

Early life tactile stimulation changes adult rat responsiveness to amphetamine[☆]

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Abstract

Previously, we have found that total maternal deprivation of rat pups, achieved through artificial rearing, leads to a number of behavioral and neurophysiological changes, suggesting a change in the dopamine system. The purpose of this study was to further investigate possible changes in the functioning of dopamine systems, associated with artificial rearing, by examining the locomotor stimulant effects of the dopamine releaser amphetamine and the dopamine reuptake inhibitor methylphenidate. Rats were mother-reared or artificially reared. Some of those artificially reared rats were provided with either a maximum level (artificially reared maximal stimulation) or a minimal level of maternal licking-like tactile stimulation (artificially reared minimal stimulation). In adulthood, rats' locomotion was measured after an injection of *d*-amphetamine (0, 0.25, 0.5 and 1.0 mg/kg) or methylphenidate (0, 2, 5 and 10 mg/kg). Locomotor activity in response to a novel environment was enhanced in artificially reared rats, although this effect habituated over three daily 1-h sessions. Both amphetamine and methylphenidate dose dependently increased locomotor activity. The effect of amphetamine, but not methylphenidate was greatly enhanced in artificially reared minimally stimulated rats. The enhancement of the effect of amphetamine by artificial rearing was not apparent in artificially reared maximal stimulation rats.

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1. Introduction

It is well established that the mammalian nervous system is plastic, particularly during early stages of development while the young mammals are in the care of their mothers. Alterations of this relationship between the young and the mother produce long lasting changes in the offspring's behavior and physiology (Pryce and Feldon, 2003; Hall, 1998; Kuhn and Schanberg, 1998). In rats, the separation of neonatal pups from their mothers produces a number of behavioral and neurophysiological changes that are

dependent on several factors, such as the duration and frequency of separations, as well as environmental factors such as temperature (Pryce and Feldon, 2003; Hall, 1998).

Periodic maternal deprivation paradigms have been utilized extensively in studies investigating the importance of early life social relationships on a number of behavioral and neurobiological systems. Typically, in these studies, rat pups are separated from their mothers for a period of time on daily basis. However, these procedures vary widely in: frequency and duration of separation, conditions of separation (whether alone or with siblings) and postnatal period over which separations occur (Pryce and Feldon, 2003; Hall, 1998). In general, however, the procedure usually involves separation from mother. It also involves daily changes in the environment and in ambient temperature as well as exposing pups to periodic food deprivation.

Recently, we have utilized a different separation paradigm, an artificial rearing (AR) paradigm, to study the effects of early maternal behavior and maternal stimulation, on later behavior.

[☆] All the procedures describe in this report conformed to the guidelines set by the Canadian Council on Animal Care and in accordance with Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research. The procedures were approved by the UTM and CAMH Animal Care Committees.

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This paradigm has a number of features that differentiate it from the more usual maternal deprivation paradigms. First, it allows us to rear rat pups without mothers (from postnatal day 2) in a controlled environment. Pups are not food deprived and the temperature of their environment is kept relatively stable. However, in addition to deprivation of mother, AR pups are also deprived of siblings, nest odors and other aspects of the usual nest environment. Hence, both approaches investigate the role of early postnatal environment and both approaches involve maternal deprivation. However, both also involve deprivation from other features of the early postnatal environment and frequently expose pups to new environments (Pryce and Feldon, 2003; Hall, 1998).

Periodic maternal deprivation studies have shown that separation of rat pups from their mothers produces a number of behavioral changes, including altered behavioral responses to primary and conditioned stimuli. These types of changes are associated with altered functioning of dopamine (DA) systems (Matthews et al., 1996). For example, periodic maternal separation produces changes in DA release in the nucleus accumbens (NAC) in response to central infusion of potassium (K^+) or systemic injections of amphetamine (Hall et al., 1999). Furthermore, repeated maternal separation has been associated with region specific alterations in DA levels, as maternally separated rats show increased levels of DA in the dorsal and ventral striatum, but decreased levels in the medial prefrontal cortex (PFC) (Matthews et al., 2001). To date, we have not studied the effects of total separation (AR) on DA physiology.

