Pharmacology, Biochemistry and Behavior 95 (2010) 100–105

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Interactions between the effects of early isolation rearing and complex housing on adult locomotor activity and sensitivity to amphetamine in rats involve noradrenergic neurotransmission

Anna M. Lomanowska, Narmeen Ammari, Gary W. Kraemer *

Department of Psychology, University of Toronto at Mississauga, 3359 Mississauga Rd N., Mississauga, ON, Canada L5L 1C6

ARTICLE INFO

Article history:
Received 12 June 2009
Received in revised form 14 December 2009
Accepted 17 December 2009
Available online 31 December 2009

Keywords:
Amphetamine
Prazosin
α-adrenergic receptor
Locomotion
Maternal deprivation
Environmental enrichment
Group housing
Artificial rearing

ABSTRACT

Increased sensitivity to the locomotor-activating effects of amphetamine in rats with a history of early-life social isolation is commonly attributed to alteration of the dopamine system. The locomotor response to amphetamine may also be due to effects on the noradrenergic system and particularly α-adrenergic receptors. The present study examined whether noradrenergic neurotransmission mediates the increased sensitivity to the locomotor effects of amphetamine resulting from early social isolation and whether this effect can be reversed by later-life social housing experience. Rats reared in complete social isolation (artificially reared, AR) exhibited higher levels of locomotor activity than maternally reared (MR) rats in response to amphetamine (0.25 mg/kg). Increased sensitivity to the locomotor effects of amphetamine in AR rats was reduced by the α-adrenergic receptor antagonist prazosin (0.5 mg/kg). Prazosin alone reduced activity in AR rats to the level of MR rats. Group housing in cages that were more complex than standard laboratory cages reduced activity in both AR and MR rats. Group housing did not decrease the sensitivity of AR rats to the locomotor effects of either amphetamine or prazosin. Differences in activity between rats in standard and complex housing conditions were not altered by drug treatments. These findings indicate that pre-weaning social experience alters the responsiveness of the noradrenergic system to drug challenges, whereas post-weaning housing experience may not, even though ongoing activity is affected. Increased activity and sensitivity to amphetamine resulting from social isolation in early life may be mediated by changes in noradrenergic α-receptor mediated neurotransmission.

1. Introduction

Social experience is critical in shaping the development of the mammalian central nervous system. Experimental manipulations in rats and monkeys that involve early social deprivation have long-lasting effects on behavior and neurobiology (Hall, 1998; Kraemer, 1992; Pryce et al., 2005). One consequence of chronic or intermittent social isolation during the typical pre-weaning period in rats is increased sensitivity to the locomotor-activating effects of psychostimulant drugs such as amphetamine (AMPH) or cocaine (Brake et al., 2004; Kehoe et al., 1998b; Lovic et al., 2006; Pryce et al., 2001). AMPH increases the synaptic release of both norepinephrine (NE) and dopamine (DA) by inhibiting neurotransmitter reuptake and reversing transport through membrane monoamine transporters (Kahlig and Galli, 2003; Seiden et al., 1993). The locomotor-stimulating effects of AMPH are commonly attributed to effects on the mesolimbic DA system (Di Chiara, 1995; Koob et al., 1998; Meaney et al., 2002). Rats reared in isolation show enhanced DA release in the nucleus accumbens in response to AMPH administration during infancy (Kehoe et al., 1998a), in adolescence (Kehoe et al., 1996), and in adulthood (Hall et al., 1999).

Nonetheless, some studies indicate that the locomotor-activating effects of AMPH are related to or even dependent on NE neurotransmission (Auclair et al., 2002; Darracq et al., 1998; Drouin et al., 2002; Vanderschuren et al., 2003; Weinshenker and Schroeder, 2007). AMPH-induced locomotor activation can be blocked by prior administration of the α-adrenergic (NE) receptor antagonist prazosin (PRAZ) either systemically or locally into the prefrontal cortex (Blanc et al., 1994; Darracq et al., 1998; Drouin et al., 2002). This indicates that stimulation of α-adrenergic receptors in the prefrontal cortex is necessary for the expression of locomotor activation in response to AMPH. NE released from cortical terminals affects a glutamate system that modulates the release of DA from the nucleus accumbens and the resulting locomotor activity (Darracq et al., 2001).

Increased locomotor responsiveness to AMPH following early-life social isolation may also be related to changes in NE neurotransmission. Rhesus monkeys isolated for varying periods shortly after birth

* Corresponding author. Tel.: +1 905 828 5297; fax: +1 905 569 4326.
E-mail address: gary.kraemer@utoronto.ca (G.W. Kraemer).

