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Short communication

Maternal cocaine exposure alters mesolimbic dopaminergic function in rat offspring

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Abstract

Hooded Lister female rats were treated with either saline or cocaine (20 mg/kg s.c.) from gestational day 10 every other day until weaning (postnatal day 25). In vivo microdialysis has shown that maternal cocaine exposure significantly decreases basal extracellular concentrations of dopamine in the nucleus accumbens of young-adult offspring (4 weeks after cessation of cocaine treatment). Moreover, the increase in extracellular dopamine levels induced by a challenge dose of K^+ (intracerebral 60 mM K^+ artificial cerebrospinal fluid (aCSF) infusion) or cocaine (15 mg/kg i.p.) was significantly attenuated in rats exposed to cocaine during perinatal life with respect to controls. The alterations in mesolimbic dopamine transmission observed in these experiments might underlie behavioral abnormalities induced in rat offspring by maternal exposure to cocaine at dose levels which do not produce gross malformations and/or overt neurotoxic effects. © 1998 Elsevier Science B.V.

Keywords: Cocaine; Perinatal exposure; Microdialysis; Nucleus accumbens; Dopamine; Rat

1. Introduction

Recent findings have shown that a number of neurobehavioral effects due to prenatal or postnatal administration of cocaine in rats could be linked to an impairment of central dopamine transmission (Bowman et al., 1997; Heyser et al., 1994; Keller et al., 1994; Meyer et al., 1992; Peris et al., 1992; Seidler et al., 1994; Spear et al., 1989), thus suggesting that the developing dopamine system is a primary target for this drug of abuse.

Only few studies have investigated the effects of perinatal (combined intrauterine and early postnatal) cocaine exposure in rats. The status of rat nervous system development over the first 2 postnatal weeks corresponds roughly to the last trimester of human neural development, and therefore combined prenatal and early postnatal exposure to cocaine may be relevant to gestational human exposure (Dobbing and Sands, 1979).

The available literature has shown that perinatal exposure to cocaine alters rat functional brainstem development (Salamy et al., 1992) and decreases the number of spontaneously active midbrain dopamine neurons in rat pups (Wang and Pitts, 1994).

Moreover, our recent findings have demonstrated that perinatal exposure to cocaine impairs visual discrimination in young-adult male rats subjected to a novel exploration object test (Giustino et al., 1996). Since mesolimbic dopamine system plays an important role in the physiological mediation of this behavioral response (Hooks and Kalivas, 1995), we hypothesized that the alterations in the exploratory activity observed in young-adult rats exposed perinatally to cocaine could be due to an impairment of dopamine transmission. Furthermore, perinatal exposure to cocaine has been shown to attenuate acute cocaine-induced hyperactivity in an open field test (Giustino et al., 1996).

Therefore, the aim of these experiments was to extend our previous investigations and to explore whether the behavioral alterations caused by maternal exposure to cocaine could be related to changes in mesolimbic dopamine function. In particular, in vivo microdialysis was used to measure extracellular dopamine concentrations in the nucleus accumbens of freely-moving young-adult male rats whose mothers were treated with cocaine during both gestation and lactation. Moreover, the influence of perinatal exposure to cocaine on the increase in extracellular

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dopamine levels elicited by acute intraperitoneal cocaine injection or intracerebral high K^+ infusion in the nucleus accumbens of young-adult male rats was also assessed.

2. Materials and methods

2.1. Animals

All experiments were performed under UK Home Office regulations and project licence number 40/01089.

Hooded Lister rats (Nottingham University breeding colony) weighing 200–230 g were housed at constant room temperature, exposed to a light cycle of 12 h/day (07:00–19:00) for 2 weeks before the experiment. Single females were placed with a male rat in the afternoon. Mating was confirmed by the presence of copulatory plug on the following morning which was designated gestational day 1. On gestational day 10, dams were weighed and randomly assigned to two groups treated with saline or cocaine, respectively. From gestational day 10 to postnatal day 25, dams were injected with 0.9% sodium chloride solution (vehicle) or with 20 mg/kg s.c. of cocaine hydrochloride every other day between 09:00 and 11:00. This treatment schedule was chosen on the basis of our recent data showing that this exposure to cocaine does not induce maternal toxicity and gross malformations and/or overt signs of neurotoxicity in rat offspring (Giustino et al., 1996). The day of the birth was defined as postnatal day 0. Pups were weaned on postnatal day 25 and male rats were used for neurochemical studies that were performed 4 weeks after weaning. One rat per litter from different litters per treatment group was used.

