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Maternal deprivation induces deficits in temporal memory and cognitive flexibility and exaggerates synaptic plasticity in the rat medial prefrontal cortex

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ABSTRACT

Early life adverse events can lead to structural and functional impairments in the prefrontal cortex (PFC). Here, we investigated whether maternal deprivation (MD) alters PFC-dependent executive functions, neurons and astrocytes number and synaptic plasticity in adult male Long-Evans rats. The deprivation protocol consisted of a daily separation of newborn Long-Evans pups from their mothers and littermates 3 h/day postnatal day 1–14. Cognitive performances were assessed in adulthood using the temporal order memory task (TMT) and the attentional set-shifting task (ASST) that principally implicates the PFC and the Morris water maze task (WMT) that does not essentially rely on the PFC. The neurons and astrocytes of the prelimbic (PrL) area of the medial PFC (mPFC) were immunolabelled respectively with anti-NeuN and anti-GFAP antibodies and quantified by stereology. The field potentials evoked by electrical stimulation of ventral hippocampus (ventral HPC) were recorded in vivo in the PrL area. In adulthood, MD produced cognitive deficits in two PFC-dependent tasks, the TMT and ASST, but not in the WMT. In parallel, MD induced in the prelimbic area of the medial PFC an upregulation of long-term potentiation (LTP), without any change in the number of neurons and astrocytes. We provide evidence that MD leads in adults to an alteration of the cognitive abilities dependent on the PFC, and to an exaggerated synaptic plasticity in this region. We suggest that this latter phenomenon may contribute to the impairments in the cognitive tasks.

1. Introduction

Early life adversity, such as emotional neglect and/or sexual, physical and psychological abuse may predispose individuals to psychiatric conditions (for review see McCrory, De Brito, & Viding, 2010). For the infant, the interaction with its mother is the most important environmental factor, since a variety of its physiological systems responds to specific elements of this interaction. The animal models of maternal separation (MS) have been useful tools to demonstrate that the disruption of mother–child interaction results in an alteration of normal growth and development of the infant. Particularly, several studies showed that long MS procedures ($\geqslant$3 h per day) induce long-lasting effects on the hypothalamo–pituitary–adrenal axis in male rats, resulting in an increased response to stress (for review see Pryce & Feldon, 2003).

We have previously developed a particular model of MS, a model of maternal deprivation (MD) which consisted of a daily separation of newborn Long-Evans pups from their mothers and also from their littermates for 3 h per day from postnatal days 1 to 14. Later, the adult 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

Abbreviations: AFR, animal facility rearing rats; ASST, attentional set-shifting task; D, maternally deprived rats; HPC-mPFC, hippocampal-medial prefrontal cortex pathway; LTP, long-term potentiation; MD, maternal deprivation; mPFC, medial prefrontal cortex; MS, maternal separation; PFC, prefrontal cortex; PrL, prelimbic area; TMT, temporal order memory task; ventral HPC, ventral hippocampus; WMT, Morris water maze task.

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shown that MD leads in male rats to an enhanced anxiety and reactivity to stress, increased preference for sucrose, hypersensitivity to the rewarding effect of morphine and morphine dependence (Mourlon et al., 2010; Vazquez, Farley, Giros, & Daugé, 2005; Vazquez, Giros, & Daugé, 2006; Vazquez, Penit-Soria et al., 2005).

The prefrontal cortex (PFC), which orchestrates the integration of cognition, emotion and action through its cortical and subcortical networks, has been described as a brain region very sensitive to the detrimental effects of the exposure to chronic stress (for review see Arnsten, 2009). The MS indeed results in various impairments of the PFC in adolescent and adult rats, including modified proteins expression (Brenhouse & Andersen, 2011; Chocyk, Dudys, Przyborowska, Maćkowiak, & Wędzony, 2010), changed dendritic morphology (Monroy, Hernandez-Torres, & Flores, 2010; Muhammad & Kolb, 2011; Pascual & Zamora-Leon, 2007) and altered neuronal activity (Benekareddy, Goodfellow, Lambe, & Vaidya, 2010;Stevenson, Halliday, Marsden, & Mason, 2008). In human, functional imaging studies reveal structural and functional impairments in the PFC in patients with psychiatric disorders, particularly those reporting childhood maltreatment or adversity (Tomoda et al., 2009; van Harmelen et al., 2010). However, to date, the details as to how the MS affects cognitive functions in rodent models and how such cognitive changes are supported at the cellular level are largely unknown. In the present study, we aimed to examine the influence of MD on cognitive performance in adult male rats. Following MS protocols, several studies have investigated behavioral tasks such as the novel object recognition task (Aisa, Tordera, Lasheras, Del Rio, & Ramirez, 2007; Benetti et al., 2009; Hulshof et al., 2011), the Morris water maze task (WMT) (Aisa et al., 2007; Grace, Hescham, Kellaway, Bugarith, & Russell, 2009; Hui et al., 2011; Huot, Plotsky, Lenox, & McNamara, 2002; Lai et al., 2006; Mello, Benetti, Cammarota, & Izquierdo, 2009; Pryce, Bettschen, Nanz-Bahr, & Feldon, 2003; Uysal et al., 2005; Zhu et al., 2010) and the radial arm maze task (Sandstrom & Hart, 2005). The majority of these studies described cognitive impairments in MS rats, with the exception of Pryce et al. (2003), who observed an improvement in memory performance, and some studies showing no effects (Grace et al., 2009; Lai et al., 2006). Here, we chose to use two tasks in which the performance relies critically on the PFC and its networks as demonstrated by inactivation or lesion of the PFC. First, the temporal order memory task (TMT) assesses the ability of rats to discriminate objects that have been encountered at different times in the past (Hannesson, Howland, & Phillips, 2004; Mitchell & Laiacona, 1998). Second, the attentional set-shifting task (ASST) is equivalent to the Wisconsin card-sorting test used in human subjects to diagnose frontal lobe damage; in ASST, complex stimuli differ along perceptual dimensions, allowing the assessment of the capacity of rats to acquire, maintain and shift attentional set (Birrell & Brown, 2000; McAlonan & Brown, 2003). We completed these studies by testing the spatial learning of AFR and D rats in the WMT, for which the role of the PFC does not appear to be critical (for review see Wang & Cai, 2008).