0091-3057/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2009.12.013

are hypersensitive to AMPH with regard to behavior and increased release of NE, but not DA metabolite, into cerebrospinal fluid (Kraemer et al., 1984). Repeatedly isolated female rats have increased levels of NE in the dorsal hippocampus compared to controls (Matthews et al., 2001), but there are no differences in NE levels between repeatedly isolated and control rats in the nucleus accumbens (Zhang et al., 2006). Repeatedly isolated rats also have greater levels of NE released from the paraventricular nucleus of the hypothalamus in response to stress, but they do not differ from control rats in the number of NE receptors in this region (Liu et al., 2000). Administration of the NE agonist clonidine leads to greater suppression of food-conditioned locomotor activity in repeatedly isolated rats (Matthews et al., 1996). However, the effects of early-life social isolation of rats on NE function associated with the locomotor response to psychostimulants are unknown.

The first aim of this study was to determine whether augmented responses to AMPH in rats reared in social isolation could be reduced by pretreatment with the α-adrenergic receptor antagonist PRAZ, and therefore be attributable to changes in the NE rather than the DA system. Rat pups were completely isolated from the mother and littermates using a method of artificial rearing (AR) (Gonzalez et al., 2001; Hall, 1975). This allows for considerable control of environmental variables as well as provision of nourishment during social isolation in infancy. Lovic et al. (2006) reported that AR rats display greater activity levels than maternally reared (MR) rats in response to AMPH at all doses used (0.25, 0.5, and 1.0 mg/kg). The lowest dose (0.25 mg/kg) was selected for the present study because it was shown to substantially increase activity levels in AR but not MR rats. This allowed for the investigation of increased AMPH sensitivity in AR rats outside of the typical locomotor-activating effects of this drug observed in MR rats.

The second aim of this study was to determine whether post-weaning housing conditions would affect the sensitivity of AR rats to the locomotor effects of AMPH, the effects of PRAZ, and/or the PRAZ antagonism of AMPH effects. Differential social housing conditions after weaning affect activity levels in response to a novel environment or psychostimulant administration (Bowling and Bardo, 1994; Hellemans et al., 2004; Schrijver et al., 2002; Varty et al., 2000). Enrichment of the social environment also ameliorates some of the deleterious behavioral effects produced by pre-natal stress, alcohol exposure, or repeated isolation from the mother (Chapillon et al., 2002; Darnaudery and Maccari, 2008; Francis et al., 2002; Hannigan et al., 2007). Rats in this study were housed either in standard laboratory conditions with two rats per cage, or in larger, more complex three dimensional environments, with four rats per cage and climbing poles leading to platforms above floor level. Overall, the locomotor response of AR and MR rats housed in standard or complex environments, following treatment with AMPH and PRAZ alone and in combination, was measured in automated activity boxes.

2. Methodology

2.1. Subjects

Forty-eight male offspring of 12 primiparous Long-Evans rat dams obtained from Charles River Farms (St. Constant, Quebec, Canada) were used as subjects in this study. After mating, dams were housed individually in clear cages (L43×W22×H21 cm), lined with wood-chip bedding ("Beta Chip", NEPCO) with free access to water and lab chow ("5012 Rat Diet", PMI Inc). Housing rooms were maintained at a temperature of 22±1 °C and humidity of 40–50%. Lights were off between 2000 and 0800 h. All procedures were performed in accordance with the guidelines set by the Canadian Council on Animal Care and were approved by the University of Toronto at Mississauga Local Animal Care Committee.

2.2. Pup rearing conditions

On the day of parturition (post-natal day — PND 0) litters were culled to ten pups with approximately equal number of males and females. Two male pups were removed from each litter on PND 5, underwent cheek cannulation and were reared artificially thereafter (artificial rearing condition; AR, $n=24$). The remaining pups were left in the litter undisturbed until weaning, except for weekly cage changes (maternal rearing condition; MR, $n=24$).

2.3. Cheek cannulation and artificial rearing

Details of the cheek cannulation and AR procedures are described elsewhere (Burton et al., 2006; Gonzalez et al., 2001). Briefly, the cannulation procedure was performed following topical anesthesia of the cheek with lidocaine (EMLA). The cheek was then pierced to implant a polyethylene (PE10) cannula. Polysporin antibacterial cream was applied topically at the site of penetration. Immediately following cannulation each AR pup was placed into an individual plastic cup (11 cm in diameter×15 cm deep) lined with corn-cob bedding (Bed O'Cobs) and floating in a temperature controlled water bath. The temperature inside the cup was maintained at 36±1 °C. The top of the cup remained open to allow the cheek cannula to be attached to polyethylene (PE 50) tubing that was in turn connected to a syringe. Each syringe was filled with rat milk substitute formula (Messer diet). The syringes were mounted on timer-controlled infusion pumps (Harvard Apparatus Syringe, PHD 2000), which were programmed to deliver the formula for 10 min every hour, 24 h daily. Feeding via cheek cannulae began 1–2 h after the cannulation procedure. On the first day of AR pups were fed 33% of the mean body weight of ten pups per pump, with the volume increasing by 2% per day up to 51% thereafter.