In agreement with our previous findings (Giustino et al., 1996), perinatal cocaine exposure did not affect dam weight gain, litter size at birth, litter weight, and male pup weight gain (data not shown).

2.2. Microdialysis and analytical procedure

Microdialysis experiments were carried out according to the technique previously used by Saulskaya and Marsden (1995).

Concentric microdialysis probes were prepared using dialysis membrane made of acrylonitrile-sodium methallyl sulphonate (Hospal, UK, KDa 20; 300 μm o.d; 220 μm i.d.).

Rats were anaesthetized with halothane (1.5–2% in a 50:50 O_2/NO_2 mixture) and placed in a stereotaxic frame. Dialysis probes (length: 2 mm) were implanted in the right nucleus accumbens according to the following coordinates: AP = 1.6, ML = 0.9, from bregma and V = 7.8 mm from the dura with the incisor bar set at -3.3 mm (Paxinos and Watson, 1986). The probe was fixed to the skull using two stainless steel screws and acrylic dental cement. The inlet of the probe, since the beginning of the implantation up to the end of the experiment, was attached to a liquid swivel (Harvard Apparatus, South Natick, MA), positioned over the cage to allow free movement of the rat during the experiment. The swivel was continuously connected to a microinfusion pump (CMA/100 CMA Microdialysis) set at 1 μl/min, perfusing artificial cerebrospinal fluid (aCSF) containing 140 mM NaCl, 3 mM KCl, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$, 1.2 Na_2HPO_4, 0.27 mM NaH_2PO_4, 7.2 M glucose, pH = 7. Animals were allowed 24 h to recover from surgery with food and water available ad libitum.

The day of the experiment, after the probe had been flowing for 1 h, samples were collected into polyethylene vials at 20-min (Experiment 1) or 10-min (Experiment 2) intervals.

The position of the microdialysis probe was verified by histological procedures at the end of each experiment. Only rats in which the probe was exactly located in the target area were considered in the results.

Dialysate samples were immediately injected onto a high-performance liquid chromatography-electrochemical detection system. This system consisted of an isocratic pump (Gilson), a Spherisorb column (3 μm, ODS, 10 cm length, 2 mm i.d.), a Rheodyne injector with a 10-μl injector loop, and an electrochemical detector (BAS LC 3) equipped with a glassy carbon electrode set at $+0.7$ V versus Ag/AgCl reference electrode.

The mobile phase containing 0.15 M NaH_2PO_4 2 H_2O, 1 mM EDTA, 0.5 mM sodium octane sulfonate and 10% methanol was adjusted to pH = 3 using phosphoric acid and pumped through the system at 0.2 ml/min. The detection limit (signal to noise ratio = 3) was 10 fmol/10 μl.

2.2.1. Experiment 1

2.2.1.1. Effect of cocaine challenge (15 mg/kg i.p.) on extracellular dopamine concentrations. Once a stable basal dopamine output was obtained (no more than 10% differences between three consecutive samples) rats were given a challenge dose of cocaine (15 mg/kg i.p.). 10 μl of each dialysate sample (20 μl) were injected into the high performance liquid chromatography system and dopamine levels (fmol/10 μl) were measured. The remaining 10 μl of each sample were used for measurements of other neurotransmitters (data not reported in the present study).

2.2.2. Experiment 2

2.2.2.1. Effect of intracerebral 60 mM K^+ aCSF infusion on extracellular dopamine concentrations. Once a stable basal dopamine output was obtained (no more than 10% differences between three consecutive samples) rats were given a 60 mM K^+ aCSF infusion for 50 min. Dialysate samples (10 μl) were injected into the high performance liquid chromatography system and dopamine levels (fmol/10 μl) were measured.