However, recently, we reported that pups that are reared without mothers, through artificial rearing, show changes in DA mediated behaviors (Swerdlow et al., 2001; Parwani et al., 2000; Tunbridge et al., 2004; Fletcher et al., 2003; Winstanley et al., 2005). AR pups show reduced prepulse inhibition (PPI) of the startle response, and elevations in locomotor activity and impulsive behaviour (DRL-20s) (Lovic and Fleming, 2004, 2006; Burton et al., 2006). Also, in females, artificial rearing produces deficits in the attentional set-shifting task (ASST) (Lovic and Fleming, 2004).

One of the factors that may explain the AR effect on these behaviors is the absence of licking stimulation inherent in this deprivation model. We have found that if we provide additional tactile 'stroking stimulation' to artificially reared pups we can reverse many of the behavioral and physiological changes associated with artificial rearing (Burton et al., 2006; Lovic and Fleming, 2006, 2004; Gonzalez and Fleming, 2002). These results are consistent with a growing literature showing that pups that receive more licking stimulation show reductions in their stress responses as well as alterations of hippocampal glucocorticoid receptors and a variety of other behavioral and physiological events (Fish et al., 2004; Liu et al., 1997). In addition, simulations of maternal licking, provided by experimenters, can reverse aspects of effects produced by maternal deprivation (Pryce and Feldon, 2003; Van Oers et al., 1998; Pauk et al., 1986).

Based on these findings that artificially reared rats show deficits in PPI and ASST (Lovic and Fleming, 2004) and impulsive behaviour (tests sensitive to changes in the dopamine system) and that 'stroking' reverses these effects, we were in-

terested in assessing whether motherless rearing produces changes in this neurotransmitter system. We investigated these changes by examining the effects of artificial rearing on DA-dependent locomotor activity induced by the DA releaser amphetamine and the DA re-uptake inhibitor methylphenidate.

2. Methods

2.1. Subjects

Fifty-four male Sprague–Dawley rats were used in this study. All rats, including the dams, were born at University of Toronto at Mississauga animal vivarium, which houses rats that were originally obtained from Charles River Farms in St. Constant, Quebec, Canada. Once the rats reached 60–70 days of age, they were transported to Centre for Addiction and Mental Health (CAMH) where they were tested. Throughout the study, the rats were pair-housed, with the same age and sex, non-experimental conspecifics, in medium size (W 26 × L 38 × H 21 cm) plastic cages with ad lib access to rat Purina Chow food and water. The room temperature and humidity were maintained at 22 °C and 40–50%, respectively. Lights were off between 2000 and 0800 h. All the testing was conducted between 0930 and 1830 h. All procedures conformed to the guidelines set by the Canadian Council on Animal Care and were approved by the CAMH Animal Care Committee.

2.2. Artificial rearing

Dams gave birth and on the day of parturition (postnatal day—PND 0) their litters were culled to approximately eight males and five females. On PND 2, three males were removed from the nest, two of which were implanted with a cheek cannula and raised artificially (AR; for detailed description of artificial rearing, see Gonzalez et al., 2001), while the third was sham operated and returned to his mother (mother-reared sham, MR-SHAM). The fourth male sibling was not manipulated and was designated as control (mother-reared control, MR-CON). Hence, dams were left with five male and five female pups in the nest. Two male siblings that received cheek cannulae were randomly assigned to one of two conditions: (1) artificially reared with minimal maternal-like stimulation (AR-MIN: 30-s anogenital stimulations per day—one in the morning and one at night in order to stimulate urination and defecation) or (2) artificially reared with maximal maternal-like stimulation (AR-MAX: in addition to two 30-s anogenital stimulations, these rats also received eight, 2-min general body stimulations per day; see below for further details of the procedure). Group numbers were as follows: (1) AR-MIN, $n = 14$, (2) AR-MAX, $n = 12$, (3) SHAM, $n = 14$, (4) CON, $n = 14$. A total of 14 litters was used. Only one rat per group was derived from each litter.

