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The dopamine D1 receptor agonist SKF 38393 improves temporal order memory performance in maternally deprived rats

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ABSTRACT

Previously, we showed that maternal deprivation (MD) (3 h/day, postnatal-day 1–14) impaired the performance at adulthood in the object temporal order memory task (TMT) that principally implicates the medial prefrontal cortex (mPFC). Dopamine (DA) transmission in the PFC may play a critical role in the achievement of the TMT. Here, to investigate whether MD could results in dysfunction of the DA system in the mPFC, we assessed in this region the tissue contents and extracellular levels of DA and its metabolites, as the density of D1 receptor. Besides we examined whether an agonist of the DA receptor D1, the SKF38393, could have a beneficial effect on the performance of deprived (D) rats in the TMT. We observed that MD induced a significant reduction of the extracellular level of DOPAC in the mPFC and in the density of the D1 receptor in the anterior cingulate cortex, a sub-region of mPFC. On the other hand, we observed that an acute systemic injection of a D1 receptor agonist, SKF38393, was effective to correct the memory deficiency of D rats in the TMT, when administered before the retrieval phase. We showed that a stress suffered by rats during the perinatal period led to dysfunction of the adult DA system, possibly triggering greater vulnerability to cognitive and mood disorders. Interestingly, an acute administration of a D1 receptor agonist in adulthood was sufficient to improve the deficit in the temporal memory. A better understanding of this phenomenon would permit the development of treatments adapted to patients with a history of early traumatic experiences.

1. Introduction

Early life stress and childhood maltreatment increases the risk of developing psychopathology accompanied by reduced cognitive function in later life (Teicher et al., 2003). For the infant, the interaction with his mother is the most important environmental factor, since a variety of his physiological systems responds to specific elements of this interaction. Maternal separation is a commonly used model of early life neglect.

Our model of maternal deprivation (MD), a variant of maternal separation, consists of a daily separation of newborn Long-Evans pups from their mother and from their littermates for 3 h per day from postnatal days 1 to 14. In adulthood, maternally deprived (D) rats are compared with animal facility rearing (AFR) rats, which have experienced human intervention for animal care (Pryce & Feldon, 2003). We have shown that MD leads in male rats to different type of impairments or neurobiological alterations. An enhanced anxiety and reactivity to stress was observed as well as an increased preference for sucrose, a hypersensitivity to the rewarding effect of morphine, a morphine dependence, a hyposensitivity of the effect of a dopamine D3 receptor agonist, deficits in cognitive flexibility and an exaggerated synaptic plasticity in the medial prefrontal cortex (mPFC) (Baudin et al., 2012; Mourlon et al., 2010; Vazquez, Farley, Giros, & Daugé, 2005; Vazquez, Giros, & Daugé, 2006; Vazquez, Penit-Soria, Durand, Besson, Giros et al., 2005, 2007).

During the last decade, several studies using different behavioural tasks have shown that maternal separation can lead to memory impairments in adult rat. This was demonstrated with the novel object recognition task (Aisa, Tordera, Lasheras, Del Rio, & Ramirez, 2008; Hulshof et al., 2011), the Morris water maze task (Aisa, Tordera, Lasheras, Del Rio, & Ramirez, 2007; Hui et al., 2011; Huot, Plotsky, Lenox, & McNamara, 2002; Mello, Benetti,

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Cammarota, & Izquierdo, 2009; Uysal et al., 2005; Zhu et al., 2010) and the radial arm maze task (Sandstrom & Hart, 2005). In addition, we have recently demonstrated that rats subjected to MD performed poorly in the object temporal order memory task (TMT) (Baudin et al., 2012). This task, adapted from the object recognition task by Mitchell and Laiacona (1998), assesses the ability to remember the temporal order of appearance of items and thus discriminate objects encountered at different times in the past.

In rat, several studies provided support that the mPFC is involved in memory for temporal order. It was initially shown that mPFC lesions induced memory deficits on tests of temporal order memory for spatial locations (Chiba, Kesner, & Reynolds, 1994; Kesner & Holbrook, 1987). Moreover, performance in the TMT relies critically on the mPFC and its networks as demonstrated by inactivation or lesion of the mPFC (Barker, Bird, Alexander, & Warburton, 2007; Hannesson, Howland, & Phillips, 2004; Mitchell & Laiacona, 1998). On the other hand, experimental data suggest the involvement of dopamine (DA) transmission in the object temporal order memory. Indeed, administration of an agonist of the D1 receptor before the memory testing trial of the TMT improves the abilities to retrieve previously acquired temporal information (Hotte, Naudon, & Jay, 2005). In the present study, we investigated whether MD resulted in changes in the contents of DA and its metabolites in the mPFC, as well as in their extracellular levels quantified after microdialysis and in the density of D1 receptors. Finally, we investigated whether the D1 agonist SKF 38393 administered before the retrieval phase in the TMT, could have a beneficial effect on the performance of D rats.