Each morning the pups were removed from the cups, weighed, and had their cheek cannulae flushed with 0.1 ml of sterile water. New syringes were filled with fresh diet and the infusion pumps were programmed according to the pups' new mean weight. Twice per day (morning and night) each pup was picked-up from its cup, gently held in an upright position, and had its anogenital region stimulated for 30 s with a warm, wet, camel hair paintbrush to induce urination and defecation. Pump feeding ended on PND 17. Each pup was transferred from its cup into an individual small cage (L27×W17×H13 cm) lined with woodchip bedding and supplied with a water bottle, regular rat chow, and milk formula mixed with powdered chow ("5012 Rat Diet", PMI Inc). Daily weighing of AR pups continued until PND 21.

2.4. Weaning and housing conditions

Pups were weaned from their respective rearing conditions on PND 21. At this time, two male MR pups were selected from each original litter. All rats were weighed, ear notched for identification, and placed into either standard (STD) or complex (CPX) housing conditions. Thus, four experimental groups were formed: AR-STD, AR-CPX, MR-STD and MR-CPX with 12 rats per group to start. One rat in the AR-CPX group died during the experiment.

All rats were housed with cage mates originating from the same rearing condition. Rats in the standard condition were housed two per cage in clear cages (L 43×W 22×H 21 cm) for the remainder of the experiment. Rats in the complex condition were initially housed four per cage in large clear cages (L 48×W 37×H 21 cm). On PND 35 they were transferred to large transparent acrylic glass cages (W 50×L 50×H 50 cm), four rats per cage. Rats were provided with two climbing poles positioned diagonally across the cage, each with two resting platforms. One of these poles led to the food hopper and water bottle such that the rats were required to climb the pole to the highest platform to obtain food and water. All cages were lined with woodchip bedding and contained plastic enrichment tubes.

Table 1
Experiment layout.

Session	Drug treatment
1	Habituation to novel environment — no drug injections
2–7	Habituation to double injections — SAL/SAL
8–9	SAL/AMPH, SAL/SAL (counterbalanced)
10–12	SAL/SAL
13–14	PRAZ/SAL, SAL/SAL (counterbalanced)
15	SAL/SAL
16	PRAZ/AMPH

SAL, saline; PRAZ, prazosin; AMPH, amphetamine.

2.5. Locomotor activity

Locomotor activity was assessed in 16 clear acrylic glass boxes (L 43×W 22×H 25 cm) with clear, ventilated acrylic glass lids. The boxes were separated by opaque screens to prevent rats from seeing each other. Each box was equipped with two arrays of 16×16 infrared photo-beams, spaced 2.5 cm apart (constructed by the Centre for Addiction and Mental Health; Toronto, ON). The bottom array was positioned 3 cm above the floor of the chamber and recorded horizontal movement. The top array was positioned 15 cm above the floor and recorder rearing activity. The arrays were connected to a computer via an interface that detected photo-beam interruptions (beam breaks). Each activity session lasted for 120 min and the number of beam breaks on the bottom array was recorded in 5 min bins and used as an index of locomotor activity. Activity sessions were conducted every other day in a dimly lit testing room. Each rat was always tested in the same activity box. Activity testing started when rats were approximately 70±2 days of age. On the first day of testing rats were placed into the activity boxes without any injections in order to ascertain their baseline activity level in a novel environment.

2.6. Drug injections

D-amphetamine hydrochloride (AMPH; 0.25 mg/kg; Sigma, St. Louis, MO) and prazosin hydrochloride (PRAZ; 0.5 mg/kg; Sigma, St. Louis, MO) were dissolved in sterile saline vehicle (SAL; 0.9% NaCl). All injections were administered intraperitoneally at a volume of 1.0 ml/kg.

Each activity testing session involved a double injection regimen. The first injection contained PRAZ or SAL and the second injection contained AMPH or SAL. Therefore, the treatment conditions were SAL/SAL, SAL/AMPH, PRAZ/SAL and PRAZ/AMPH. Each set of drug and vehicle injections was administered over two sessions according to a repeated measures crossover design. Each rat was placed into its activity box immediately after the first injection. It was removed from its activity box 30 min later, given the second injection, and returned to the activity box for another 90 min.

Habituation to the double injection regimen took place over six activity sessions during which rats received SAL/SAL. The effects of SAL/AMPH were measured in two subsequent sessions followed one week later by three more SAL/SAL-only habituation sessions. The effects of PRAZ/SAL were then measured over two sessions. Following an additional SAL/SAL-only session, the effects of PRAZ blockade of AMPH-induced activity (PRAZ/AMPH) were measured in the last session. The order of drug treatments is outlined in Table 1.

2.7. Data analyses

The total number of beam breaks during 10 min intervals of each 120 min session was used as a measure of individual locomotor activity. Mean activity for habituation sessions was computed for the entire duration of each test (120 min). Mean activity for the drug treatment sessions was calculated for 90 min after the second injection. Repeated measures analysis of variance (ANOVA) was used to compare activity across drug treatment sessions (within group repeated measures factor) with between group factors of rearing condition (AR or MR) and housing condition (STD or CPX). Statistical analyses were conducted using SPSS 16.0 (SPSS Inc), with the rejection level set at $p<0.05$.