2.2.1. Cheek cannulae implants

Male pups (PND 2) were weighed prior to surgery, anesthetized in a bell jar with approximately 1–2 ml of halothane (2-Bromo-2-Chloro-1,1,1-Trifluoroethane, B.P., MTC Pharmaceuticals) and implanted with cheek cannulae (Gonzalez et al.,

2001). The procedure lasted less than 1 min and the pups woke up within 2 min. SHAM rats were anesthetized in an identical fashion to AR rats. A sheathed leader wire was inserted through the pups' cheeks but the cannulae were not implanted. The SHAM rats were allowed to fully wake before they were returned to their nests. In addition, they were marked with an odorless and tasteless (to humans) food coloring dye to distinguish them from CON animals.

2.2.2. Pup rearing

After the surgical implantation of the gastric cannulae, the pups were housed individually in plastic cups (11 cm in diameter \times 15 cm deep), which fitted into a second weighted cup. Both cups floated in a temperature controlled water aquarium (water maintained at $\sim 36^\circ\text{C}$). The housing cups contained corn-cob bedding (Bed O' Cobs). The tops of the cups remained open to allow cheek cannulae tubing to emerge and connect to nearby syringes containing milk formula. The infusion of milk formula (Messer diet; University of Iowa) was executed and controlled by timer-controlled infusion pumps (Harvard Apparatus Syringe, PHD 2000). The pumps were programmed to infuse the formula for 10 min every hour, 24 h daily. The amount of milk formula the pumps delivered was based on a specific fraction of the mean pup weight. We started by giving pups formula volume equal to 33% of their body weight. The amount was increased 1% each day.

Every morning the pups were disconnected from the pumps, removed from the cups, weighed and their tubing was flushed with 0.1 cc of distilled water. New syringes containing fresh formula were set up and the pump's infusion rate was reprogrammed according to the new pup weight per pump. AR-MIN rats were stimulated twice a day, 30 s each (morning and night; the required minimum) with warm, wet, camel hair paintbrush, in order to stimulate urination and defecation. Only the pups' anogenital region was stimulated. Previous experience with this paradigm has indicated that a wet brush, as oppose to a dry brush, facilitates urination and defecation. At the end of the anogenital stimulation, pups were quickly dried off by being momentarily placed on soft tissue paper. During anogenital stimulations, pups were gently held, by an experimenter, in an upright position. AR-MAX rats were stimulated eight times a day (2 min of body stimulation) in addition to two regular anogenital stimulations (30 s each). These stimulations were carried out from the day the pups were placed on the pumps (PND 3 or 4) to PND 16. The stimulations were done using a dry, soft camel-hair paintbrush (between 0900 and 2100 h). A dry brush was used in order to minimize heat loss. Pups were not touched by the experimenter during non-anogenital stimulations. On PND 17–18, all AR rats were taken off the pumps, placed individually into small cages (W 15 cm \times L 22 cm \times H 10 cm) and provided with milk formula, regular rat chow as well as the mixture of formula and rat chow.

2.2.3. Weaning and groups

On PND 21, artificially reared rats were paired up with mother reared, non-experimental, social partners with whom they remained until the adult tests. Mother reared rats were weaned from their mother and paired together (MR-SHAM and MR-CON

—from the same litter). All the rats were weighed and left undisturbed, except for the weekly cage changes, until adulthood.

2.3. Locomotor activity

The effects of amphetamine and methylphenidate on locomotor activity were assessed in four large, clear Plexiglas activity chambers (Med Associates Inc., St. Albans, VT, USA). The apparatus was a square box (W 43 cm \times L 43 cm \times H 30 cm) equipped with an array of 16 \times 16 photodetectors, spaced 2.5 cm apart and positioned 2.5 cm above the floor of the chamber. The boxes were connected via an interface to a computer that detected interruptions of the photodetectors. Distance traveled was computed from these interruptions and was used as an index of ambulatory activity.

