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Insulin-like growth factor 1 reduces age-related disorders induced by prenatal stress in female rats

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Abstract

Stress during the prenatal period can induce permanent abnormalities in adult life such as increased anxiety-like behavior and hyperactivity of hypothalamo-pituitary–adrenal (HPA) axis system. The present study was designed to investigate whether prenatal stress could induce spatial learning impairment in aged female rats. Furthermore, since it has been recently reported that insulin-like growth factor 1 (IGF-1) attenuates spatial learning deficits in aged rats and promotes neurogenesis in the hippocampus, we assessed the impact of a chronic infusion of IGF-1 on age-related disorders. Our results show that females stressed during prenatal life exhibit learning impairments in the water maze task. Chronic IGF-1 treatment restores their spatial abilities, reduces their HPA axis dysfunction and increases plasma estradiol levels. Parallel to these effects, chronic IGF-1 up-regulates neural proliferation in the dentate gyrus of the hippocampus. These findings support the hypothesis of an early programming of the vulnerability to some neurological diseases during senescence and reinforce the potential therapeutic interest of IGF-1 during brain aging.

Keywords: Perinatal environment; Stress; Learning; Water maze; Dentate gyrus; Neural cells proliferation; BrdU; Neurotrophin; Glucocorticoids; HPA axis; Estradiol; Aging

1. Introduction

Stressful events occurring during early life could increase vulnerability to the effects of stress later in life [19]. In rats, chronic stress during pregnancy exerts profound long-term influences on the offspring [33,54]. Prenatal stress induces an increase of the hypothalamo-pituitary–adrenal (HPA) axis activation in adult animals that is associated with a reduction in the number of hippocampal corticosteroid receptors [25,34]. This can be evidenced by a more prolonged elevation of plasma corticosterone after exposure to stress [34,51,55,56]. These HPA dysfunctions have been reported in young and aged animals, therefore suggesting a permanent effect of early stress [51]. In the brain, the main target of adrenal steroids is the hippocampal formation, which is involved in spatial memory processes [13]. Hippocampal neurons show remarkable plasticity, involving long-term potentiation, dendritic remodeling and neurogenesis, as well as a strong vulnerability to stressful experiences and to aging processes [20,38]. A recent study has provided evidence of a decrease of hippocampal neurogenesis after prenatal stress [28] and it was previously reported that prenatal stress increased age-related learning impairments [51]. Thus, HPA axis alterations by prenatal stress may be involved in the spatial memory impairments observed during aging, in agreement with the hypothesis of a "feed-forward" cascade whereby prolonged exposure to glucocorticoids damages the hippocampus and leads to cognitive deficits [45,46].

Extensive research suggests that exercise could have benefits for health and cognitive function particularly in aged individuals [9,11]. IGF-1 appears to play a major role in the effects of exercise on brain [6]. It regulates neurotrophic

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response after injury [7], brain vasculature [47], brain glucose consumption [8], increases mRNA of brain-derived neurotrophic factor [6] and stimulates hippocampal neurogenesis [2,50]. Interestingly, aging is associated with reductions in the plasma and brain levels of IGF-1 [49].

Although considerable evidences show a link between stress, HPA axis dysfunction, memory disorders and aging, only one study has addressed the effect of prenatal stress on cognition in aged male rats [51] and nothing is known on the consequences of prenatal stress in aged females. Furthermore, females are known to be more vulnerable to stress [24] and exhibit an hyperactivity of the HPA axis function in comparison to male animals [57]. The aim of the present study was then to characterize the cognitive effect of prenatal stress in aged female rats and to determine whether IGF-1 could correct age-associated disorders. Therefore, we evaluated the spatial learning abilities of 24 month-old females that had been exposed to prenatal stress and we tested the effect of chronic infusions of IGF-1 on spatial performances, HPA axis function, estradiol levels and cell proliferation in the dentate gyrus.