3. Results

3.1. Response to novel environment

Table 2 shows the means of total beam breaks during the first exposure to a novel environment (activity boxes). AR rats were more active than MR rats ($F_{(1, 43)}=5.14$, $p=0.029$) and rats housed in a STD environment were more active than rats housed in a CPX environment ($F_{(1, 43)}=6.86$, $p=0.012$). There was no significant interaction between the effects of rearing and housing. The greatest difference in activity levels in response to a novel environment was between AR-STD and MR-CPX rats.

3.2. Habituation to injections

Table 2 displays the means of total beam breaks during six sessions of habituation to the double injection procedure, 30 min after the first injection and 90 min after the second injection, averaged over two consecutive sessions. Activity during the 30 min after the first injection significantly decreased over subsequent session (main effect of session: $F_{(2, 86)}=11.50$, $p<0.001$). AR rats were significantly more active than MR rats (main effect of rearing: $F_{(1, 43)}=4.91$, $p=0.032$) and rats housed in STD environments were significantly more active than rats housed in CPX environments (main effect of housing: $F_{(1, 43)}=18.36$, $p<0.001$) during the 30 min after the first injection. During the 90 min after the second injection there was a significant

Table 2
Mean totals (±SEM) of beam breaks during the first exposure to the testing environment (no injections) and habituation to saline injections.

Treatment			Standard housing		Complex housing	
			Artificial rearing	Material rearing	Artificial rearing	Material rearing
			($n=12$)	($n=12$)	($n=11$)	($n=12$)
Novel environment — no injections		120 min[a,b]	5285(±619)	3921(±368)	3770(±253)	3185(±367)
Saline double injection sessions[c]	1–2	30 min[a,b]	2047(±101)	1669(±89)	1584(±68)	1398(±100)
		90 min[b]	2764(±576)	1658(±240)	1304(±128)	1236(±189)
	3–4	30 min[a,b]	1972(±195)	1735(±127)	1422(±65)	1301(±82)
		90 min[b]	2730(±505)	1878(±352)	1277(±160)	1166(±122)
	5–6	30 min[a,b]	1722(±147)	1557(±113)	1361(±65)	1172(±73)
		90 min[b]	2317(±376)	2023(±372)	1552(±202)	1035(±116)

[a] Main effect of rearing, $p<0.05$.
[b] Main effect of housing, $p<0.05$.
[c] Means collapsed over two activity sessions; top rows indicate total beam breaks 30 min after first injection; bottom rows indicate total beam breaks 90 min after second injection.

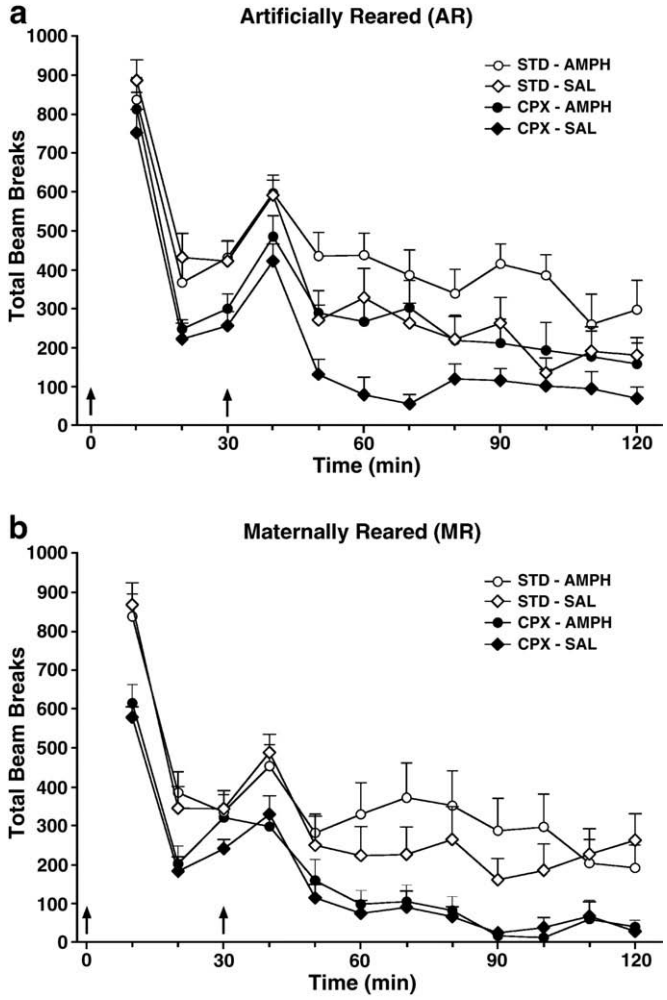

Fig. 1. Locomotor activity (mean ± SEM beam breaks) in response to an injection of saline (SAL) followed by an injection of SAL or AMPH in (a) AR rats and (b) MR rats. Arrows indicate time points when injections were administered. (STD, standard housed; CPX, complex housed; $n = 11–12$ rats per group).

session × rearing × housing interaction ($F_{(2, 86)} = 4.44$, $p = 0.015$). Rats housed in STD environments were significantly more active than rats housed in CPX environments during sessions 1–2 ($F_{(1, 43)} = 7.73$, $p = 0.008$), sessions 3–4 ($F_{(1, 43)} = 10.78$, $p = 0.002$), and sessions 5–6 ($F_{(1, 43)} = 8.98$, $p = 0.005$), but there were no significant differences between rearing groups during any of the sessions.