2.3. Statistical analysis

All data were expressed as mean ± SEM.

Statistical analysis of basal dopamine concentrations was performed using two-way analysis of variance (ANOVA) for repeated measures (three consecutive samples collected before cocaine challenge or high K^+ infusion, respectively) with treatment as the between-subject factor and time as the within-subject factor. Actual and absolute dopamine increases (with respect to the last basal value) induced by acute cocaine or high K^+ infusion were evaluated by two-way ANOVAs for repeated measures, respectively. Tukey's test was used to perform individual within-group and between-groups comparisons.

3. Results

3.1. Experiment 1

3.1.1. Effects of cocaine challenge on extracellular dopamine concentrations in the nucleus accumbens of perinatally saline- and cocaine-exposed rats

The results are reported in Fig. 1. A two-way ANOVA for repeated measures of basal dopamine concentrations (three consecutive samples collected before cocaine challenge) showed the following differences: (i) between treatments ($F(1,11) = 8.24$; $P < 0.01$); (ii) between times ($F(2,22) = 0.37$; n.s.); (iii) between treatments × times ($F(2,22) = 1.89$; n.s.). These results indicate that perinatal treatment with cocaine significantly decreases basal dopamine levels in the nucleus accumbens of young-adult rats. Since differences between times and between treatments × times were not significant, post-hoc tests for individual comparisons were not performed.

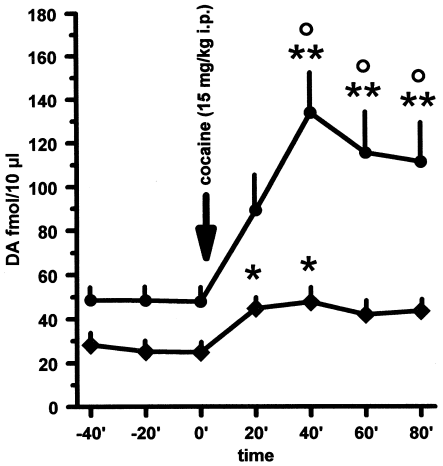

Fig. 1. The effects of cocaine challenge (15 mg/kg i.p.) on extracellular dopamine (DA) concentrations in the nucleus accumbens of rats exposed perinatally to saline • ($n = 6$), or cocaine ♦ ($n = 7$). Data were expressed as the mean ± SEM. Significant differences (Tukey's test): *, $P < 0.05$; **, $P < 0.01$ vs. last basal sample (actual dopamine concentrations). Absolute dopamine increases (mean fmol ± SEM) = (i) saline-exposed rats: 41.2 ± 11.6; 90.8 ± 11.3; 67.7 ± 4.6; 63.5 ± 3.3; (ii) cocaine-exposed rats: 20 ± 3.7; 22.8 ± 4.2; 17.6 ± 4.6; 18.9 ± 3.6. Significant differences between absolute dopamine increases (Tukey's test): °, $P < 0.01$ vs. perinatal cocaine.

A two-way ANOVA for repeated measures of changes in extracellular dopamine concentrations (actual values) elicited by a challenge dose of cocaine (last basal value and four consecutive samples after cocaine challenge) gave the following differences: (i) between treatments ($F(1,11) = 23.31$; $P < 0.0005$); (ii) between times ($F(4,44) = 38.0$; $P < 0.0001$); (iii) between treatments × times ($F(4,44) = 14.08$; $P < 0.0001$).

Within-group comparisons (Tukey's test) showed that acute cocaine administration induces a significant increase in extracellular dopamine concentrations (actual values) with respect to the last basal sample in both saline- and cocaine-exposed rats.

In order to exclude that the altered responsiveness to cocaine challenge exhibited by perinatally cocaine-exposed rats with respect to control animals could reflect differences in basal extracellular dopamine concentrations, a two-way ANOVA for repeated measures of absolute extracellular dopamine increases induced by cocaine challenge with respect to the last basal sample was performed.

