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Research Report

Exposure to prenatal stress has deleterious effects on hippocampal function in a febrile seizure rat model

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ABSTRACT

Prenatal stress has been shown to result in the development of a number of neurological disorders in the offspring. Most of these disorders are a result of an altered HPA axis resulting in higher than normal glucocorticoid levels in the affected neonate. This leaves the offspring prone to immune challenges. Therefore the aim of the present study was to investigate the effects of prenatal stress and febrile seizures on behavior and hippocampal function. Pregnant dams were exposed to restraint stress during the third trimester. Following birth, febrile seizures were induced in two week old pups using lipopolysaccharide and kainic acid. A week later, anxiety-like behavior and navigational ability was assessed. Trunk blood was used to measure basal corticosterone concentration and hippocampal tissue was collected and analyzed. Our results show that exposure to prenatal stress increased basal corticosterone concentration. Exposure to prenatal stress exacerbated anxiety-like behavior and impaired the rat's navigational ability. Exposure to prenatal stress resulted in reduced hippocampal mass that was exacerbated by febrile seizures. However, exposure to febrile seizures did not affect hippocampal mass in the absence of prenatal stress. This suggests that febrile seizures are exacerbated by exposure to early life stressors and this may lead to the development of neurological symptoms associated with a malfunctioning hippocampus.

1. Introduction

Febrile seizures are characterized by abnormal excitation of neurons following an infection that leads to an immune response and an increase in core body temperature (Gatti et al., 2002; Riazi et al., 2010). The inflammatory response associated with febrile seizures involves the secretion of pro-inflammatory cytokines, in particular interleukin-1 beta (IL-1β) (Vezzani and Baram, 2007; Choy et al., 2014). Cytokines are endogenous peptide hormones that trigger the activation of the hypothalamic-pituary-adrenal (HPA) axis during an infection or when the body is under stress (Haddad et al., 2002; Sorrells and Sapolsky, 2007). Cytokines can be produced systemically (Riazi et al., 2010; Reid et al., 2013) as well as

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by the central nervous system particularly the hippocampus (Gatti et al., 2002). It has been established that cytokines regulate cell differentiation in the developing brain as well as memory and learning in the adult hippocampus (Wang and Shuaib, 2002; Lehtimaki et al., 2003). Hyper-secretion of IL-1β has been shown to result in neuronal excitotoxicity in the hippocampus by inhibiting the re-uptake of glutamate by astrocytes leading to neuronal cell death (Ye and Sontheimer, 1996). Studies have shown that an acute systemic injection of LPS during early neural development may lead to neuronal malformation in the hippocampus leading to disruptions in learning and memory as well as changes in synaptic plasticity (Aloe et al., 1999; Shaw et al., 2003). Spencer et al. (2005) showed that a single systemic injection of LPS on postnatal day (PND) 14 rat pups followed by an open field and a novel object tests resulted in anxiety-like behavior. Injection of the glutamate agonist kainic acid has been shown to induce neuronal death via the activation and release of proinflammatory cytokines such as interleukin-1beta (IL-1β) and tumour-necrosis factor alpha (TNF-α) in the central nervous system (Cho et al., 2008). Prenatal exposure to high levels of glucocorticoids has been shown to result in a malfunctioning HPA axis thus impairing normal immune system response to infections (Weinstock, 1997; Glaser and Kiecolt-Glaser, 2005; Charil et al., 2010). It has been shown that exposing a pregnant rat dam to restraint stress or bright flashing light resulted in decreased hippocampal glucocorticoid receptors in the offspring resulting in higher than normal corticosterone levels (Szuran et al., 2000). In this study we investigated whether febrile seizures in rats exposed to prenatal stress impaired memory recall and exacerbated anxiety-like behavior. We also looked at whether prenatal stress and febrile seizure exposure had an adverse effect on hippocampal apoptotic cell death and whether this led to a decrease in the size of the hippocampus.

