INTRODUCTION

Inflammation of 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 (Church et al., 2000). Furthermore, microglia, the primary immune competent cells of the brain, have been shown to be GABAergic cells, which express GABA-B type receptors (Koth et al., 2004). Early characterizations of AD first described alterations in astrocyte location and activation in the disease and increasingly, differences in the total abundance of GABA within the brains of AD patients have recently been reported. Combined, these data provide support for the hypothesis that astrocytes regulate microglia 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 these microglia, thereby reducing the number of pro-inflammatory cytokines present within the brain (Sotelo et al., 2012). In the present study, we examined the effects of the GABA(B) antagonist baclofen on chronic inflammation in relation to the expression of 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 this effect was lost after two weeks of injections. The administration of baclofen also rescued 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 populations.

EXPERIMENTAL PROCEDURE

Subjects

Thirty 3 male Sprague Dawley rats (300g) 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). All animals were individually housed in a standard animal facility with a 12-hour light, dark cycle with food and water available ad libitum throughout the course of the experiment. All procedures were performed in accordance with the institutional Animal Care and Use Committee and NIH guidelines.

Drug Administration:

As part of a larger experiment, stereotactic surgeries were performed on all animals under anesthetic conditions and ketamine/dexmedetomidine anesthesia. 8ml of artificial cerebrospinal fluid (ACSF) was slowly infused into each lateral ventricle using the stereotaxic coordinates 0.7mm posterior, 1.4mm lateral to Bregma, and 3.5mm ventral to the surface of the skull. Following a recovery period of one week after surgery, animals received intraperitoneal (i.p.) injections of LPS (0.5mg/kg), saline (1ml/kg) twice a week for seven weeks for a total of 14 injections. As part of a larger experiment, stereotaxic surgeries were performed on all animals under aseptic conditions and ketamine/dexmedetomidine anesthesia. 8ml of artificial cerebrospinal fluid (ACSF) was slowly infused into each lateral ventricle using the stereotaxic coordinates 0.7mm posterior, 1.4mm lateral to Bregma, and 3.5mm ventral to the surface of the skull. Following a recovery period of one week after surgery, animals received intraperitoneal (i.p.) injections of saline (0.5mg/kg), saline (1ml/kg) twice a week for seven weeks. Four hours following LPS or Saline injections, animals received i.p. injections of baclofen (1mg/kg) or saline (1ml/kg) resulting in the administration of LPS. 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 milk. 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 milk. 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 milk. 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 milk.

Figures

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

Figure 2. Mean latency, swim speed, and percent thigmotaxis for (AD) for animals in the Morris water task. (p < 0.05 compared to control).

Figure 3. Mean proportion of time in quadrants and average number of quadrant crossings (uSEM) during the probe trial. (p < 0.05 compared to control).

Total Aβ oligomeric protein levels were significantly elevated in animals administered LPS. No differences were seen between LPS and LPS-Bac animals.

CONCLUSION

■ Baclofen attenuated the pyrogenic response evoked through the administration of LPS.

■ Baclofen rescued learning and memory deficits seen in animals administered LPS.

■ LPS and LPS-Bac animals show a significant increase in total Aβ oligomeric protein levels.

■ Combined, these data provide support for the role of the GABA(B) receptor in modulating chronic neuroinflammation.

REFERENCES


