Human & Experimental Toxicology (2007) **26:** 303–309
http://het.sagepub.com

Postnatal exposure to cocaine in rats housed in an enriched environment: effects on social interactions

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This study was undertaken to evaluate the effects of environmental enrichment (EE) in rats exposed to cocaine during the first month of postnatal life by examining several categories of social behaviour (play fighting, social investigation, comfort behaviours and invitation to play). Wistar rats were divided in four groups: pups exposed to cocaine hydrochloride (15 mg/kg body weight/day), sc, in two daily doses, from postnatal day (PND) 1 to 28 and reared in EE; exposed to cocaine as previously described and reared in standard environment (SE); saline-exposed and reared in EE; pups saline-exposed and reared in SE. On PND 21, 24 and 28, social interactions were examined for 10 min. Results show that cocaine animals reared in SE decreased the frequency of play solicitation. Control animals reared in EE exhibited decreased play fighting and social investigation behaviours compared to SE-reared rats. Animals postnatally exposed to cocaine when reared in EE displayed more comfort and invitation to play behaviours and decreased social investigation compared with SE-reared animals. The results suggest that in rats postnatally exposed to cocaine, EE rearing elicited differences in both processing of environmental stimuli and a response to social challenges. *Human & Experimental Toxicology* (2007) **26,** *303–309*

Key words: cocaine; development; enriched environment; social interactions

Introduction

Juvenile rats engage in distinctive forms of interactive social behaviours and a separation can be made between forms of social behaviour related and unrelated to play.[1,2] Social behaviours related to play occur mainly before sexual maturation, with a peak at the midpoint of the periadolescent period, while other forms of social repertoire occur during the entire life span, such as social investigation and social contact behaviour.[2–4] Play behaviour facilitates different aspects of social development, all of which contribute to the acquisition of adequate social functioning.[5] Play is crucial for establishing social organization in a group and for the development of the ability to express and understand intraspecific communicating signals.[5]

Behavioural studies have indicated that social play is a separate and relevant category of behaviour and have reported that play behaviour and social investigation are influenced differentially by drug treatments.[6–8] These studies suggest that behaviours related to play may be regulated through neuronal systems different from those that regulate social behaviours unrelated to play.[9,10] It was found that the opioid system has an important role in regulation and expression of social play, namely in the motivational and rewarding aspects of play behaviour, which are thought to be regulated by the endogenous opioid system.[9,11] The implication of the reward system in the regulation of social play suggests that long-term changes in this system probably will alter the expression of social play.

Cocaine reinforcing properties utilize, partially, the same circuits implicated in the reinforce properties of opiates.[12] Dopaminergic and serotonergic systems are altered after cocaine exposure and are

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Received 30 September 2005; revised 28 February 2006; accepted 16 March 2006

10.1177/0960327106070458

also implicated in social behaviours.[13] Studies linking cocaine and social interaction have yielded conflicting data.[7,14–19] For example, Harrison and colleagues reported a significant increase of aggression in hamsters treated with low-dose cocaine (chronic adolescent treatment: 0.5 mg/kg), whereas social communication and sexual motivation remained unchanged.[7] Wood and Spear also reported increased aggression in rats prenatally exposed to cocaine (40 mg/kg),[20] while other groups have reported decreased aggression (acute treatment: 30 mg/kg),[18] deficits in play (prenatal treatment: 40 mg/kg),[17] increased play in rats postnatally exposed to cocaine (20 mg/kg),[13] lower response to solicitation from conspecifics, or no differences in play behaviour (postnatal treatment: 40 mg/kg).[16] These discrepancies in published data may be related to the variety of test paradigms, animal models and dosing regimens that have been utilized. However, there is some agreement in research findings, which suggest that exposure to drugs during development may lead to persistent abnormalities of brain systems and behaviour. These permanent alterations in the development of brain circuits that processes reward or reinforcement may result in great vulnerability to addictive behaviours in adulthood.[21]

There are indications that either formal training on complex spatial tasks or living in spatially complex environments (environmental enrichment (EE)) may alter brain neurochemistry, brain weight and behaviour in rats.[22] Environments that supply a great variety of incentives provide a learning space to the animal with more possibilities of interaction, manipulation and exploration.[23] Exploration indicates learning, which probably alters behavioural sequences (for review see ref. [24]). A complex environment provides opportunities not only for social play but also for object interaction. Several studies found evidence for neurogenesis in response to EE (for review see ref. [25]), which might explain its beneficial effects on the course of neurodegenerative diseases,[26] ageing[27] and recovery from brain injury.[28] The stimulation provided by EE, applied early in life, alters both brain and behaviour and may be beneficial for behavioural development.[24]

The first objective of the present study was to analyse the effects of postnatal exposure to cocaine on social behaviour development. The second objective was to verify whether the postnatal environmental condition (EE/standard) affects the expression of social behaviours in rats exposed to cocaine during the first month of postnatal life.

