INTRODUCTION

Inflammation in the brain (neuroinflammation) has been associated with a number of neurodegenerative diseases, including Alzheimer’s disease (AD) (Siddiqui et al., 2012). Within the brain, inflammation is defined broadly as prolonged activation of the brain’s immune cells, known as glial cells. Excessive activation of glial cells within the brains of AD patients is a hallmark of the disease, however the mechanism by which this contributes to disease pathology is relatively unclear (Li et al., 2014). Recently, studies have shown that glial cells, known as astrocytes, are able to synthesize and release the inhibitory neurotransmitter GABA (Chen et al., 2000). Further, microglia, the primary immunocompetent cells of the brain, have been shown to be GABAergic cells, which express GABA B type receptors (Korth et al., 2004). Early characterizations of AD first described alterations in astrocyte location and activation in the disease and interestingly, differences in the total abundance of GABA within the brains of AD patients have recently been reported. Combined, these provide support for the hypothesis that astrocytes regulate microglial activity through the release of GABA acting at GABA B type receptors. The activation of GABA B receptors may serve to reduce the activation status of microglia thereby reducing the number of pro-inflammatory cytokines present within the brain (Streit et al., 2002). In the present study, we examined the effects of the GABA B agonist baclofen on chronic inflammation in rats administered lipopolysaccharide (LPS). LPS is a bacterial endotoxin derived from the cell wall of gram-negative bacteria and is capable of mounting an immune response through the activation of toll-like receptor 4 (TLR4). Our data indicate that the administration of baclofen initially attenuated the pyrogenic effects of LPS administration, though the effect was lost after two weeks of injections. The administration of baclofen also reduced deficits in spatial learning and memory seen in animals chronically administered LPS. Furthermore, a significant increase in the total abundance of AB oligomers, believed to play a role in the pathology of AD, was seen in the brains of animals chronically administered LPS. Together, these data provide evidence that the modulation of GABA B receptor function altered the immune response evoked by activation of TLR4. These data also provide support for a potential role of GABA B in modulating alternate immune activity seen in AD pathology.

EXPERIMENTAL PROCEDURE

Subjects: 30 male Sprague Dawley rodents (n=30) were used in this experiment. Subjects were divided into three groups (n=10/group) and randomly assigned to one of three treatment schedules: Saline-Saline (control), LPS-Saline (LPS), or LPS-Baclofen (LPS-Bac).

Drug Administration: As part of a larger experiment, stereotactic surgeries were performed on all animals under asaic conditions and ketamine/xylazol/detomidine anesthesia. 8ml, of artificial cerebrospinal fluid (ACSF) was slowly infused into each lateral ventricle using the stereotactic coordinates 0.7mm anterior, 1.4mm lateral to Bregma, and 3.5 mm ventral to the surface of the skull. Following a recovery period of one week after surgeries, animals received intra-peritoneal (i.p.) injections of LPS (0.1mg/kg), saline (1ml/kg) twice a week for seven weeks for a total of 14 injections. Four hours following LPS or Saline injections, animals received i.p. injections of baclofen (1mg/kg) or saline (1ml/kg) resulting in the three treatment groups: Saline-Saline (control), LPS-Saline (LPS), and LPS-Baclofen (LPS-Bac).

Temperatures: To ensure an immune response was evoked by the administration of LPS, rectal temperatures were tracked prior to drug administration and at 1, 2, and 3-day intervals post injection throughout the course of the experiment. All procedures were performed in accordance with the institutional Animal Care and Use Committee and NHG guidelines.

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Morris Water Task: The Morris water task was conducted in a white circular tank, 1.8 m in diameter, 75 cm in height, and 4.7 mm in thickness. To mask the hidden platform, each morning the water was made opaque with the addition of white non-toxic paint. For each subject, a 10cm x 10cm square platform was placed in the center of one of the four quadrants of the tank, 1.5 cm below the water. At the start of each trial, rats were placed into the maze and given sixty seconds to find the hidden platform located below the surface of the water. If after sixty seconds the animal was unsuccessful in locating the hidden platform, a trained experimenter guided the animal to the hidden platform. Once reaching the platform, animals were given twenty seconds to orient themselves to the distal spatial cues. Each animal performed four trials each day for a total of 24 trials per week. The width of the bridge was increased from the maze and selective search behavior was recorded for each animal. Following the probe trial, two days of visible training in which the hidden platform was replaced with a visible platform was conducted in order to detect any visual or motor deficits.

CONCLUSION

Modulatory Effects of GABA(B) Receptor Facilitation in a Model of Chronic Inflammation

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RESULTS

Figure 1. Mean temperatures immediately prior to injections and at 1, 2, and 3 post-injection day intervals. (*p < 0.05 compared to controls). Error bars denote a Standard Error of Mean (SEM).

Figure 2. Mean latency, swim speed, and percent thigmotaxis for each group. (*) p < 0.05 compared to controls.

Figure 3. Mean proportion of time in quadrants and average number of arm crossings during the Morris water task probe trial. (*p < 0.05 compared to controls).

Figure 4. Protein levels proportion to control (±SEM) in hippocampal tissue collected from animals. (⁎ p < 0.05) Representative Western Blot image.

REFERENCES