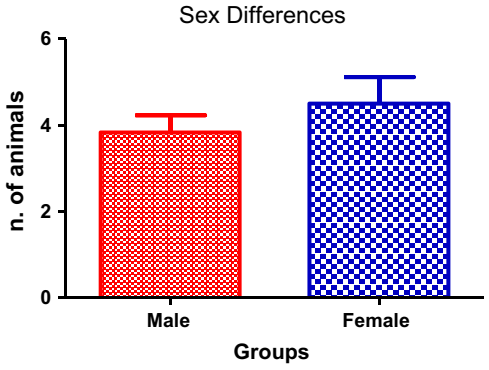

Fig. 1 – Graph showing male and female rats tested in the light dark box. No significant differences were present in the rats in relation to anxiety-like behavior. Data presented as mean ± SEM.

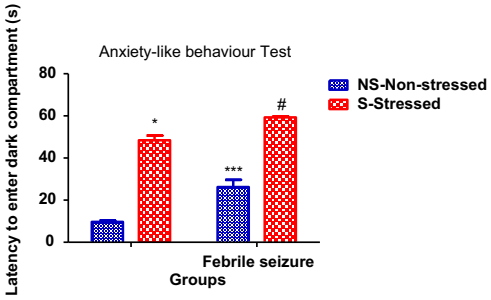

Fig. 2 – Graph showing latency in finding the dark compartment of the light/dark box during the test session in the following groups: non-stressed (NS), stressed (S), non-stressed-febrile seizure (NS-FS), stressed-febrile seizures (S-FS), $n=6$ per group. *(NS vs S, $p<0.05$), **(NS-FS vs S-FS, $p<0.001$), * (NS vs NS-FS $p<0.05$) and #(S vs S-FS, $p<0.05$). Data presented as mean ± SEM.**

2. Results

2.1. Sex difference on anxiety-like behavior

There were no significant difference in animal behavior in the light dark box (Male vs Female, $p=0.3452$). Data presented in Fig. 1.

2.2. Anxiety-like behavior

The following groups were assessed for anxiety-like behavior non-stressed (NS), stressed (S), non-stressed with febrile seizures (NS-FS) and stressed with febrile seizures (S-FS).

A stress effect was evident as rats took longer (increased latency) to enter the dark box ⁎(NS vs. S, $F_{(1.36)}=293$, $p<0.001$) and ** (NS-FS vs S-FS, $F_{(1.36)}=293$, $p<0.001$) A febrile seizure effect was also evident as the rats took longer to find the dark compartment in both the NS and S rats *** (NS vs. NS-FS, $F_{(1.36)}=42.76$, $p<0.0001$) and #(S vs S-FS, $F_{(1.36)}=293$, $p<0.001$). Data presented in Fig. 2.

2.3. Navigational ability

The time taken to navigate the light dark box with the partitions in place was also assessed. There was a stress effect as exposure to prenatal stress increased the time taken to navigate the box. ⁎ (NS vs. S, $F_{(1.36)}=275$, $p<0.001$) and ** (NS-FS vs. S-FS, $F_{(1.36)}=275$, $p<0.001$). We also found a febrile seizure effect in the stressed animal ***(S vs S-FS, $F_{(1.36)}=38.96$, $p<0.001$). Data presented in Fig. 3.

2.4. Plasma corticosterone concentration

There was a stress effect as exposure to prenatal stress resulted in higher basal corticosterone concentration. *(NS vs. S, $p<0.05$). Data presented in Fig. 4.

2.5. Hippocampal mass

Hippocampal tissue was measured in the non-stressed (NS), stressed (S), non-stressed with febrile seizures (NS-FS) and stressed with febrile seizures (S-FS) groups. There was a stress effect as exposure to prenatal stress resulted in a reduced hippocampal mass in both control and febrile seizure exposed rats *(NS vs S, $F_{(1.36)}=25.73$, $p<0.05$) and **(NS-FS vs S-SFS, $F_{(1.36)}=25.73$, $p<0.05$). There was a febrile seizure effect