All rats were first habituated to the apparatus by placing them in the activity chamber for 1 h on three occasions, approximately a day a part. On the test days, rats were placed in the activity chamber for a 30-min habituation period followed immediately with an injection of one of four doses of amphetamine HCl (0, 0.25, 0.5 and 1 mg/kg) or methylphenidate HCl (0, 2, 5 and 10 mg/kg). Following the injection, locomotor activity was assessed during a 90-min period. Separate groups of animals were used for amphetamine and methylphenidate testing. The doses were administered in an order determined by a Latin square. Rats had 2–3 days rest in between each locomotor test. Amphetamine-HCl was obtained from Health and Welfare, Ottawa, Canada, and methylphenidate HCl was obtained from Medisca Pharmaceutique (Saint Laurent, Quebec, Canada). Both drugs were dissolved in 0.9% saline and administered intraperitoneally, in a volume of 1 ml/kg.

2.4. Statistical analyses

Group comparisons were analyzed using repeated measures analysis of variance (ANOVA). Total activity for each session and drug dose was used as a repeated measure variable. There were no differences between MR-SHAM and MR-CON groups on any tests; thus, these two groups were combined. Since we were interested in differences between MR rats and AR-MIN and AR-MAX rats, multigroup one-way ANOVAs were followed by Dunnett post hoc tests, with MR rats as the control group. The level of significance was $p < 0.05$. All statistical analyses were made using SPSS 11.5 for Windows.

3. Results

3.1. Locomotor activity

3.1.1. Habituation

Prior to the assessment of locomotor activity levels in response to drug injections, all rats were first habituated to the activity boxes on three separate occasions (1 h each). Group differences were assessed using repeated measures analysis of variance (3 sessions \times 3 groups) using the total distance traveled for each sessions ($F_{(2,43)} = 4.64$, $p = 0.015$). Dunnett post hoc tests indicated that AR-MIN ($p = 0.019$) and AR-MAX rats

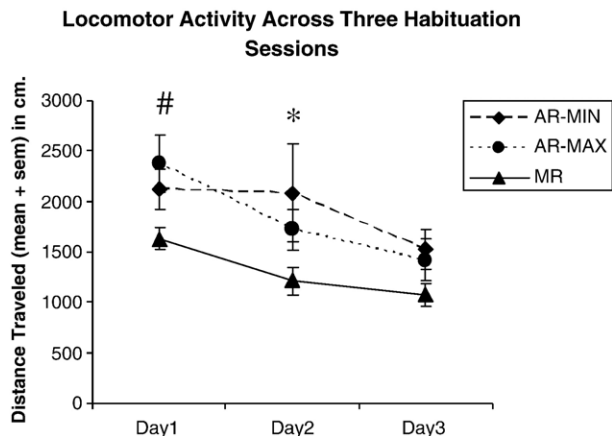


Fig. 1. The figure depicts mean (plus S.E.M.) distance traveled during three, 1-h habituation sessions. There was a main effect of group treatment. # Dunnett post hoc test indicated that AR-MAX group was significantly more active than the control group (MR) during the first habituation session ($p < 0.007$). *Same type of analysis also indicated that AR-MIN group was significantly more active than the control group (MR) during the second habituation session ($p < 0.05$).

($p = 0.048$) were significantly more active than the MR rats (see Fig. 1). As can also be seen in Fig. 1, rats' activity decreased over the three sessions ($F_{(1,43)} = 48.85$, $p < 0.0001$). There was no group by session interaction. We also had an *a priori* hypothesis about the last habituation session. We predicted that the groups should not be significantly different by the last habituation session (prior to drug testing). One-way ANOVAs indicated that neither AR-MAX nor AR-MIN group was significantly more active than the MR group during the last habituation session.

