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Research report

Spatial cognition and sexually dimorphic synaptic plasticity balance impairment in rats with chronic prenatal ethanol exposure

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HIGHLIGHTS

- Study focuses on sex-specific effects of prenatal ethanol exposure.
- MWM test and electrophysiological recording were performed.
- A new index to measure the impairment of synaptic plasticity balance was developed.
- Ethanol has sexually dimorphism on spatial cognition and synaptic plasticity balance.
- Imbalance synaptic plasticity could be an underlying mechanism of cognitive deficits.

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ABSTRACT

Prenatal ethanol exposure can lead to long-lasting impairments in the ability of rats to process spatial information, as well as produce long-lasting deficits in long-term potentiation (LTP), a biological model of learning and memory processing. The present study aimed to examine the sexually dimorphic effects of chronic prenatal ethanol exposure (CPEE) on behavior cognition and synaptic plasticity balance (SPB), and tried to understand a possible mechanism by evaluating the alternation of SPB. The animal model was produced by ethanol exposure throughout gestational period with 4 g/kg bodyweight. Offspring of both male and female were selected and studied on postnatal days 36. Subsequently, the data showed that chronic ethanol exposure resulted in birth weight reduction, losing bodyweight gain, microcephaly and hippocampus weight retardation. In Morris water maze (MWM) test, escape latencies were significantly higher in CPEE-treated rats than that in control ones. They also spent much less time in the target quadrant compared to that of control animals in the probe phase. In addition, it was found that there was a more severe impairment in females than that in males after CPEE treatment. Electrophysiological studies showed that CPEE considerably inhibited hippocampal LTP and facilitated depotentiation in males, while significantly enhanced LTP and suppressed depotentiation in females. A novel index, developed by us, showed that the action of CPEE on SPB was more sensitive in females than that in males, suggesting that it might be an effective index to distinguish the difference of SPB impairment between males and females.

1. Introduction

Alcohol consumed by mothers during pregnancy reaches the fetus through the placental barrier and can parallel blood levels [1], and consequently it has an effect on fetal brain development. Children prenatally exposed to alcohol could suffer from serious behavioral problems and cognitive deficits [2,3]. Brain imaging studies identified structural changes in various brain regions of these children including the cerebellum, basal ganglia, corpus callosum and hippocampus [4]. In addition, brain development continues to be detrimentally affected after the prenatal insult, and the impairments of brain regions may be in line with the neurochemical deficiency of children prenatally exposed to alcohol [5].

Abbreviations: CPEE, chronic prenatal ethanol exposure; LTP, long-term potentiation; SPB, synaptic plasticiy balance; fEPSPs, field excitatory postsynaptic potentials; MWM, Morris water maze; IT, initial training stage; SET, space exploring test; RT, reversal training; CNS, central nervous system; HPA, hypothalamic-pituitary-adrenal; CM, control male; PM, pair-fed male; EM, CPEE male; CF, control female; PF, poair-fed female; EF, CPEE female; *LTPI*, long-term potentiation index; *DEPI*, depotentiation index; *SPBI*, synaptic plasticity balance index; *DI*, directional index.

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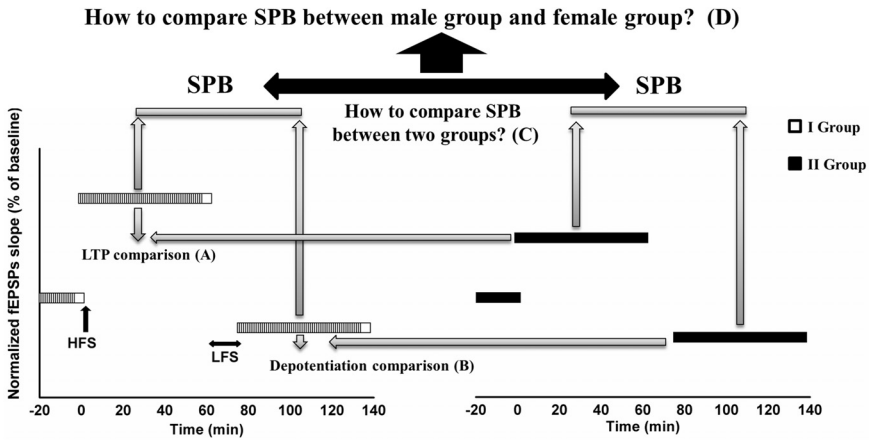

Fig. 1. The limitation of traditional approaches. The alterations of both LTP and depotentiation were analyzed by traditional approaches (A) and (B), respectively. However, it was hard to directly compare the alternations of SPB (including LTP and depotentiation) between I group and II group (C). Due to sex-specific difference, the comparison of SPB was difficult to perform between male and female groups (D).

