to each dose of nicotine tested ($F(1,18)=6.701$, $P<0.05$; $F(1,18)=5.383$, $P<0.05$; $F(1,18)=12.266$, $P<0.01$ for doses 0.1, 0.2, and 0.4 mg/kg, respectively). This increased response was mainly due to an increased sensitivity to the locomotor effects of nicotine during the first hour following the injection (see details in Fig. 2 legend).

The results of this study show that a manipulation of the early environment can modify the sensitivity of an individual to the psychomotor-stimulant effects of nicotine. Indeed, the dose-dependent increase in locomotor activity induced by nicotine at doses up to 0.4 mg/kg is potentiated by prenatal stress. This effect of prenatal stress appears to be specific to nicotine since the same animals do not show any modifications in their response to novelty or to a control injection.

The enhanced sensitivity to nicotine in PreS rats suggests that prenatal stress modifies the pathway involved in the psychomotor-stimulant effects of nicotine. These effects of nicotine are mediated by an increase in dopamine (DA) overflow in the terminal regions of the mesolimbic system [6,13,23], which appears to be due to the binding of nicotine to the nicotinic receptors located in the ventral tegmental area (VTA) [17,19]. Thus, acute intra-VTA, but not intra-accumbens, injection of nicotine produces increased locomotion that is blocked by injection of a nicotinic receptor antagonist into the VTA [24]. Although no data are yet available on the effects of prenatal stress on nicotinic receptors, it seems possible that prenatal stress induced changes directly at the level of the nicotinic receptors, such as changes in their concentration or binding capacities in the VTA.

Alterations of the locomotor response to nicotine in PreS rats could also be due to modifications of the hypothalamo-pituitary-adrenal (HPA) axis sensitivity to nicotine. Nicotine increases corticosterone secretion [5], which is involved in the locomotor effects of the drug. Thus, depletion of corticosteroids attenuates both nicotine-induced dopamine release and the activating effects seen at low doses of nicotine [28]. Given that PreS rats exhibit an increased secretion of corticosterone in response to various stressors [1,14,16], corticosteroids may be involved in the present effects of prenatal stress. Indirect evidence based on amphetamine studies reinforce this hypothesis. Animals that spontaneously display higher corticosterone secretion have an increased sensitivity to the psychomotor and reinforcing effects of amphetamine, which is due to corticosterone-induced DA release [21,26]. Interestingly, PreS animals also exhibit an increased sensitivity to amphetamine [8]. Thus, it seems legitimate to hypothesize that corticosterone may be a causal factor in the increased sensitivity of PreS animals to nicotine.

Finally, prenatal stress-induced modifications of the dopaminergic mesoaccumbens system cannot be excluded. This hypothesis, though, seems unlikely because prenatal stress increases DA turnover in the prefrontal cortex and decreases it in the striatum and nucleus accumbens (NAcc) [34]. These modifications would suggest a decrease in locomotor response to nicotine rather than the increase observed here. However, one study reported an absence of effect of prenatal stress on DA levels in the NAcc when measured in vivo [33]. Thus, in the absence of additional
data, a direct effect of prenatal stress on the DA system cannot be eliminated completely.

In conclusion, while it is generally acknowledged that genetic factors play a predominant role in behavioral and pharmacological responses to nicotine, this study indicates that early environment may also play a major role in an individual’s sensitivity to nicotine. Recent research (both infra-human and human) implies that vulnerability to nicotine dependence is related to an elevated initial sensitivity to nicotine and that the development of tolerance is more rapid and self-administration more extensive in such individuals [22]. Thus, the results of this study strongly suggest that prenatal stress may be a causal factor in determining vulnerability to nicotine addiction. In addition, taken together with the finding that prenatal stress increases vulnerability to amphetamine addiction, this study indicates that prenatal stress may profitably be used to study the neural substrates underlying some aspects of increased vulnerability to drug addiction and to throw light on the etiology of the disorder.

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