3.1.2. Amphetamine-induced locomotor activity

All three groups of rats were tested with four doses of amphetamine (0, 0.25, 0.5 and 1.0 mg/kg) during four 90-min

Amphetamine Induced Locomotor Activity

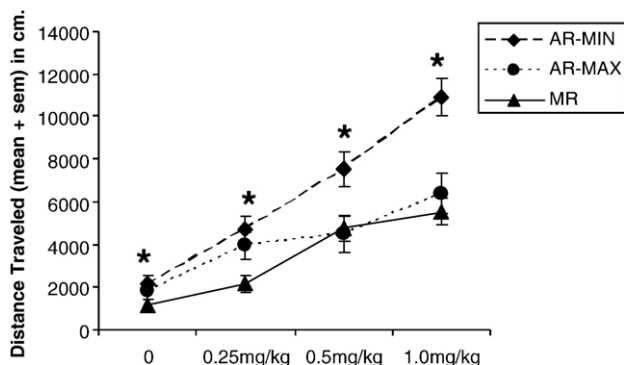


Fig. 2. Distance traveled in response to amphetamine. Repeated measures—significant group differences ($p < 0.0001$), significant effects of amphetamine dose ($p < 0.0001$) and a significant group by dose interaction effect ($p < 0.002$). Dunnett post hoc tests—AR-MIN group was significantly more active than the MR group ($p < 0.0001$). AR-MAX rats were not different from MR rats ($p > 0.334$). *One-way ANOVAs indicated that AR-MIN rats had significantly higher locomotor activity level from MR rats at 0 mg/kg ($p < 0.028$), 0.25 mg/kg ($p < 0.004$), 0.5 mg/kg ($p < 0.033$) and 1 mg/kg amphetamine doses ($p < 0.05$).

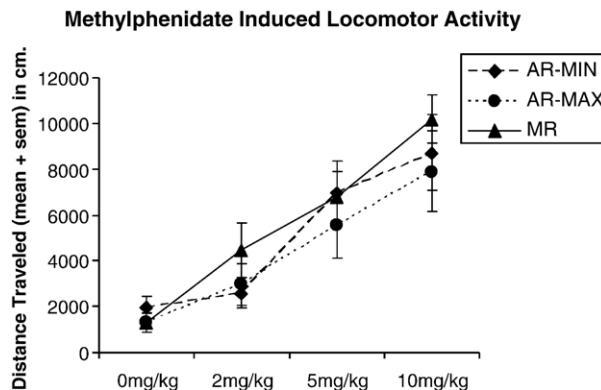


Fig. 3. Distance traveled in response to injections of methylphenidate. There was a significant effect of dose ($p < 0.05$), but groups did not respond differently at any dose of methylphenidate.

sessions. Repeated measures analyses of variance (4 doses \times 3 groups) of total distance traveled during these sessions indicated a significant group difference ($F_{(2,23)} = 14.64$, $p = 0.0001$), a significant effect of amphetamine dose ($F_{(1,23)} = 153.88$, $p = 0.0001$) and a significant group by dose interaction ($F_{(2,23)} = 8.1$, $p = 0.002$). Dunnett post hoc tests indicated that for activity the AR-MIN group was significantly different from the MR group ($p = 0.0001$). AR-MAX rats were not different from MR rats ($p = 0.334$) (see Fig. 2). One-way ANOVAs indicated that AR-MIN rats had significantly higher locomotor activity compared to MR rats at 0 mg/kg ($p = 0.028$), 0.25 mg/kg ($p = 0.004$), 0.5 mg/kg ($p = 0.033$) and 1 mg/kg amphetamine doses ($p = 0.0001$).

3.1.3. Methylphenidate-induced locomotor activity

A separate set of rats were tested for their locomotor activity in response to an injection of methylphenidate (0, 2, 5 and 10 mg/kg). Repeated measures analysis of variance (4 doses \times 3 groups) indicated a significant main effect of dose ($F_{(1,24)} = 105.753$, $p = 0.0001$), but not of group ($p = 0.401$); the dose \times group interaction was also not significant ($p = 0.547$) (see Fig. 3).

3.1.4. Body weights

In order to address the issue of physiological/nutritional effects of artificial rearing, we analyzed groups' body weights and did not find group differences ($F_{(2,53)} = 0.9$, $p = 0.4$).