A previous review showed that prenatal alcohol exposure sexually and differentially affected hypothalamic-pituitary-adrenal (HPA) axis activity and regulation as well as was associated brain regions including the hippocampus [6]. Thus, it is possible that sex differences in CNS development are mediated by sexually dimorphic effects of alcohol on HPA axis activity, and/or by altered HPA–gonadal interactions in CPEE offspring. Particularly, both human and animal studies illustrated that prenatal ethanol exposure re-programmed the fetal HPA axis and consequently HPA tone was increased throughout life [6].

Ample data from previous investigations indicated that the hippocampus was particularly sensitive to the effects of prenatal alcohol exposure [7–11]. It has traditionally been associated with regulation of spatial cognition [12,13]. Additionally, our previous studies found that the spatial cognition of CPEE male rats was impaired drastically, including learning and memory and reacquisition ability [14]. Notably, hippocampal synaptic plasticity was often used as an important functional index to understand how memories were formed at the cellular level [15,16]. Although long-term potentiation (LTP) was well known to underlie learning and memory, long-term depression (LTD) was regarded as a crucial mechanism related to the acquisition of a comprehensive spatial map [17]. It therefore was important to assess the balance/flexibility of synaptic plasticity, which reflected the connection of synaptic potentiation and depression between neurons [14,18,19]. We unexpectedly found that the adverse effects of CPEE on long-term synaptic plasticity impaired the synaptic balance and flexibility, and further damaged the synaptic function, which could elucidate the diversely crude performance in MWM tests [14].

Recently, several relevant studies showed that the female brain of both humans and rodents was more susceptible to neurotoxic insult during chronic ethanol exposure [20,21]. Using high-resolution, volumetric MRI, a greater decreased magnitudes of brain volumes were observed in female alcoholics women, while after fewer years of heavy drinking the microcephaly occurred earlier in female alcoholics than that in male ones [22]. On the contrary, other studies suggested that the expressions of neurotrophin receptors TrkA, TrkB, TrkC, and p75, which were vital to CNS development [23,24], were variable in diverse brain regions while the alternations were generally more prevalent in males than that in females [25]. In a similar vein, a greater reduction in brain glucose metabolism was found in male subjects compared to that in female ones, possibly reflecting sexual dimorphism in ethanol's modulation of GABAergic neurotransmission. Consequently, the neurobiological mechanisms underlying sex differences in stress reactivity following prenatal ethanol exposure are very complex and it needs further investigation.

Logically, a hypothesis was raised that CPEE made a sex-specific impact on the hippocampal synaptic plasticity. From the perspective of neuroelectrophysiology and molecular biology, synaptic plasticity balance is an endowed capability that regulates efficiency of synaptic transmission [26], which may serve to increase the signal to noise ratio between the potentiated synapses and the depressed synapses [27,28]. The alterations of either LTP or depotentiation might be measured between groups by comparing Fig. 1(A) and (B). Due to sex-specific differences, it is almost impossible to perform a comparison of sex-specific SPB (comparison (D) in Fig. 1). Therefore, it is hard to directly evaluate the characteristics of sexual impairment in SPB between males and females. In the present study, we aim to explore the sex-specific spatial cognition and SPB impairments of CPEE offspring. Furthermore, to fill the gap in performing the comparison of SPB alternations between male and female, a novel index was developed for providing a further understand of sex-specific role induced by CPEE.

2. Materials and methods

2.1. Breeding and animals

Four- to five-month-old adult virgin female (200–250 g) Wistar rats were purchased from the Laboratory Animal Center, Academy of Military Medical Science of People's Liberation Army, P.R. China. All animals were group-housed with free access to water and food in plastic cages (48 cm × 20 cm × 18 cm) in an established animal house having a 12 h light (lights on at 07:00 AM), namely 12 h dark cycle and a thermo regulated environment. Two females were paired with two male (2:2) for a period of 4–5 days until mating was confirmed by observation of a copulatory plug or the presence of sperm in a vaginal rinse under a microscope. The day that mating was confirmed and recorded as embryonic day 0 (E 0). All experiments were performed according to the protocols approved by the Committee for Animal Care at Nankai University and in accordance with the practices outlined in the NIH Guide for the Care and Use of Laboratory Animals.