Material and methods

Subjects and protocol of drug exposure

Rats used in this study were offspring born from Wistar females purchased from the colony of the Gulbenkian Institute of Science, Oeiras, Portugal. They were bred at the Institute of Molecular and Cell Biology, University of Porto, Portugal. All procedures used were approved by the Portuguese Agency for Animal Welfare (General Board of Veterinary Medicine). Animals were housed in a temperature- and humidity-controlled colony room maintained on a 12/12 hour light/dark cycle, with free access to food and water. On the day after birth, PND 1, litters were culled to eight pups, gender balanced, and pups weighed and marked with a felt-tip pen for identification. Rats were assigned to four groups: one group of rats was exposed to cocaine hydrochloride (COC) (Sigma Chemical Co., St. Louis, MO) in a dose of 15 mg/kg body weight/day in 0.9% saline (SAL), sc, split in two daily doses (8:30 a.m. and 6:00 p.m.), from PND 1 to PND 28 and reared in an EE (COC/EE). Animals in the second group were exposed to cocaine, as described above, and reared in a standard environment (SE) (COC/SE). The control groups comprised rats saline-injected (0.9%), in the same protocol, and reared in an EE (SAL/EE), as well as rats saline-injected and reared in SE (SAL/SE). Six different litters were assigned to each experimental group, one male and one female from each litter were used for social interaction testing. Pups were weaned on PND 21.

Housing conditions

EE: large acrylic cage ($100 \times 70 \times 70$ cm) with wooden bedding and equipped with various objects (PVC tubes, ping-pong and paper balls, wood objects, ladders, toys) that were replaced every 3 days. SE: standard acrylic cage type III, living directly on wooden bedding without any objects.

Behavioural testing: social interactions

Social interactions were assessed in three periods of development: PND 21 – weaning and beginning of play fighting behaviours,[29] PND 24 and 28 – prepubescent period. The social interaction test was performed in a sound-attenuated room, during the dark part of the light cycle. The testing arena consisted in a PCV cage measuring $60 \times 53 \times 40$ cm with a wood shaving covered floor and containing the following objects: three ladders, a block and a syringe. The arena was illuminated by an infrared light mounted 1 m above it. The test was carried

out between 4 p.m. and 5 p.m., 6.5 hours after the daily drug treatment. Considering a 2-hour half-life after subcutaneous administration, this period allows enough time to eliminate the acute effects of cocaine (reviewed in ref. [30]). Behaviour sessions were record by a video camera (SONY DCR-TRV9E), for 10 min, after allowing a 5-min period for habituation to the test arena. Testing was performed using the four female or the four male siblings and over the three periods tested the same sole rat was observed by focal-animal method. The following behavioural categories were analysed using the software Observer 4.1 (Noldus Information Technology, Netherlands): frequency of play fighting behaviours, divided into play-dominant (wrestling, boxing, pouncing, aggressive grooming, on-top-posture, chase, attack) and play-submissive (pining, escape, evade) behaviours; comfort behaviours (social grooming and pile up behaviour); play solicitation (crawling over/under, nose); social investigation (sniffing the cospecific's body including anogenital area) and total frequency social interaction.

Data analyses

Behavioural data were analysed by a four-way analysis of variance (ANOVA) (environment × treatment × gender × age) considering repeated measures for age. As this ANOVA did not indicate a significant effect of the gender factor, data were collapsed across gender and reanalysed by a three-way ANOVA (environment × treatment × age) with repeated measures for age. *t*-test comparisons were conducted to investigate all possible meaningful significant differences, considering a significance level of 5%. All tests were run using the software Statistica version 5.5 (Statsoft Inc., 1999).

Results

Data analysis by ANOVA revealed a significant main effect of environment for all analysed behavioural categories except for submissive play fighting. Concerning the interaction between environment and cocaine exposure, different results were observed for different behavioural categories.

Within the play-solicitation category, there was a main effect of environment [$F(1,43) = 6.71$, $P < 0.05$] and significant interaction of environment × treatment [$F(1,43) = 5.14$, $P < 0.05$]. Post hoc analysis of these data revealed that COC/EE rats increased play solicitation on PND 21 [$t(22) = -3.2$; $P < 0.01$] and PND 28 [$t(22) = -2.4$; $P < 0.05$] when compared to the COC/SE rats (Figure 1A). Further testing revealed that on PND 24 rats postnatally exposed to cocaine and reared in SE (COC/SE) significantly decreased the frequency of play solicitation [$t(22) = 3.9$; $P < 0.01$] (Figure 1A) when compared to the control group SAL/SE.