4. Discussion

Artificially reared rats showed increased locomotor activity in a novel environment and in response to amphetamine, but not in response to methylphenidate. Increased locomotor activity in response to amphetamine was reversed in artificially reared rats that were provided with maternal licking-like stimulation (AR-MAX). Increased locomotor activity in novel environments and response to amphetamine is thought to be regulated by the dopamine system. This suggests that artificial rearing and tactile stimulation can alter the dopamine system.

AR rats were significantly more active in the activity boxes during the first two activity tests, but not during the third habituation session. Therefore, the AR rats seem to be more active in

response to novelty, but this effect habituates. These findings are in contrast with previous reports (Brake et al., 2004; Matthews et al., 1996) indicating that repeated periods of maternal separation do not alter novelty-induced locomotion. These differences might reflect differences in the types of ‘maternal deprivation’ utilized. In the Brake et al. (2004) and Matthews et al. (1996) studies, pups were kept within the litter during maternal deprivation. In our paradigm pups are maternally deprived but they are also deprived of social contact with siblings and other aspects of nest environment. Hence, it is possible that the inconsistencies between our study and previous studies, utilizing ‘traditional’ maternal deprivation, might be due to differences in sibling contact.

Novelty-induced hyperactivity is regulated by the DA system (Hooks and Kalivas, 1995). DA depletions in nucleus accumbens attenuate novelty-induced locomotor activity (e.g., Koob et al., 1981) and dopamine antagonists decrease novelty-induced locomotor activity without affecting the habituated locomotor activity (Hooks and Kalivas, 1995; Bardo, Bowling and Pierce, 1990). In fact, the same brain circuitry is involved in mediating the effects of amphetamine on locomotor activity (Hooks and Kalivas, 1995). This would explain the fact that AR-MIN rats showed novelty-induced locomotor hyperactivity and increased sensitivity to amphetamine. However, AR-MAX rats also showed novelty-induced locomotor hyperactivity but not increased sensitivity to amphetamine. While both novelty- and amphetamine-induced locomotor activity are mediated by the DA system(s), it is possible the artificial rearing and early life tactile stimulation affect different aspects of this system. Hence, artificial rearing produces an increase in novelty-induced and amphetamine-induced locomotor activity but tactile stimulation can only reverse increased sensitivity to amphetamine-induced locomotor activity.

Artificial rearing produced a dose-dependent increase in sensitivity to amphetamine, as AR-MIN rats were significantly more active at each dose of amphetamine. As can be seen in Fig. 2, at all doses of amphetamine, AR-MIN rats showed approximately double the locomotor activity shown by MR rats. These findings indicate that artificial rearing produces increased sensitivity to the locomotor stimulant effects of amphetamine. Strikingly, artificially reared rats that were provided with tactile stimulation (AR-MAX) were not significantly different from the mother-reared rats. However, since AR-MAX rats were not significantly different from mother-reared rats, we suggest that the lack of tactile stimulation, experienced by artificially reared rats is the cause of this increased sensitivity. From here, we conclude that early life tactile stimulation is a significant factor influencing the adult sensitivity to amphetamine. While we observed that tactile stimulation can have an effect on amphetamine responsiveness, we do not know if other aspects of early life environment that were absent during artificial rearing (e.g., social stimulation from siblings, nest odors, etc.) would have the same effect. Our data indicate that tactile stimulation is sufficient in alternating adult responsiveness to amphetamine.

While the various treatment groups were differentially sensitive to the locomotor activating effect of amphetamine, there were no group differences in their responses to methylphenidate at any dose. This discrepancy in response to two dopamine