This analysis showed the following differences: (i) between treatments ($F(1,11) = 39.45$; $P < 0.0001$); (ii) between times ($F(3,33) = 12.04$; $P < 0.0001$); (iii) between treatments × times ($F(3,33) = 9.63$; $P < 0.0001$).

Between-groups comparisons (Tukey's test) indicated that cocaine-induced increase in extracellular dopamine levels (absolute increase) was significantly attenuated in perinatally cocaine-exposed rats with respect to saline-treated animals.

Finally, in order to get information about the mechanisms underlying the decreased responsivity in cocaine treated rats, a two-way ANOVA for repeated measures of log-transformed data (actual values) was performed. This analysis gave the following differences: (i) between treatments ($F(1,11) = 24.57$; $P < 0.0004$); (ii) between times ($F(4,44) = 41.7$; $P < 0.0001$); (iii) between treatments × times ($F(4,44) = 4.53$; $P < 0.005$).

3.2. Experiment 2

3.2.1. Effects of intracerebral 60 mM K^+ aCSF infusion on extracellular dopamine concentrations in the nucleus accumbens of perinatally saline- and cocaine-exposed rats

The results are reported in Fig. 2. A two-way ANOVA for repeated measures of basal dopamine concentrations (three consecutive samples collected before 60 mM K^+ aCSF infusion) showed the following differences: (i) between treatments ($F(1,10) = 7.88$; $P < 0.01$); (ii) between times ($F(2,20) = 2.52$; n.s.); (iii) between treatments × times ($F(2,20) = 2.52$; n.s.). These results confirm those obtained in the Experiment 1 showing that perinatal treat-

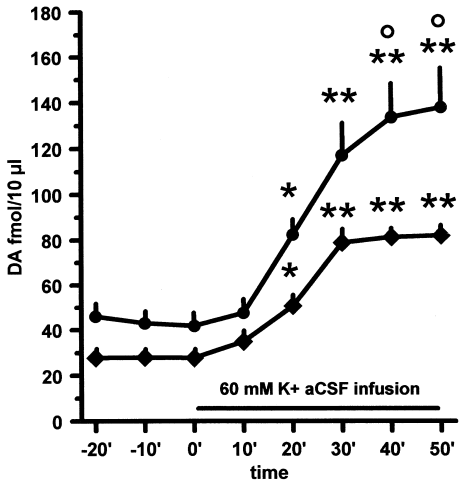

Fig. 2. The effects of 60 mM K^+ aCSF infusion on extracellular DA concentrations in the nucleus accumbens of rats exposed perinatally to saline • ($n=6$), or cocaine ♦ ($n=6$). Data were expressed as the mean ± SEM. Significant differences (Tukey's test): *, $P<0.05$, **, $P<0.01$ vs. last basal sample (actual dopamine concentrations). Absolute dopamine increases (mean fmol ± SEM) = (i) saline-exposed rats: 5.7 ± 4.4; 37.2 ± 7; 75.2 ± 12; 91.8 ± 13.8; 96 ± 15; (ii) cocaine-exposed rats: 7.4 ± 3.2; 23.2 ± 6; 51 ± 5.5; 53.7 ± 5; 54.3 ± 5.4. Significant differences between absolute dopamine increases (Tukey's test): °, $P<0.05$ vs. perinatal cocaine.

ment with cocaine significantly reduces basal dopamine levels in the nucleus accumbens of young-adult rats. Since differences between times and between treatments × times were not significant, post-hoc tests for individual comparisons were not performed.

A two-way ANOVA for repeated measures of changes in extracellular dopamine concentrations (actual values) elicited by high K^+ infusion (last basal value and five consecutive samples after the beginning of high K^+ infusion) gave the following differences: (i) between treatments ($F(1,10)=8.67$; $P<0.02$); (ii) between times ($F(5,50)=67.5$; $P<0.0001$); (iii) between treatments × times ($F(5,50)=5.09$; $P<0.001$).

