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Research article

Ceftriaxone pretreatment reduces the propensity of postpartum depression following stroke during pregnancy in rats

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HIGHLIGHTS

- Ischemic stroke increases the propensity to develop depression in humans and laboratory animals.
- We hypothesized that ischemic stroke in pregnancy may increase the risk for the development of postpartum depression (PPD).
- We found that 15 min bilateral common carotid arteries occlusion during pregnancy enhanced depressive-like behaviors in dams.
- Ceftriaxone pretreatment prevented loss of glutamate transporter (GLT-1) expression in the medial prefrontal cortex (mPFC).
- Ceftriaxone pretreatment reduced the propensity for the development of PPD.

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ABSTRACT

Objective: Ischemic stroke increases the propensity to develop depression in humans and laboratory animals, and we hypothesized that such an incidence during pregnancy may increase the risk for the development of postpartum depression (PPD).
Materials and methods: To test this hypothesis, we used bilateral common carotid arteries occlusion (BCCAO) to induce transient cerebral ischemia in pregnant rats, and evaluated its effects on subsequent development of PPD in dams. Additionally, we investigated whether ceftriaxone pretreatments before the induction of brain ischemia could alter the propensity of PPD.
Results: We found that 15 min BCCAO during pregnancy enhanced immobility time and reduced the frequency of swimming or climbing behaviors in the forced swim test, and decreased the sucrose preference in dams at postpartum day 21. Such behavioral alterations were associated with lower level of GLT-1 expression in the medial prefrontal cortical regions (mPFC) of PPD dams. Specifically, mPFC GLT-1 expression levels in dams with ischemia history were correlated with sucrose preference levels at postpartum day 21. Finally, ceftriaxone pretreatment (200 mg/kg/day, 5 days) before the 15 min BCCAO prevented the development of PPD, and prevented the reduction of GLT-1 expression in the mPFC.
Conclusions: Taken together, our results suggested that ceftriaxone pretreatment before brain ischemia during pregnancy may reduce the propensity for the development of PPD by preventing the loss of GLT-1 expression in the mPFC.

1. Introduction

Stroke is a devastating event when it happens during pregnancy. While the overall rate of stroke during pregnancy is very low, recent studies have shown that the stroke incidence has been steadily increasing in recent years [1]. Nearly 50% of strokes during pregnancy are ischemic strokes [2]. However, most pregnant women with ischemic stroke do not receive acute stroke reperfusion therapy, partly due to the high risks of this therapy for fetus. Therefore, preventing the incidence of stroke and mitigating the damage of ischemic stroke during pregnancy is critical for pregnant women who are at high risk of stroke.

Postpartum depression (PPD) is a prevalent disorder, which happens in approximately 20–50% of women [3], with as high as 19% of women developing the depression during the first 3 months postpartum [4]. Women who suffer from PPD often experience feelings

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of inadequacy and hopelessness, which may last from months to years after the childbirth. Various studies have shown that PPD plays a damaging role in the relationship between mother and infant and can result in suboptimal development of cognition and emotion in child. This, in turn, likely increases the risk of depression in the affected children and young adolescents [5–8]. Despite the prevalence and consequences of PPD, little is known about the biological mechanisms underlying the pathophysiology of this disorder. Particularly, it is still not very clear about the risk factors that might contribute to the development of PPD. Given that ischemic stroke increases the propensity to develop depression in humans and laboratory animals [9], we postulated that stroke incidence during pregnancy may increase the risk for the development of PPD.

Using magnetic resonance imaging, it was demonstrated that glutamate levels in the medial prefrontal cortical regions (mPFC) are increased in patients with PPD [10]. Furthermore, *N*-methyl-D-aspartate (NMDA) antagonist ketamine has a rapid onset of antidepressant activity in human patients [11,12]. These studies suggested that increased glutamatergic neurotransmission in the mPFC may be critical for the development of PPD. Furthermore, glutamatergic neurotransmission in the central nervous system is tightly controlled by glutamate transporters. Specifically, presynaptic glutamate is deposited into the vesicles via vesicular glutamate transporter (VGLUT) in order to be synaptically released via calcium influx induced action potentials. After synaptic release, glutamate can act on both ionotropic and metabotropic glutamate receptors [13]. The neurotransmitter activity is limited in time by the action of glutamate transporters, which are responsible for the glutamate re-uptake from the synaptic cleft [14,15]. Five members of excitatory amino acid transporters (EAAT) family, EAAT1 through 5, have been found in humans. They play a critical role in removing excessive glutamate from the extracellular space and preventing the potential damage from excitotoxicity [14,16–18].