2. Material and methods

2.1. Maternal deprivation procedure

Experimental procedure and animal care were performed in accordance with local committee guidelines and the European Communities Council Directive of November 24, 1986 (86/609/EEC). Two cohorts of 20 and 26 pregnant Long-Evans rats (Janvier, Le Genest St. Isle, France) were received on day 14 of gestation. The dams gave birth 1 week after inclusion. MD was performed as previously described (Baudin et al., 2012; Mourlon, Naudon, Giros, Crumeyrolle-Arias, & Daugé, 2011; Mourlon et al., 2010). On the postnatal day 1, litters were cross-fostered culled to eight to twelve pups, half females-half males randomly chosen. Neonates of the maternal deprivation group were individually placed in temperature (30–34 °C) and humidity-controlled cages. D pups were isolated 3 h daily (2 pm–5 pm) from days 1 to 14. AFR pups remained with their mothers during this period and received no specific handling other than changing the bedding in their cages once a week. On day 22, pups were weaned and housed in groups of two or three. Only male rats were included in the study and each individual has been used only for one of the biochemical quantifications or for the TMT experiment. All the experimentations were performed on rats from the first cohort, with the exception of the measurement of extracellular DA that was performed on rats from the second cohort.

2.2. Homogenate preparation for HPLC determination

Rats (109–110 days old; AFR, $n = 12$; D, $n = 12$) were killed by decapitation. The mPFC was collected and homogenised with a Potter–Elvehjem type homogenizer in 1 mL ice cold perchloric acid 0.1 N containing 0.1% cysteine. The homogenates were centrifuged (10,000*g*, 10 min at 4 °C). The supernatants were filtered by pressure through 0.45-μm filters (Millipore, Ireland) and then stored at −80 °C until use. The pellets were resuspended in NaOH (0.1 M) and used for protein determination.

2.3. Surgery and brain dialysis

Surgery and microdialysis experiments were performed as previously described in Vazquez, Penit-Soria et al. (2005) (slightly modified).

Surgery: Rats (90–120 days old; AFR, $n = 7$; D, $n = 8$) were anesthetized by i.p. injection of chloral hydrate (400 mg/kg) and unilaterally implanted with stainless steel cannula guide (CMA 11, CMA/Microdialysis, Phymep, Paris) in the mPFC. The stereotaxic coordinates were: anteriority +3 mm, laterality +0.6 mm from bregma, depth −2.8 mm from the skull surface (Paxinos & Watson, 2005). Then the guide cannula was fixed to the skull with dental cement and inox screws. The microdialysis experiment was conducted 8–10 days after guide cannula implantation.

Brain dialysis: The evening before the experiment, the rats were transferred to the experimental cage ($40 \times 40 \times 40$ cm) with *ad libitum* access to food and water to habituate the rats to this new environment and to the connection system of the dialysis. The next morning, the microdialysis probe (diameter 0.25 mm; CMA 11, CMA/Microdialysis, Phymep, Paris) was inserted through guide cannula into the mPFC. The freely moving rat was continuously perfused with a dialysis buffer: NaCl 140 mM, KCl 4 mM, $CaCl_2$ 1.2 mM, $MgCl_2$ 1 mM, Na_2HPO_4 1.9 mM, NaH_2PO_4 0.1 mM, pH = 7.4, at a rate of 2 μL/min by means of a seringue pump (Precinorm; Infors, Bottmingen, Switzerland) via a channel liquid swivel. After 2 h of perfusion, three samples were collected for 20 min each in tube containing 20 μL of perchloric acid 1 M and cysteine 0.1% and maintained in dry ice. The samples were stored at −80 °C until the quantification of DA and its metabolites.

Histological control: After microdialysis experiment, rats were killed by decapitation. The brains were removed, frozen then cut on a microtome (Leitz, Wetzlat, Germany), and the slices (30 μm) were stained with cresyl violet. The position of the probe was estimated according to the atlas of Paxinos and Watson (2005). Probes that traversed >70% of the mPFC were considered to be placed correctly.

2.4. HPLC determination of DA and its metabolites

Levels of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 3-methoxytyramine (3MT) in homogenates prepared from mPFC or dialysates obtained from mPFC were determined using a reverse-phase ion-pair HPLC system with electrochemical detection. The HPLC system consisted of a pump (LC10AD VP, Shimadzu, Kyoto, Japan) connected to a C18 reversed phase column Supelcosil (3.0×150 mm, 3 μm, Sigma–Aldrich, Bellefonte, PA, USA) coupled to an electrochemical detector (Decade II, Antec, Leyden, Netherlands) with a glassy carbon electrode set at 0.6 V vs. Ag/AgCl reference electrode. The mobile phase consisted in KH_2PO_4 73.4 mM, methanol 125 mL/L, octan-1-sulphonic acid sodium salt 0.46 mM and Na_2EDTA 0.15 mM at pH 3.75. This solutions was filtered through 0.45-μm cellulose acetate filters (Millipore) and delivered at a 0.4 mL/min flow rate. Twenty-microlitre samples were injected into the HPLC system by means of an automatic device (AS300, Spectra Physics, San Jose, CA, USA). Chromatograms were recorded and integrated by PC integration Azur software (Datalys, Le Touvet, France).

2.5. Autoradiographic labelling of the dopamine D1 receptor

Rats (84–89 days old; AFR, $n = 10$; D, $n = 10$) were killed by decapitation. Their brains were quickly removed and frozen in isopentane at −30 °C. Twenty micrometer-thick frontal brain sections (anteroposteriority 5.16 mm to 2.52 mm from bregma according to Paxinos and Watson (2005)) were cut at −20 °C, thaw-mounted on Superfrost Plus® slides and stored at −80 °C