3.3. Response to amphetamine

As an example of repeated measures effects, Fig. 1 shows activity over 10 min intervals in response to the first injection of SAL and the second injection of SAL or AMPH in AR (Fig. 1a) and MR (Fig. 1b) rats. Overall, activity was highest in the first interval, declined up to the 30 min interval, and then increased following the second injection. Rats reared in STD housing had higher activity levels in the first 30 min of testing (main effect of housing: $F_{(1, 43)} = 21.84$, $p < 0.001$). The effects of differential drug treatment could not occur prior to the second injection, therefore analyses of data obtained in all drug

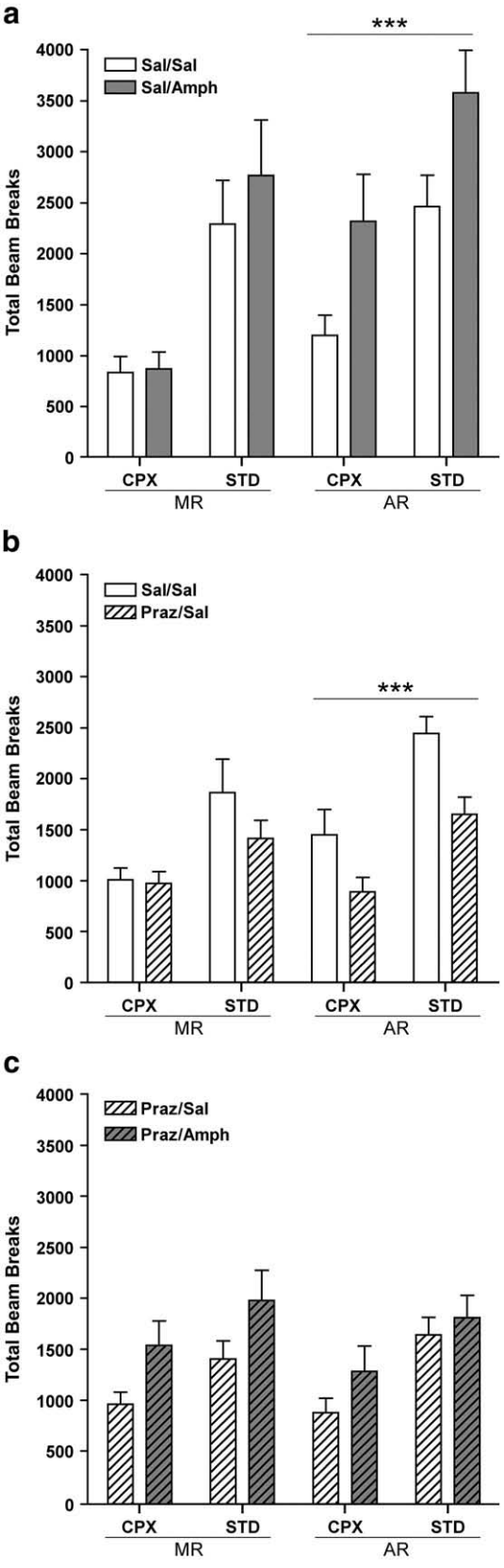

Fig. 2. Locomotor activity in response to treatments with saline/saline (SAL/SAL) in comparison to (a) saline/amphetamine (SAL/AMPH) and (b) prazosin/saline (PRAZ/SAL), as well as (c) PRAZ/SAL in comparison to prazosin/amphetamine (PRAZ/AMPH). Scores represent mean totals (± SEM) of beam breaks during the 90 min interval following the second drug injection. Only AR rats demonstrated a significant increase in activity following SAL/AMPH treatment (a) as well as a significant decrease in activity following PRAZ/SAL treatment (b) compared to SAL/SAL treatment. Treatment with PRAZ abolished the differences in activity between AR and MR rats in response to administration of SAL/SAL and SAL/AMPH (c). Rats housed in the standard condition (STD) were more active than rats housed in the complex (CPX) condition across all treatments, $p < 0.005$. *** Significant effect of drug treatment across rearing conditions, $p < 0.005$. ($n = 11–12$ rats per group).

treatment conditions were based on the 90 min time interval from 30–120 min. These results are presented in Fig. 2. Fig. 2a illustrates the response to treatment with SAL/AMPH in comparison to treatment with SAL/SAL. Rats housed in the STD environment had higher levels of activity than rats housed in the CPX environment (main effect of housing: $F_{(1, 43)} = 18.67$, $p < 0.001$). The interaction between the effects of drug treatment and rearing condition was significant ($F_{(1, 43)} = 11.04$, $p = 0.002$). Activity increased after AMPH administration in AR rats but not in MR rats ($F_{(1, 22)} = 35.05$, $p < 0.001$).

