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

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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

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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.