Concerning play-fighting behaviour, ANOVA revealed a main effect of environment for the dominant behaviour [$F(1,43) = 7.08$, $P < 0.05$], and post hoc analysis showed only that rats SAL/EE decreased play-dominant behaviours on PND 21 [$t(22) = 2.24$; $P < 0.05$], PND 24 [$t(22) = 3.33$; $P < 0.01$] and PND 28 [$t(22) = 2.2$; $P < 0.05$] when compared to SAL/SE (see Figure 1B). For play submissive behaviour no significant differences due to environment or drug exposure were observed (see Figure 1C).

For social investigation, ANOVA analysis determined both a main effect of environment [$F(1,43) = 41.28$, $P < 0.01$] and drug treatment [$F(1,43) = 4.12$, $P < 0.05$]. On the three evaluated ages, post hoc analysis of data revealed that SAL/EE rats decreased social investigation on PND 21 [$t(22) = 5.4$; $P < 0.001$], PND 24 [$t(22) = 3.9$; $P < 0.001$] and PND 28 [$t(22) = 4.49$; $P < 0.001$] when compared to SAL/SE animals (see Figure 1D). Post hoc analysis also showed a decrease in social investigation for the COC/EE group (when comparing to the COC/SE group) on both PND 24 [$t(22) = 2.9$; $P < 0.01$] and PND 28 [$t(22) = -2.2$; $P < 0.05$] (see Figure 1D). In addition, we observed an increase in social investigation for COC/EE animals when comparing to SAL/EE animals on PND 28 [$t(22) = -2.4$; $P < 0.05$].

Analysis of data concerning total social interaction revealed a main effect of environment [$F(1,43) = 22.65$, $P < 0.01$] and significant interaction for environment and drug treatment [$F(1,43) = 4.88$, $P < 0.05$]. Further *t*-testing determined also an increase in total interaction in rats exposed to cocaine and reared in an EE (COC/EE) when compared to the saline group reared in an EE (SAL/EE) on PND 28 [$t(22) = -2.2$; $P < 0.05$]. Additionally, there was a decrease in total interaction for control rats reared in an EE (SAL/EE) when compared to rats control rats reared in standard cages (SAL/SE), which was consistent at all tested ages: PND 21 [$t(22) = 4.7$; $P < 0.001$], PND 24 [$t(22) = 5.2$; $P < 0.001$] and PND 28 [$t(22) = 4.2$; $P < 0.001$] (see Figure 1E).

Comfort behaviour analysis determined a main effect of environment [$F(1,43) = 11.14$, $P < 0.01$]. Post hoc tests revealed only that COC/EE rats show more comfort behaviours on PND 24 [$t(22) = -3.32$; $P < 0.01$] and PND 28 [$t(22) = -2.5$; $P < 0.05$] than COC/SE animals (see Figure 1F).

