

Effects of Maternal Infection on Anxiety and Depression-like Behaviours of Offspring

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Introduction

LPS and some cytokines can activate the hypothalamic–pituitary–adrenal (HPA) axis and affect brain development in pregnant mice. Maternal infection during pregnancy is a risk factor for several psychiatric illnesses with neurodevelopmental origin. In this study we have evaluated the effects of exposure of pregnant mice to the bacterial lipopolysaccharide (LPS) on anxiety and depression-related behaviour of male offspring.

Methods

Pregnant NMRI mice were treated with intra-peritoneal administration of LPS (120, 240 and 480 µg/kg) at the 10th gestational day. Induction of the pro-inflammatory cytokines, TNF-α, IL-1β and IL-6, was measured in maternal serum 1.5h following maternal LPS challenge. All of the pregnant rats were allowed to give birth and nurture their offspring normally. Number of animals in each litter was standardized (3 males and 3 females/dam), in order to standard milk availability. Pups were weaned on postnatal day 21 (PD 21), and offspring housed (four animals from the same treatment/cage). Pregnant mice and male offspring divided to control and experimental groups (n = 7/ group for pregnant females; n = 7-10 with 2 pup each litter for the adulthood behaviors). Adult male offspring were chosen randomly for each test.

Anxiety-related behaviour of the male offspring (at postnatal day 70) was studied using elevated plus maze (EPM) test. EPM is a wooden, plus-shaped apparatus that elevated to the height of 50 cm above the floor. This maze is composed of two open arms (30cm×5cm), and two enclosed arms (30cm×5cm×15cm), each arm have an open roof. The maze was placed in the center of a quiet and dimly lit room. Following their respective treatment, mice were placed individually in the center of the plus-maze, facing one of the open arms. Behavioral data were collected by a “blind” observer who quietly sat 1 m behind one of the closed arms of the maze, using a time meter. The observer measured: (1) time spent in the open arms, (2) time spent in the closed arms, (3) number of entries into the open arms, and (4) number of entries into the closed arms during the 5-min test period. An entry was defined as all four paws in the arm. The maze was cleaned with distilled water after each mice was tested. For the purpose of analysis, open-arm activity was quantified as the amount of time that the mice spent in the open arms relative to the total amount of time spent in any arm ($\text{open}/\text{total} \times 100$), and the number of entries into the open arms was quantified relative to the total number of entries into any arm ($\text{open}/\text{total} \times 100$). The total number of arms entered, as well as the total number of closed arms entered was used as indexes of general locomotor activity. Anxiety test of pregnant mice was carried out 1.5 hours after injection of the LPS and anxiety test of offspring was carried out at postnatal day 60.

Forced swimming test was applied for evaluating the depression-like behaviour. Forced swimming test (FST) was performed as described, with minor modifications. Mice were forced to swim individually in a vertical glass cylinder (height 30 cm, diameter 15 cm) filled with water maintained at 24–26°C to a depth of 15 cm. After testing in the water, mice were removed and allowed to dry in a heated enclosure. Duration of immobility (making only minimal movements to keep the head above water or floating), swimming (movement of all four legs with body aligned horizontally in the water), and climbing (movement of all four legs with body aligned vertically in the water) were measured from videotapes by a trained blind observer. The total duration of each of the three behavioral parameters, immobility, swimming and climbing, was separately recorded by different

observation sessions. To examine the robustness of this method, we compared the immobility time separately measured and that calculated by subtracting total time by the sum of swimming and climbing times.

Results and conclusions

Our results demonstrate that LPS administration induces a significant increase in TNF- α , IL-1 β , IL-6 and corticosterone levels in maternal serum. However, in offspring, prenatal LPS administration has no significant effects on serum cytokines, corticosterone levels and depression-like behaviour, while decreasing the anxiety levels.

Ethical Statement

The study was approved by the Ethics Committees of *University of Erlangen-Nürnberg* and the experimental protocol is in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.