3.4. Response to prazosin

Fig. 2b shows activity in response to treatment with PRAZ/SAL in comparison to treatment with SAL/SAL. Rats housed in the STD environment had higher levels of activity than rats housed in the CPX environment (main effect of housing: $F_{(1, 43)} = 18.79$, $p < 0.001$). There was also a significant interaction between the effects of drug treatment and rearing condition ($F_{(1, 43)} = 6.46$, $p = 0.015$). Activity decreased in response to treatment with PRAZ in AR rats but not in MR rats ($F_{(1, 22)} = 36.31$, $p < 0.001$). An examination of Fig. 2b reveals that treatment with PRAZ/SAL reduced SAL/SAL activity in AR rats down to the level of MR rats.

3.5. Inhibition of amphetamine-induced activity by prazosin

Fig. 2c shows activity in response to treatment with PRAZ/AMPH in comparison to treatment with PRAZ/SAL. Rats housed in the STD environment had higher levels of activity than rats housed in the CPX environment (main effect of housing: $F_{(1, 43)} = 9.28$, $p = 0.004$). PRAZ/AMPH resulted in overall higher activity levels compared to PRAZ/SAL treatment (main effect of drug treatment: $F_{(1, 43)} = 14.96$, $p < 0.001$), but there were no significant interactions of treatment with rearing or housing conditions. This indicates that treatment with PRAZ abolished the differences in activity between AR and MR rats in response to administration of SAL/SAL and SAL/AMPH.

4. Discussion

The results of the present study indicate that noradrenergic neurotransmission involving α-adrenergic receptors plays a role in the increased sensitivity of rats with a history of early social isolation to the locomotor effects of AMPH. AR rats showed increased activity compared to MR rats in response 0.25 mg/kg of AMPH. The α-adrenergic receptor antagonist PRAZ (0.5 mg/kg) blocked this augmented response to AMPH in AR rats. PRAZ/SAL also reduced activity in AR rats to the level of MR rats. Group housing in cages that were more complex than standard laboratory conditions reduced activity in both AR and MR rats, but sensitivity of AR rats to the effects of either AMPH or PRAZ was not reduced. Differences in activity between rats in standard and complex housing conditions were not altered by either drug treatment. These results demonstrate that the locomotor response to drugs acting on the noradrenergic system was altered by pre-weaning rearing conditions, but not by post-weaning housing conditions.

AR rats in this study showed increased activity levels compared to MR rats in response to a novel environment and administration of saline injections. This profile of locomotor activity is similar to previous studies of adult rats with a history of early-life social isolation (Brake et al., 2004; Kalinichev et al., 2002; Kehoe et al., 1998b; Lovic et al., 2006; Pryce et al., 2001). The NE system is activated by an array of stressful stimuli (Morilak et al., 2005). The double injection procedure and placement in an activity box is stressful, and PRAZ/SAL administration reduced activity in relation to this treatment in AR rats to the level of MR rats. This indicates that the increased activity exhibited by AR rats may be dependent on stimulation of α-adrenergic receptors, and the NE system may be more readily activated in AR rats.

The reduction in activity levels in both AR and MR rats following housing in a complex environment is comparable to the results of previous studies of environmental enrichment effects (Bowling and Bardo, 1994; Hellemans et al., 2004; Schrijver et al., 2002; Varty et al., 2000). These differences in activity following differential housing conditions are probably not dependent on the stimulation of α-adrenergic receptors because treatment with PRAZ/SAL did not reduce the activity of standard housed rats to the level of complex housed rats. Previous studies show that housing in an enriched environment produces functional changes in mesolimbic dopamine neurotransmission (Bowling et al., 1993). It is possible that changes in this neurotransmitter system mediate the effects of post-weaning complex housing on locomotor activity observed in the present study.

The effects of complex housing on the locomotor response to SAL/AMPH were somewhat surprising. MR rats housed in a complex environment showed virtually no increase in activity in response to the first injection of SAL/AMPH, but their activity level was increased in response to treatment with PRAZ/AMPH. Although the data may be interpreted to suggest that pretreatment with PRAZ enhanced the effects of AMPH in this group, the most likely explanation is that the repeated injection and drug treatment protocol used in this study resulted in the enhancement of AMPH effects. This also suggests that the effects of repeated exposure to amphetamine may depend on rearing and housing conditions.

The finding that complex housing did not reduce the sensitivity of AR rats to the effects AMPH or PRAZ is analogous to effects reported by Kraemer et al. (1984) in rhesus monkeys reared in isolation and subsequently housed in social groups. There were no observable differences between isolation and mother-reared monkeys at baseline, but AMPH administration produced profound differences in social behavior in previously isolated monkeys. Altered responsiveness to AMPH in isolation-reared monkeys was associated with increased levels of NE, but not DA or serotonin metabolites in cerebrospinal fluid. Previous work in AR rats indicates that intervention during rearing, in the form of maternal-like tactile stimulation, reduces sensitivity to AMPH (Lovic et al., 2006). Together, these findings suggest that pre-weaning experience affects the responsiveness of the NE system to drug challenges, whereas post-weaning housing experience may not, even though ongoing activity is affected.