Brain anoxia or ischemia can trigger robust release of glutamate causing the death of neurons, leading to mental or physical disorders [19–21]. Ceftriaxone treatment can enhance the expression of EAATs in the mPFC in laboratory animals [22–24]. Based on these facts, we hypothesized that brain ischemia during pregnancy may increase the risk of PPD via the reduction of mPFC GLT-1 expression, and upregulation of mPFC GLT-1 expression using ceftriaxone may prevent such deleterious effects of brain ischemia during pregnancy on the subsequent development of PPD. Therefore, in the present study, we used bilateral common carotid arteries occlusion (BCCAO) to induce transient cerebral ischemia in pregnant rats and evaluated its effects on the subsequent development of PPD. In addition, in order to increase mPFC GLT-1 expression, we pretreated the pregnant rats with ceftriaxone before the BCCAO procedure, and investigated whether ceftriaxone pretreatments could alter the propensity of PPD after brain ischemia during pregnancy. Finally, we investigated the postpartum expression of glutamate transporter 1 (GLT-1) in the mPFC in rats, and confirmed the effects of ceftriaxone treatments on GLT-1 expression in the same brain region.

2. Materials and methods

2.1. Animals

Female Sprague-Dawley rats (n = 50 on gestational day GD3) at 10–12 weeks old and weighing 200–250 g and non-pregnant, age and weight matching female Sprague-Dawley rats (n = 20) were supplied from Shanghai Laboratory Animal Center. Upon arrival, rats were housed individually. The room for housing the animals in the Animal Center was equipped with lights providing a 12-h light/dark cycle (light on 7:00–19:00) and was controlled for temperature (23 ± 1 °C). Rats were given food and water *ad libitum* except during the limited periods of the experiments. The day after arrival (*i.e.*, GD 4), animals were weighed and assigned to the experimental groups. The assignments were counterbalanced based on weight. On GD6, some rats started to receive intraperitoneal injections of either saline (1 ml/kg/day) or ceftriaxone (200 mg/kg/day) for 5 consecutive days. After parturition, rats remained housed with their pups until weaning at postnatal day (PND) 21. The majority of litters have an equal number of male pups (n = 4) and female pups (n = 4). Excess pups were cross-fostered by dams when litters were fewer than 8 pups [25,26]. Previous studies have shown that this procedure has a minimal impact on postpartum behavior in dams [26,27]. In order to not disrupt mother-pup interactions, animals were remained in cages undisturbed for 12 days except the cage bedding changes following parturition. The timeline of the experiments is shown in Fig. 1. The local Institutional Animal Care and Use Committee approved all animal experiments. The housing and treatment of the rats followed the guidelines of the "Guide for the Care and Use of Laboratory Rats" (Institute of Laboratory Animal Resources, Commission on Life Sciences 2011).

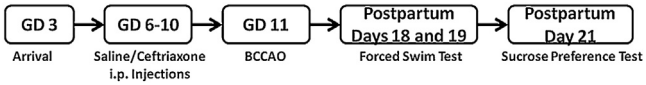

Fig. 1. Timeline and schedule of experiments. GD – gestational day. BCCAO – bilateral common carotid arteries occlusion. In separate groups of animals, dams received i.p. injections of ceftriaxone (200 mg/kg/day) or saline (1 ml/kg) from GD 6–10. Some dams also underwent sucrose preference test at GD 8.

2.2. Ceftriaxone treatment

To test the effects of ceftriaxone pretreatment on PPD after stroke during pregnancy, separate groups of rats started to receive intraperitoneal injections of either saline (1 ml/kg/day) or ceftriaxone (200 mg/kg/day) at GD6 for 5 consecutive days. This dose of Ceftriaxone was chosen based on the published data showing that ceftriaxone at 200 mg/kg/day administered to rats for 5 days is associated with up-regulating the glutamate transporter in the mPFC in laboratory animals [22–24].

2.3. Transient occlusion of bilateral common carotid arteries

The BCCAO to induce transient cerebral ischemia was conducted at the middle of the gestation (*i.e.*, at gestational day 11) as previously described [28,29]. Briefly, isoflurane (3%) was used to induce surgical anesthesia with in a mixture of nitrous oxide and oxygen (70:30), and anesthesia was maintained with isoflurane (1.5%) delivered via a nose mask. Body temperature was maintained at 37 ± 0.5 °C using a heating pad until the animals recovered from the anesthesia, and the rectal temperature was monitored during the procedure. An anterior midline incision was made in the neck, and both common carotid arteries were then exposed and loosely encircled with 3–0 silk to lift the vessels and facilitate the later occlusion. Microaneurysm clips (Surgipro Surgical Micro Vessel Clips, 50–80 g closing pressure) were used to introduce the occlusion of both common carotid arteries on each vessel for a period of 5 or 15 min followed by the removal of the clips. Sham-operated animals were subjected to the same anesthesia and surgical procedures without clipping the carotid arteries. The skin incision was then sutured. All animals received 0.5 ml acetated Ringer's solution subcutaneously 30 min and 24 h after the ischemia. Slight weight lost was seen in the day after the surgical procedure in sham group (2.8 ± 1.1 g), 5 min BCCAO group (2.5 ± 1.8 g) and 15 min BCCAO group (3.4 ± 1.6 g) of rats. However, weight loss was not significantly different between groups.