agonists could be explained by differences in the mechanisms of action of amphetamine and methylphenidate. Methylphenidate acts as a dopamine and norepinephrine, transporter blocker, preventing the reuptake of these monoamines by the presynaptic neuron (Swanson and Volkow, 2003), whereas amphetamine exerts its effects mainly through the release of dopamine from the presynaptic neuron (Seiden et al., 1993). Because methylphenidate acts at the level of the transporter its ability to increase extracellular levels of DA, and therefore to stimulate locomotor activity, is dependent on the endogenous tone of DA neurons. The fact that locomotor responses to methylphenidate were not altered by artificial rearing suggests that the normal spontaneous activity of dopaminergic neurons is not affected by artificial rearing. Recently, Brake et al. (2004) have reported that that maternal deprivation produces reduced levels of dopamine transporter in the nucleus accumbens (core) and striatum. It seems unlikely that our manipulations produced changes at the transporter level, as our groups did not differ in response to methylphenidate (dopamine transporter reuptake inhibitor). Both methylphenidate and amphetamine elevate extracellular levels of dopamine over the dose ranges used here (Cadoni et al., 1995; Gerasimov et al., 2000). However, it is likely that amphetamine, as a dopamine releaser, produced greater levels of dopamine, perhaps proportional to the levels of activity at each drug level (see Figs. 2 and 3). This increase in dopamine is critical for the expression of the locomotor stimulant effects of both drugs since drug-induced locomotion is blocked by dopamine receptor antagonists (Koob et al., 1981). The fact that AR-MIN rats showed an increased sensitivity to amphetamine, but not to methylphenidate, would suggest artificial rearing did not alter the number or sensitivity of DA receptors. Given that it seems unlikely that AR has altered either the functional status of DA transporters or receptors, this leaves the possibility that our treatment has altered the intraneuronal aspects of DA functioning. For example, AR-MIN rats could have increased synthesis, storage and releasability of DA. Findings by Matthews et al. (2001) reporting increased DA levels in the striatum and PFC of maternally deprived rats support this hypothesis. The findings of Hall et al. (1999) are perhaps also relevant here. Using *in vivo* microdialysis, these authors found that pups deprived of maternal contact for 6h daily from PND 5 to 20 showed enhanced extracellular levels of DA in the nucleus accumbens following a challenge with amphetamine or high levels of K⁺ perfusate. This neurochemical response would be predicted to lead to enhanced locomotion in response to amphetamine, as seen here. However, while our study utilized artificial rearing, which includes maternal, sibling and nest deprivation, the above studies utilized periodic maternal deprivation.

Early life maternal deprivation is associated with several neurophysiological processes. A number of studies have shown that maternal licking of rat pups alters the functioning of the HPA axis (Francis and Meaney, 1999). Rat pups that are licked more have more “adaptive” stress response. They are able to suppress overactivity of the HPA-axis faster, once the stressors have disappeared. Maternally deprived rat pups show increased behavioral and endocrine reactivity to stress (Francis and Meaney, 1999). Increased maternal licking is correlated with an

increased number of glucocorticoid receptors in the hippocampus, which play a role in the negative feedback system of the HPA-axis. In addition, it has been shown that the HPA-axis can influence the functioning of the DA system in adult rats (Tzschentke, 2001). There is evidence that glucocorticoids regulate DA growth factors during development (Engele and Lehner, 1995). However, it is possible that the change in the dopamine system, seen in artificially reared rats, might be independent of the HPA-axis effects. Maternal deprivation has also been associated with a reduction in DNA synthesis and ornithine decarboxylase (an obligatory enzyme for normal cell growth and development), abnormal neuroendocrine secretions and suppression of cell responses to trophic hormones (growth hormone, insulin and prolactin) (Kuhn and Schanberg, 1998). Kuhn and Schanberg (1998) found that the lack of tactile stimulation, during maternal deprivation, is responsible for these effects; hence, indicating the importance of licking and other 'hidden regulators' in the mother-litter relationship that affect physiological development of the offspring (Hofer, 1994). While the studies reviewed in this paper (including our own) differ on several methodological aspects, they all suggest that early life tactile stimulation has long-lasting effects on offspring physiology and behavior. However, a direct relationship between early life tactile stimulation and changes in the DA system, through microdialysis or voltametry, in the different DA brain sites has yet to be established.

Finally, these results using the AR paradigm provide an interesting animal model for the effects of early institutionalization or stimulus deprivation in children in a variety of settings (Kreppner et al., 2001; Kuhn et al., 1991; Field et al., 1986) some of who show hyperactivity, impulsivity and inattention (Kreppner et al., 2001).

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