The housing conditions used in this study enhanced the complexity of social interaction as well as non-social features of the environment. Rats in the complex housing condition experienced a more physically challenging environment. This variable alone or in combination with social experience may be important in shaping the activity profile of rats in the complex condition. A previous study of AR rats found no differences in activity levels in the open field following social or isolation housing in standard cages during adolescence (Lomanowska et al., 2006). However, rats in the present study were group housed in the complex environment for a much longer period of time. Further investigation is required to dissociate the effects of social and non-social factors on activity levels following housing in a complex environment.

Overall, the results of this study suggest that α-adrenergic NE receptors are involved in mediating the increased activity and responsiveness to AMPH of AR rats; perhaps by changes in the location or density of α-adrenergic NE receptor expression in the prefrontal cortex. While the DA system is the final common pathway regulating expression of motor behavior, the most parsimonious interpretation of the results is that effects of early social isolation on adult activity and increased sensitivity to AMPH are mediated by effects on the NE system. Conversely, the effects of post-weaning housing conditions on activity and sensitivity to AMPH do not appear to be dependent on the stimulation of α-adrenergic NE receptors and

further research is required to investigate the mechanisms mediating these effects.

Acknowledgments

This work was supported by a grant from NSERC to G.W. Kraemer and a graduate scholarship from NSERC to A.M. Lomanowska. The authors thank Andrew Choi for assistance with activity testing.

References

Auclair A, Cotecchia S, Glowinski J, Tassin JP. D-amphetamine fails to increase extracellular dopamine levels in mice lacking alpha 1b-adrenergic receptors: relationship between functional and nonfunctional dopamine release. J Neurosci 2002;22:9150–4.

Blanc G, Trovero F, Vezina P, Herve D, Godeheu AM, Glowinski J, et al. Blockade of prefronto-cortical alpha 1-adrenergic receptors prevents locomotor hyperactivity induced by subcortical D-amphetamine injection. Eur J NeuroSci 1994;6:293–8.

Bowling SL, Bardo MT. Locomotor and rewarding effects of amphetamine in enriched, social, and isolate reared rats. Pharmacol Biochem Behav 1994;48:459–64.

Bowling SL, Rowlett JK, Bardo MT. The effect of environmental enrichment on amphetamine-stimulated locomotor activity, dopamine synthesis and dopamine release. Neuropharmacology 1993;32:885–93.

Brake WG, Zhang TY, Diorio J, Meaney MJ, Gratton A. Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioural responses to psychostimulants and stressors in adult rats. Eur J Neurosci 2004;19:1863–74.

Burton C, Lovic V, Fleming AS. Early adversity alters attention and locomotion in adult Sprague-Dawley rats. Behav Neurosci 2006;120:665–75.

Chapillon P, Patin V, Roy V, Vincent A, Caston J. Effects of pre- and postnatal stimulation on developmental, emotional, and cognitive aspects in rodents: a review. Dev Psychobiol 2002;41:373–87.

Darnaudery M, Maccari S. Epigenetic programming of the stress response in male and female rats by prenatal restraint stress. Brain Res Rev 2008;57:571–85.

Darracq L, Blanc G, Glowinski J, Tassin JP. Importance of the noradrenaline-dopamine coupling in the locomotor activating effects of D-amphetamine. J Neurosci 1998;18: 2729–39.

Darracq L, Drouin C, Blanc G, Glowinski J, Tassin JP. Stimulation of metabotropic but not ionotropic glutamatergic receptors in the nucleus accumbens is required for the D-amphetamine-induced release of functional dopamine. Neuroscience 2001;103: 395–403.

Di Chiara G. The role of dopamine in drug abuse viewed from the perspective of its role in motivation. Drug Alcohol Depend 1995;38:95–137.

Drouin C, Blanc G, Villegier AS, Glowinski J, Tassin JP. Critical role of alpha1-adrenergic receptors in acute and sensitized locomotor effects of D-amphetamine, cocaine, and GBR 12783: influence of preexposure conditions and pharmacological characteristics. Synapse 2002;43:51–61.

Francis DD, Diorio J, Plotsky PM, Meaney MJ. Environmental enrichment reverses the effects of maternal separation on stress reactivity. J Neurosci 2002;22:7840–3.

Gonzalez A, Lovic V, Ward GR, Wainwright PE, Fleming AS. Intergenerational effects of complete maternal deprivation and replacement stimulation on maternal behavior and emotionality in female rats. Dev Psychobiol 2001;38:11–32.

Hall WG. Weaning and growth of artificially reared rats. Science 1975;190:1313–5.

Hall FS. Social deprivation of neonatal, adolescent, and adult rats has distinct neurochemical and behavioral consequences. Crit Rev Neurobiol 1998;12:129–62.

Hall FS, Wilkinson LS, Humby T, Robbins TW. Maternal deprivation of neonatal rats produces enduring changes in dopamine function. Synapse 1999;32:37–43.