Within-group comparisons (Tukey's test) showed that 60 mM K^+ aCSF infusion induces a significant increase in extracellular dopamine concentrations (actual values) with respect to the last basal sample in both saline- and cocaine-exposed rats.

A two-way ANOVA for repeated measures of absolute extracellular dopamine increases induced by 60 mM K^+ aCSF infusion with respect to the last basal sample showed the following differences: (i) between treatments ($F(1,10)=4.85$; $P<0.05$); (ii) between times ($F(4,40)=64.08$; $P<0.0001$); (iii) between treatments × times ($F(4,40)=5.63$; $P<0.001$).

Between-groups comparisons (Tukey's test) showed that 60 mM K^+ aCSF-induced increase in extracellular dopamine levels (absolute increase) was significantly attenuated in perinatally cocaine-exposed animals with respect to controls.

Finally, a two-way ANOVA for repeated measures of log-transformed data (actual values) gave the following differences: (i) between treatments ($F(1,10)=13.10$; $P<0.005$); (ii) between times ($F(5,50)=117.78$; $P<0.0001$); (iii) between treatments × times ($F(5,50)=1.59$; n.s.).

4. Discussion

The results of the present study indicate that maternal exposure to cocaine (from gestational day 10 until weaning) reduces mesolimbic dopamine function in young-adult male rats. Lack of significant changes in maternal and pup weight gain suggests that nutritional deficiency was not a factor in the cocaine offspring outcome.

In particular, in vivo microdialysis experiments have shown a significant decrease in extracellular concentrations of dopamine in the nucleus accumbens of rats perinatally exposed to this drug of abuse. These changes have been observed 4 weeks after the cessation of cocaine treatment.

Our recent findings (Giustino et al., 1996) have shown an impairment in visual discrimination (novel exploration object test) in young-adult male rats exposed perinatally to the same cocaine treatment schedule used in the present study. Considering the role of the mesolimbic dopamine system in the physiological mediation of this behavior (Hooks and Kalivas, 1995), the decrease in basal extracellular dopamine levels occurring into the nucleus accumbens of young-adult rats exposed to cocaine during perinatal life might account, at least in part, for the alterations in their response to novelty.

Previous studies (Wang and Pitts, 1994) have shown that perinatal cocaine exposure decreases the number of spontaneously active midbrain dopamine neurons in neonatal rats. Moreover, adult rats prenatally exposed to cocaine have been found to exhibit fewer spontaneously active dopamine neurons in the substantia nigra pars compacta and the ventral tegmental area with respect to control animals (Minabe et al., 1992). According to Heyser et al. (1994), the decrease in neuronal activity in the dopamine system shown by these electrophysiological studies is consistent with behavioral changes suggesting a possible impairment in dopamine functioning in animals treated with cocaine during development (Spear et al., 1989; Meyer et al., 1992).

In this study, we have also found that perinatal cocaine reduces high K^+-evoked dopamine output in the nucleus accumbens of young-adult rats. These changes, that further confirm a decreased activity of the dopamine system due to developmental exposure to cocaine, are in agreement with the results obtained by Wang et al. (1995) showing that prenatal cocaine treatment reduces mesocortical K^+-

evoked [^{3}H]dopamine release in rabbits via changes (sensitization) in terminal presynaptic dopamine autoreceptors.

It is of interest to point out that these preclinical observations are consistent with the results of human studies demonstrating that neonatal cerebrospinal fluid concentrations of homovanillic acid are significantly lower after gestational cocaine exposure (Needleman et al., 1993).

Moreover, the present neurochemical experiments indicate that developmental cocaine exposure affects biochemical responsivity to acute cocaine in young-adult rats. In particular, the increase in extracellular dopamine levels induced by a challenge dose of cocaine in the nucleus accumbens of rats exposed to cocaine during both pregnancy and lactation was significantly attenuated with respect to control animals. These data parallel those obtained in previous behavioral experiments showing that cocaine-induced hyperactivity in young-adult rats was significantly reduced by maternal treatment with this drug (Giustino et al., 1996).

