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Research report

Maternal deprivation induces depressive-like behaviours only in female rats

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ABSTRACT

Maternal deprivation (MD) has been developed to study the effects of early adverse experiences on behaviour and neurobiology. It has been proposed to represent a potential animal model of major depression. The purpose of our study was to examine the responses induced by MD in male and female adult Long-Evans rats in tasks designed to explore depressive-like behaviours (forced swimming test (FST), repeated open space swim test (OSST), sucrose solution consumption) and in the novel object recognition and object location tasks. A consistent sexual dimorphism was observed in the responses of male and female rats that underwent MD. In male rats, MD led to increased transitions between behaviours in the FST and increased consumption and preference for sucrose (1%) in comparison with non-deprived rats. In female rats, MD induced a decreased swimming activity on the second day of the OSST and reduced the cognitive performance in an object location task. In both sexes, MD did not alter the swimming activity in the FST and the performance in a novel object recognition task. These divergent responses in male and female rats can be related to the gender differences which exist in depression. However, due to the low amplitude of responses obtained in our study, the MD model in Long-Evans rats does not seem to mimic symptoms of major depression. In contrast, our present results suggest the use of the MD model, especially in females, as a model of the dysthymia, a mild chronic-depressive condition, which has been related to poorer maternal relationship.

1. Introduction

Early adverse life experiences represent one of the major risk factor for the development of mental disorders such as major depression. The early postnatal period is characterized by considerable plasticity of the developing nervous system. As such, the early postnatal environment is critical in its capacity to influence adult behaviour. Preclinical studies have provided direct evidence that early life stress leads to heightened responsiveness to stress and alteration in the hypothalamo-pituitary-adrenal system throughout the lifespan [27,59,62]. Among the paradigms used to study early adverse life events, long maternal separation in rodent mimics the early life neglect/loss of parents in humans and has been presented as one of the most potent natural stressor during development. Maternal separation has been developed to examine the consequences of early adverse experiences on behaviour and neurobiology. This model has been described as a model of vulnerability to drug dependence, anxiety, stress-induced illness and depression (reviewed in [5,22,26,49,72,73]).

Particularly, the maternal separation has been proposed to represent a potential animal model of major depression. For instance, in adult male rats that experienced maternal separation, antidepressants can normalized anxiety-like behaviour, endocrine stress response and preference for ethanol (reviewed in [30,40]). On the other hand, one study indicated that adult separated male rats presented impaired avoidance in a learned helplessness procedure in comparison with control rats [65].

In several studies, separated male rats showed a higher immobility in the forced swimming test (FST), which was interpreted accordingly as a depression-like behaviour [1,19,42,43]. Indeed, immobility in the FST has been described as a symptom of behavioural despair and has been proposed to represent

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a depression-like state [60]. This latter assertion is open to extensive discussion although all the major classes of antidepressants are known to decrease the duration of immobility [10,80]. Similarly, several studies in male showed a decrease in sucrose consumption as a result of maternal separation, which is thought to reflect anhedonia [1,30,66,67]. However, the higher immobility in the FST and the decreased preference for sucrose were not found in all maternal separation studies [46,48,68]. Furthermore, some studies have even described opposite behaviours, such as lower immobility in the FST [67] and increased preference for sucrose [52,72,73]. Despite the well-known higher prevalence in women (for review see [13,35,47,76]), the majority of studies seeking to link the model of maternal separation and depressive-like behaviour has been conducted almost exclusively in male rats. Among the studies in females, sucrose preference has not been shown to be modified [47,51,67], and swimming activity in the FST has been described either as decreased [2] or unaffected [67].

In our maternal deprivation (MD) model, Long-Evans pups are separated from their mother and littermates 3 h/day from the age of 1–14 days. Later, adult deprived (D) rats are compared with non-deprived rats, which have experienced human intervention for animal care. This latter control group was named animal facility rearing (AFR) group [61]. We have previously shown that MD leads in male rats to an enhancement of anxiety, increased preference for sucrose, hypersensitivity to the rewarding effect of morphine and morphine dependence, accompanied by hypoactivity of the enkephalinergic systems and by changes of D3 dopamine receptors functioning in the brain [72–75].

So far we have not explored MD as a model of vulnerability to depression. Owing the co-morbidity between anxiety, depression and addiction, we are now interested to search on the impact of MD on depressive-like behaviours in both sexes. The goal of our study was to investigate whether MD, in male and female Long-Evans rats, may produce depression-like states of helplessness or anhedonia, and an alteration of cognitive performance, which is clearly associated with depression (for reviews see [7,12,33]). To answer these questions we have measured their swimming activity in the FST and in a variant of the FST, the open space swim test (OSST), assessed their sucrose consumption with a two-bottle-choice drinking paradigm and evaluated their memory performance in a non-spatial and a spatial memory tasks, the novel object recognition task and the object location task.

2. Materials and methods

2.1. Subjects

Four series of pregnant Long-Evans rats on day 14 of gestation (Janvier, Le Genest St. Isle, France) were used to generate 4 lots of females and males (lot A, lot B, lot C and lot D).

The dams gave birth 1 week ± 12 h after inclusion. Litters and adult rats were housed in clear plastic cages in a well ventilated, temperature-controlled (22 ± 1 °C) and humidity-controlled (50 ± 5%) environment on a 12 h light/dark cycle (lights on from 8:00 a.m. to 8:00 p.m.). Dams received rat chow and water *ad libitum*, and the cages and all of the shavings were changed only once per week to avoid excessive handling. "Principles of laboratory animal care" were followed. The experimental procedure and care of the animals were in accordance with local committee guidelines and the European Communities Council Directive of November 24, 1986 (86/609/EEC).