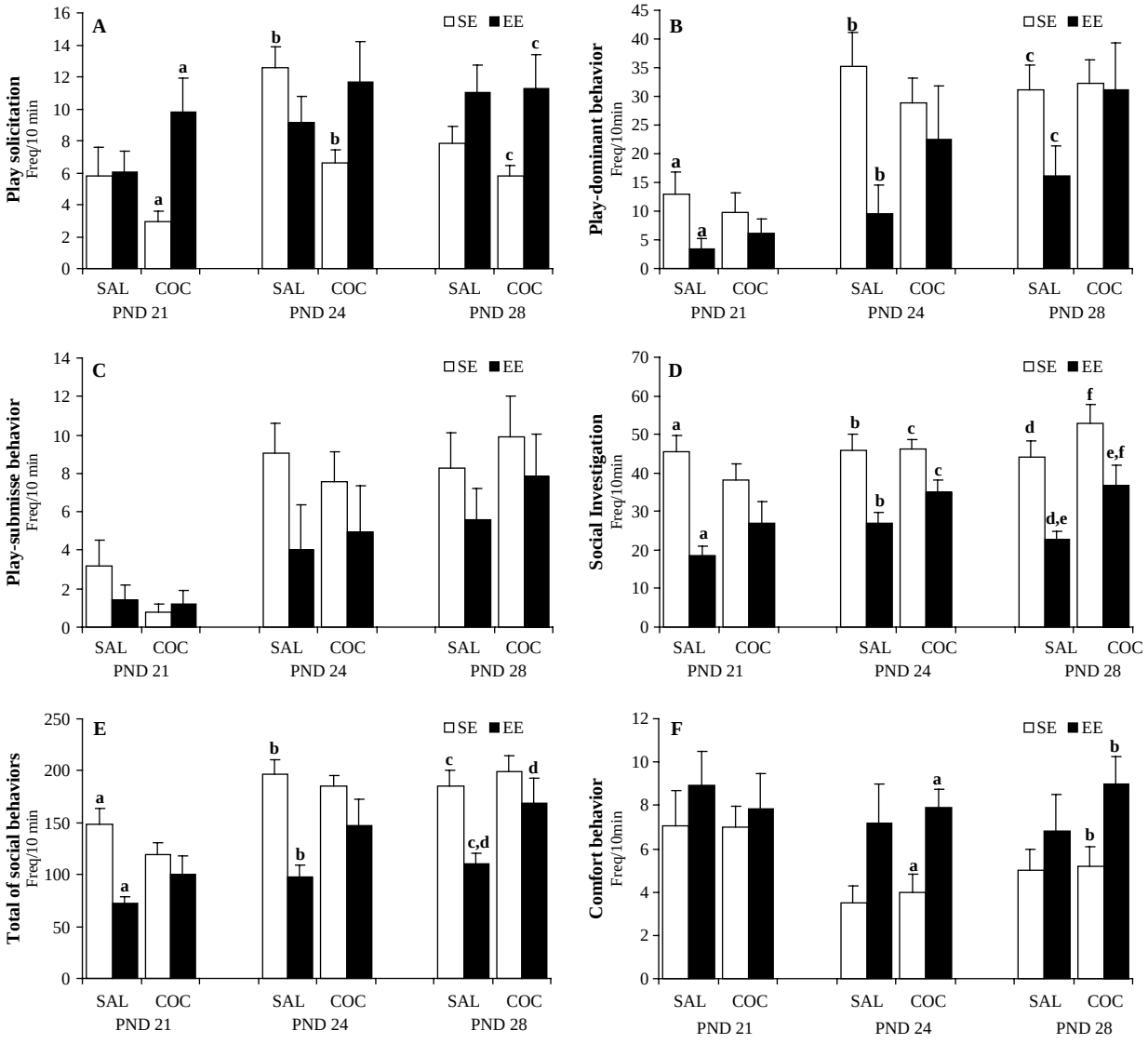

Figure 1 Effects of postnatal cocaine exposure and environmental enrichment on frequencies of the following behavioural categories in a social interaction test (columns marked with the same letter are significantly different from each other): (A) play solicitation, $^{a,b}P < 0.01$, $^{c}P < 0.05$; (B) play-dominant behaviours, $^{a,c}P < 0.01$, $^{b}P < 0.05$; (C) play-submissive behaviours; (D) social investigation, $^{a,b,d}P < 0.001$, $^{c}P < 0.01$, $^{e,f}P < 0.05$; (E) total social interaction, $^{a,b,c}P < 0.001$, $^{d}P < 0.05$; and (F) comfort behaviours, $^{a}P < 0.01$, $^{b}P < 0.05$. Data are represented as frequency means ± SEM for a 10-min period of testing.

Discussion

In an attempt to find effects of postnatal cocaine exposure on rat social behaviour we have examined the effects of chronic cocaine exposure on several behavioural categories of social interaction during the prepubescent period. In the rat, the first month of postnatal life is a particularly sensitive developmental period in which environmental influences can have a significant effect on subsequent behavioural development.[7]

In the present study, COC/SE animals decreased play solicitation when compared to SAL/SE. In the juvenile rat, specific behaviours classified as play solicitation include pouncing, tail-pulling, crawling over/under and darting, and precede bouts or sequences of play fighting.[3] Play solicitation has been described as a set of behaviours functionally inciting to social play.[11] Some studies report that animals prenatally exposed to cocaine decreased solicitation to play.[14,16,17] Previous research shows that rats prenatally exposed to cocaine were less attractive as playmates during the adolescent play period.[17] Animals postnatally exposed to cocaine may be also less attractive to play partners due to alterations induced by cocaine exposure. The decrease in play solicitation after postnatal cocaine suggests a reduction of attention from the play

partners, which may be related to altered medial prefrontal cortex (mPFC) function. Diminished dopamine turnover in this area is associated with behavioural decline[31] and likely to be caused by exposure to cocaine.[32] Also, exposure to cocaine was reported to alter dopamine transporter and autoreceptor functions, as well as general plasticity, which has implications at a behavioural level.[33,34]