Hannigan JH, O'Leary-Moore SK, Berman RF. Postnatal environmental or experiential amelioration of neurobehavioral effects of perinatal alcohol exposure in rats. Neurosci Biobehav Rev 2007;31:202–11.

Hellemans KG, Benge LC, Olmstead MC. Adolescent enrichment partially reverses the social isolation syndrome. Brain Res Dev Brain Res 2004;150:103–15.

Kahlig KM, Galli A. Regulation of dopamine transporter function and plasma membrane expression by dopamine, amphetamine, and cocaine. Eur J Pharmacol 2003;479: 153–8.

Kalinichev M, Easterling KW, Holtzman SG. Early neonatal experience of Long-Evans rats results in long-lasting changes in reactivity to a novel environment and morphine-induced sensitization and tolerance. Neuropsychopharmacology 2002;27:518–33.

Kehoe P, Shoemaker WJ, Triano L, Hoffman J, Arons C. Repeated isolation in the neonatal rat produces alterations in behavior and ventral striatal dopamine release in the juvenile after amphetamine challenge. Behav Neurosci 1996;110:1435–44.

Kehoe P, Shoemaker WJ, Arons C, Triano L, Suresh G. Repeated isolation stress in the neonatal rat: relation to brain dopamine systems in the 10-day-old rat. Behav Neurosci 1998a;112:1466–74.

Kehoe P, Shoemaker WJ, Triano L, Callahan M, Rappolt G. Adult rats stressed as neonates show exaggerated behavioral responses to both pharmacological and environmental challenges. Behav Neurosci 1998b;112:116–25.

Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. Neuron 1998;21:467–76.

Kraemer GW. A psychobiological theory of attachment. Behav Brain Sci 1992;15: 493–541.

Kraemer GW, Ebert MH, Lake CR, McKinney WT. Hypersensitivity to D-amphetamine several years after early social deprivation in rhesus monkeys. Psychopharmacology (Berl) 1984;82:266–71.

Liu D, Caldji C, Sharma S, Plotsky PM, Meaney MJ. Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinepherine release in the hypothalamic paraventricular nucleus. J Neuroendocrinol 2000;12: 5–12.

Lomanowska AM, Rana SA, McCutcheon D, Parker LA, Wainwright PE. Artificial rearing alters the response of rats to natural and drug-mediated rewards. Dev Psychobiol 2006;48:301–14.

Lovic V, Fleming AS, Fletcher PJ. Early life tactile stimulation changes adult rat responsiveness to amphetamine. Pharmacol Biochem Behav 2006;84:497–503.

Matthews K, Hall FS, Wilkinson LS, Robbins TW. Retarded acquisition and reduced expression of conditioned locomotor activity in adult rats following repeated early maternal separation: effects of prefeeding, D-amphetamine, dopamine antagonists and clonidine. Psychopharmacology (Berl) 1996;126:75–84.

Matthews K, Dalley JW, Matthews C, Tsai TH, Robbins TW. Periodic maternal separation of neonatal rats produces region- and gender-specific effects on biogenic amine content in postmortem adult brain. Synapse 2001;40:1–10.

Meaney MJ, Brake W, Gratton A. Environmental regulation of the development of mesolimbic dopamine systems: a neurobiological mechanism for vulnerability to drug abuse? Psychoneuroendocrinology 2002;27:127–38.

Morilak DA, Barrera G, Echevarria DJ, Garcia AS, Hernandez A, Ma S, et al. Role of brain norepinephrine in the behavioral response to stress. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:1214–24.

Pryce CR, Bettschen D, Bahr NI, Feldon J. Comparison of the effects of infant handling, isolation, and nonhandling on acoustic startle, prepulse inhibition, locomotion, and HPA activity in the adult rat. Behav Neurosci 2001;115:71–83.

Pryce CR, Ruedi-Bettschen D, Dettling AC, Weston A, Russig H, Ferger B, Feldon J. Long-term effects of early-life environmental manipulations in rodents and primates: potential animal models in depression research. Neurosci Biobehav Rev 2005;29: 649–74.

Schrijver NC, Bahr NI, Weiss IC, Wurbel H. Dissociable effects of isolation rearing and environmental enrichment on exploration, spatial learning and HPA activity in adult rats. Pharmacol Biochem Behav 2002;73:209–24.

Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: effects on catecholamine systems and behavior. Annu Rev Pharmacol Toxicol 1993;33:639–77.

Vanderschuren LJ, Beemster P, Schoffelmeer AN. On the role of noradrenaline in psychostimulant-induced psychomotor activity and sensitization. Psychopharmacology (Berl) 2003;169:176–85.

Varty GB, Paulus MP, Braff DL, Geyer MA. Environmental enrichment and isolation rearing in the rat: effects on locomotor behavior and startle response plasticity. Biol Psychiatry 2000;47:864–73.

Weinshenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacology 2007;32:1433–51.

Zhang XY, Kehoe P, Kosten TA. Neonatal isolation alters estrous cycle effects on ventral striatal extracellular monoamine levels. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:504–11.