2. Materials and methods

2.1. Animals and prenatal stress procedure

Sprague Dawley female rats were maintained on a 12:12 h dark:light cycle (lights on from 8 a.m. to 8 p.m.), with free access to food and water. Manipulation of the animals was performed following the principles of laboratory animal care published by the French Ethical Committee and the rules of the European Union Normative (86/609/EEC). Special care was taken to minimize animal suffering and to set the number of animals to the minimum required. During the last week of pregnancy, from day 14 until parturition, pregnant females were individually placed in plastic transparent cylinders (7 cm diameter, 19 cm long) and exposed to bright light for 45 min [25,34]. Animals were submitted to such three daily stress sessions (9 a.m., 12 p.m. and 5 p.m.), whereas control pregnant females were left undisturbed in their home cages. After weaning (21 days old), the offspring were housed in groups of four and left undisturbed. A maximum of two females by litter were used to avoid any "litter effect". Animals with signs of respiratory distress or tumors were excluded. Two groups of 24 month-old animals were constituted: old control; old prenatally stressed. Moreover, a separate set of 2 month-old Sprague Dawley females (Charles River, France) was assigned to the young group.

2.2. Surgery

Animals were anesthetized using ketamine (50 mg/kg, i.p.) and xylazine (5 mg/kg, i.p.). A 28-gauge steel cannula (Alzet-2004® brain infusion kit) was implanted into the right lateral ventricle (from bregma, anteroposterior: 0.8 mm, lateral: 1.5 mm; coordinates based on Paxinos and Watson [40]) and connected to an Alzet® osmotic minipump that was placed subcutaneously in the neck/shoulder region. Animals subjected to prenatal stress received either vehicle (NaCl) or recombinant human IGF-1 (GroPep, Australia), delivered at a rate of 50 ng per 0.25 μl/h for 21 days (Fig. 1). The remaining old rats as well as a group of 2-month-old young females served as controls and were infused with NaCl.

2.3. Water maze

The water maze task has been validated as a valuable index of spatial learning in aged rodents [14,30]. Apparatus consisted of a plastic tank, 2 m in diameter and 0.6 m in height. The tank was filled with water ($22 \pm 2\,^{\circ}C$) to a depth of 35 cm [51,52]. The platform (10 cm diameter) was 2 cm above the surface of the water during the pretraining and 3 cm below the surface of the water during spatial learning. The pool, walls and platform were all colored black and indirect lighting was used in the room, enabling the platform to be hidden from sight. Extra-maze visual cues around the room remained in a fixed position throughout the experiment.

The timeline is illustrated in Fig. 1. Before spatial learning assessment, three sessions (consisting of three daily trials) of pretraining with a visible platform were conducted in order to train the rats to swim and climb onto the platform. This procedure allows to reduce the non-cognitive components of this task (stress reactivity, motor performances) and to control any difference between experimental groups in visual or motor abilities. Four days later, preoperative spatial learning performances were evaluated using a submerged platform (positioned in a different site from the pretraining). Three sessions were conducted, each consisting of three trials with

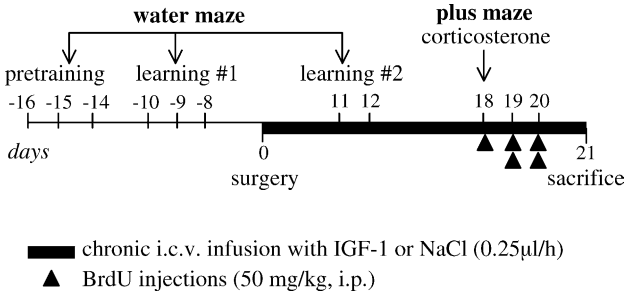

Fig. 1. Experimental design. The 24 month-old (control and subjected to prenatal stress) and 2 month-old young female rats were tested in the water maze. First, 16 days before surgery, animals received three sessions of pretraining with a visible platform, then they were evaluated for three sessions of spatial learning with a hidden platform (#1). One week later, an Alzet minipump was implanted for a chronic treatment with IGF-1 or NaCl. After 11 days of infusion, they were tested in water maze for a novel learning for two sessions (#2). After 18 days of treatment, rats were exposed 5 min in the elevated plus maze to assess anxiety levels and corticosterone secretion after stress. The same day in the afternoon, animals were injected with BrdU, then, the two consecutive days, they were treated with BrdU twice per day. Animals were killed for BrdU immunochemistry after 21 days of infusion.