Control animals reared in an EE (SAL/EE) displayed decreased play fighting when compared to SE-reared rats (SAL/SE). This result is consistent with other studies,[29,35] where a significant reduction of play-related behaviours in animals reared in an EE was shown. The reduction of social play by SAL/EE rats may reflect the fact that, in this study, rats were tested in an arena with novel objects. The novelty of the arrangements of objects may have induced the exploration of the environment.[35,36] Animals reared in an EE are more exploratory and seem to prefer to explore the novel environment instead of being engaged in social play, which would reduce attention to surroundings. An EE also decreased social investigation in SAL/EE when compared to SAL/SE-reared rats. This social behaviour, unrelated to play, has the immediate goal of exploring conspecifics.[37] Social memory, the ability to form and retain information related to conspecifics,[38] seems to be improved in EE-housed animals. This result suggests that EE facilitated the retention of specific information, which is in accordance with the increased plasticity in the hippocampus previously described.[25]

The EE attenuated the altered behavioural profile exhibited by animals postnatally exposed to cocaine. Rats postnatally exposed to cocaine, when reared in EE, display increased play solicitation compared to the COC/SE group. These results suggest that an EE enhances the attractiveness of play partners. EE allows animals to display a more extensive repertoire of natural behaviour and may provide appropriate stimulation, which facilitates coping with life events. This increased controllability reduces stress and subsequently improves welfare.[39]

Rats postnatally exposed to cocaine and reared in an EE also decreased social investigation when compared to COC/SE animals. These results suggest that EE improves social memory in rats postnatally exposed to cocaine. In fact, rats who are engaged in playful behaviour with conspecifics in an EE show increased dendritic arboration, have heavier cerebral cortices and show improved learning abilities when compared to play-deprived rats in an impoverished environment (for review see ref.[40]).

EE increased the frequency of comfort behaviours. This behavioural category includes social grooming and pile up behaviour, which can be regarded as amicable behaviours. This type of behaviour is associated with social comfort, and an increase in these behaviours can be interpreted as a strategy adopted to reduce the stress caused by a new environment. Animals housed in an EE are given more opportunities to exploit their behavioural repertoire than rats reared in SE. We observed that in a mild stress situation rats reared in an EE reduced social activity and increased social contact. This strategy reduces the stress induced by exposure to new, but not very stimulating, environments (the EE in their home cage was more complex and stimulating). Rearing conditions are an important determinant not only of cognitive ability but also of emotionality.[41,42] Rats reared in a SE did not have the same opportunities to engage in play as rats reared in an EE, and after the first contact with the test arena (PND 21), which was new and highly stimulating for SE rats, they increased play activity and decreased comfort behaviours on PND 24 and 28. For SE rats the risk of a new and mildly stressing environment may be surpassed by the new opportunity offered by a stimulating environment. The way animals exploit the new environment depends on the relative stimulus complexity afforded by that environment.[43] These results suggested that an EE experience during critical stages of development may alter the strategy employed to cope with a new situation.

In accordance, there was an increase in comfort behaviours in EE rats when compared to SE (both on PND 24 and 28), however this increase reached significance only for cocaine-exposed animals. As cocaine exposure during development alters the responsiveness to stress,[44,45] it is possible that for these animals the test environment represented a more stressful event.

Social exploration and comfort behaviour are not associated with play behaviour. These social categories, unrelated to play, seem to be regulated through different neural systems.[9] While social play seems to be primarily regulated through the opioid system,[10] cocaine is known to affect mainly the dopaminergic and serotonergic systems.[46–49] However, although these circuitries are not fully understood, there is strong evidence of direct and indirect (via GABAergic inhibition) influence of one system on the other (for review see ref. [10]). Therefore, it not reasonable to clearly distinguish possible actions of EE or cocaine in different behavioural categories either related or unrelated to play.

In summary, results suggest that chronic cocaine postnatal exposure decreases solicitation to play. It appears that the exposure to EE during critical stages of development attenuates some cocaine-induced behavioural alterations and improves social memory. The results support the notion that exposure to EE during early postnatal period in rats affects information processing and response to mild stress.

Acknowledgements

The research presented in this article was supported by a Fundação para a Ciência e Tecnologia (FCT) grant to Ana Magalhães (PRAXISXXI/BD/20075/99) and Teresa Summavielle (SFRH/BPD/20997/2004); and by Project POCTI/PSI/39491/2001 approved by FCT and supported by FEDER and by Plurianual funds from IBMC.

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