Long-term potentiation (LTP) and long-term depression are models of activity-dependent facilitation and reduction of synaptic transmission thought to underlie learning and memory (Bliss & Collingridge, 1993). It is still unknown however whether MD modifies synaptic transmission in the PFC and, if so, whether such changes are correlated with changes in executive cognitive functions. The hippocampal-medial PFC (HPC-mPFC) pathway is a monosynaptic glutamatergic projection (Ferino, Thierry, & Glowinski, 1987; Jay & Witter, 1991) that can support plastic changes as it can be potentiated, depotentiated and depressed (for review Laroche, Davis, & Jay, 2000). Importantly, this pathway is known to be involved in executive functions (Devito & Eichenbaum, 2011; Marquis, Goulet, & Dore, 2008; Wang & Cai, 2008). Therefore, we conducted a series of in vivo electrophysiological experiments to monitor synaptic responses in the HPC-mPFC pathway. We focused on LTP in the prelimbic (PrL) area of the medial PFC (mPFC) using high-frequency stimulation protocol previously described in the studies above-mentioned. In addition, as previous studies have suggested that maternal separation can lead to change in the number of cells in the brain (Leventopoulos et al., 2007; Llorente et al., 2009; Musholt et al., 2009), we tested, by immunohistochemical labeling and stereological quantification, whether MD altered the number of neurons and astrocytes in the PrL area of the mPFC.

2. Methods and materials

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). Four series of 20 pregnant Long-Evans rats were received on day 14 of gestation (Janvier, Le Genest St. Isle, France). The dams gave birth 1 week after inclusion. MD was performed as previously described (Mourlon, Naudon, Giros, Crumeyrolle-Arias, & Daugé, 2011; Mourlon et al., 2010). On the postnatal day 1, litters were cross-fostered culled to 8–12 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 (AFR, $n = 50$; D, $n = 49$) were included in the study, and each individual has been used only for one test or quantification.

2.2. TMT procedures

During the four days preceding the task, 11 AFR and 11 D rats (80 days old) were handled daily and habituated to the open-box ($100 \times 100 \times 60$ cm; lighting, 50 lux) and the test room as previously described (Naudon, Hotte, & Jay, 2007). At the fifth day, the task consisted of two consecutive sample phases and one test phase of 4 min each. In the first sample phase, rats were allowed to explore two identical objects (12–15 cm height) fixed (Patafix®) on the floor of the box in position 3 cm from the back and 12 cm from the side walls. One hour later, rats received a second sample phase with two copies of a new object. After an additional delay of 3 h, one "old object" from the 1st sample phase and one "recent object" from the 2nd sample phase were presented during the test phase. The time exploring each object (i.e. directing the nose to the object at a distance $\leqslant 2$ cm) was scored on videotape. The discrimination ratio was calculated as ((time spent exploring the old object) − (time spent exploring the recent object))/(time spent exploring both objects).

2.3. ASST procedures

The procedure was adapted from Birrell and Brown (2000). In a white open rectangular box ($45 \times 70 \times 60$ cm; lighting, 50 lux), two digging ceramic bowls (7 cm diameter, 4 cm depth) were placed at one end of the box, with a central divider between them. The bait was a piece of chocolate-flavored cereal (Chocapic®) hidden at the bottom of the bowl that contains the relevant stimulus. Chocolate powder was added to each bowl to ensure that the rat might not recognize the bait to the smell. Each bowl was defined by an odor-medium association. A removable wall separated the bowls compartment from the other half of the box and indicated