The rats from the lot A were studied in the FST (males and females AFR, D; $n = 10$). Rats of the lot B were tested in the OSST (AFR, $n = 18$; D, $n = 19$) or in object recognition tasks (males and females AFR, D; $n = 12$). Sucrose preference was measured in male rats from the lot C (AFR, $n = 8$; D, $n = 9$) and in female rats from the lot D (AFR, D; $n = 13$).

2.2. MD

MD was slightly modified from Vazquez et al. [72]. The day of birth was designated day 0. On postnatal day (PD) 1, litters were cross-fostered and culled to eight to twelve pups, half females–half males. Random redistribution of pups among dams was done to redistribute possible effects of genetic and prenatal factors and to obtain similar litter size. It cannot be excluded that litters may have suffered from prenatal stress due to the transport of pregnant rats and that cross-fostering may change maternal behaviour. However, the same procedure was applied in all pups from the AFR and D groups before deprivation, allowing valid data comparison. The litters were each assigned to an experimental group. From day 1 up to day 14, mothers were removed from their home cage and put in a new cage, the same at each separation, for 3 h, always from 1:30 to 4:30 p.m. Neonates belonging to the D group were individually placed in temperature-controlled (30–34 °C) and humidity-controlled cages divided into compartments in a room separated from their mothers. The pups' cages contained 2 cm of fresh shavings covered with absorbing paper. At the end of the deprivation period, each litter was replaced in the housing cage and the dam was transferred back to the housing cage. To reduce handling to a minimum, pups were transferred from and to their cages quickly and gently. The same procedure was applied at each deprivation. Rat pups not subjected to MD (AFR group) remained with their mothers during this period and received no special handling other than that necessary to change the bedding in their cages once per week. From PD 15 to PD 21, all pups remained with their mothers. On PD 21 or 22, pups were weaned from their mothers and housed by gender in groups of two, three or four. All animals received rat chow and water *ad libitum*.

2.3. Forced swimming test (FST)

The procedure was performed as previously described [57], according to Porsolt et al. [60] modified by Lucki and coworkers [18]. The rats were placed in individual Plexiglas cylinders (46 cm × 20 cm in diameter) filled with water (24 ± 1 °C) up to 30 cm from the bottom. The procedure consisted of two swimming sessions conducted between 9:00 and 18:00 h: a 15-min pre-test was followed 24 h later by a 5-min test (test phase). A rat was judged to be immobile when it floated and made only movements necessary to keep the head above the water. During the 5-min test phase, three behavioural parameters, immobility, swimming and climbing, were recorded. At the end of both swimming sessions, the rats were removed from the cylinders, dried with towels, placed in cages for 15 min rest and recovery, and then returned to their home cages.

2.4. Open space swimming test (OSST)

The OSST is a variant of the FST, which has been recently developed and pharmacologically validated. This test consists of successive swimming trials performed in a large pool, which induce progressive depressive-like behaviour resulting from a lack of motivation to escape [69]. In the short version of the OSST, described by Sun and Alkon [70], the rats underwent three 400-s trials at 2 h intervals during the same day. Since, the authors observed a progressive decrease of the swimming activity of female but not of male rats, we increased the trial duration to 600 s. In our version of the short OSST version, the rats were placed individually in the middle of a circular stainless-steel pool (150 cm diameter, 60 cm height) filled to a depth of 29 cm with water maintained at 24 ± 1 °C and made opaque using a white aqueous emulsion (Acusol OP 301 opacifier, Rohm Haas, France). The first day, the test consists of three 600-s trials at intervals of 2 h between the trials. It was conducted between 12:00 and 18:00 h. The next day, a forth 600-s trial was realized 15 h later. Rats were free to swim during each trial and were then returned to their home cages after drying. The swimming distance was monitored with a video tracking system, which included an overhead camera connected to an image analyzer and a computer (VideoTrack XP 2.5, View Point, Champagne-au-Mont-d'Or, France). The distance moved includes all the distance moved during the 600-s trial, as caused by active swimming as well as slow drifts.

2.5. Sucrose solution consumption

The consumption of sucrose (Sigma) solution (1%) was assessed with a two-bottle-choice drinking paradigm on AFR and D rats. During 4 days, the rats were isolated and accustomed to the presence of two bottles of water. The day preceding the sucrose solution intake test, rats were deprived of food and water for 24 h. The rats were trained to consume sucrose solution with choice of water in three sessions with 2 days of interval, as previously described [73,79]. The beverages were presented for 60 min in standard drinking bottles with a 5 cm stainless-steel spout. Bottles were reversed at each test session to control for side preference. Two days after the last training session, sucrose solution with choice of water was given for 60 min, and the sucrose solution and water consumption in ml/kg of body weight were calculated as the difference between the volume before and after drinking. The preference ratios were calculated as the amount of sucrose consumed divided by the total fluid intake.

2.6. Novel object recognition task and object location task

The novel object recognition task is based on the preference displayed by rats for investigating novel rather than familiar objects [20]. The second task, the object location task, assessed spatial memory; the rats are presented with two identical, familiar objects, one of which is in its previous location while the other is in a new location. Normal rats spontaneously spend more time exploring the object in the new location [21].