In order to get information about the mechanism underlying the reduced biochemical responsiveness in the group exposed to cocaine during perinatal life, repeated measures ANOVAs used to make the conclusions in Figs. 1 and 2 were reexamined using log-transformed data.

The results showed that ANOVA of log-transformed data (Experiment 1, cocaine challenge) still showed a significant interaction between treatments and time, whereas the interaction between treatments and time disappeared in the ANOVA dealing with Experiment 2 (high K^+ challenge).

The results, indicating that the same proportional change occurs in basal and stimulated (high K^+ infusion) conditions, suggest that perinatal exposure to cocaine may induce some alterations affecting both basal and K^+ stimulated release, such as a loss of dopaminergic innervation or a reduced vesicular dopamine concentration.

On the other hand, the lack of the same proportional change in basal and stimulated conditions following cocaine challenge could be indicative of an additional loss of a specific mechanism sensitive to cocaine stimulation in rats perinatally exposed to cocaine.

The results of the present study suggest that the effects of prolonged cocaine exposure on the developing dopamine system may differ from those found in mature animals. In fact, previous findings have shown that repeated treatment with cocaine during adulthood leads to an enhanced effect of a cocaine challenge on dopamine release (Kalivas and Duffy, 1990; Pettit et al., 1990). Increases of both biochemical and behavioral responses to cocaine after a previous administration of this drug is a commonly observed phenomenon referred to as sensitization (Zahniser and Peris, 1992). However, conflicting findings exist regarding the influence of developmental exposure to cocaine on later biochemical and behavioral responsiveness to a cocaine challenge. Increases or decreases in the responsivity to cocaine have been reported in rats exposed to this drug during gestation (Ferrari and Riley, 1994; Heyser et al., 1992; Keller et al., 1994, 1996; Meyer et al., 1992; Miller and Seidler, 1994; Peris et al., 1992; Sobrian et al., 1990). The discrepancy in the results may be explained by several variables, such as the period of developmental exposure, the dose, the time of postnatal assessment, and the sex of the subject. Moreover, neonatal cocaine treatment does not seem to affect the responsiveness to acute administration of cocaine (Barron et al., 1994; Meyer and Yacht, 1993). In this regard, recent studies using early postnatal cocaine exposure have failed to elicit long-lasting sensitization unless the chronic treatment is initiated near weaning age (see the work of Bowman et al., 1997, for references).

The neurochemical alterations observed in the present study could be partly attributable to a decrease in oxygen availability produced by developmental exposure to cocaine.

In fact, it has been previously shown (Woods et al., 1987) that cocaine induces dose-dependent ischemia in uterine circulation. According to Weese-Mayer et al. (1994), this ischemia results in periods of brain hypoxia which could negatively affect neuronal development. In particular, these authors have demonstrated that prenatal cocaine exposure enhances the vulnerability of the dopamine system to the stress of hypoxia, possibly through alterations in neurotrophic activity. Our recent findings, confirming that the developing brain is extremely vulnerable to hypoxia (De Salvia et al., 1995), have also shown that relatively mild reduction in oxygen availability during development attenuates amphetamine-induced increase in extracellular dopamine concentrations in the nucleus accumbens of rat offspring (unpublished data).

Interestingly, cocaine-exposed human neonates exhibit two distinctive neurobehavioral syndromes. It has been hypothesized that a hyperexcitable syndrome is attributable to direct actions of cocaine on the fetal nervous system, whereas a depressive syndrome is secondary to hypoxemia and intrauterine growth retardation (Lester et al., 1991).

In summary, perinatal cocaine exposure alters mesolimbic dopamine function in young-adult rats at dose levels which do not produce maternal toxicity, gross morphological defects and/or overt signs of neurotoxicity in the offspring.

The neurochemical changes induced by perinatal cocaine exposure in the young-adult offspring (decrease in basal extracellular dopamine levels, attenuation of cocaine- and high K^+-evoked increase in extracellular dopamine levels in the nucleus accumbens) might underlie behavioral alterations observed in rats exposed perinatally to this drug of abuse (Giustino et al., 1996).

Acknowledgements

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