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Systemic lipopolysaccharide administration impairs retrieval of context–object discrimination, but not spatial, memory: Evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation

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ABSTRACT

Neuroinflammation is implicated in impairments in neuronal function and cognition that arise with aging, trauma, and/or disease. Therefore, understanding the underlying basis of the effect of immune system activation on neural function could lead to therapies for treating cognitive decline. Although neuroinflammation is widely thought to preferentially impair hippocampus-dependent memory, data on the effects of cytokines on cognition are mixed. One possible explanation for these inconsistent results is that cytokines may disrupt specific neural processes underlying some forms of memory but not others. In an earlier study, we tested the effect of systemic administration of bacterial lipopolysaccharide (LPS) on retrieval of hippocampus-dependent context memory and neural circuit function in CA3 and CA1 (Czerniawski and Guzowski, 2014). Paralleling impairment in context discrimination memory, we observed changes in neural circuit function consistent with disrupted pattern separation function. In the current study we tested the hypothesis that acute neuroinflammation selectively disrupts memory retrieval in tasks requiring hippocampal pattern separation processes. Male Sprague–Dawley rats given LPS systemically prior to testing exhibited intact performance in tasks that do not require hippocampal pattern separation processes: novel object recognition and spatial memory in the water maze. By contrast, memory retrieval in a task thought to require hippocampal pattern separation, context–object discrimination, was strongly impaired in LPS-treated rats in the absence of any gross effects on exploratory activity or motivation. These data show that LPS administration does not impair memory retrieval in all hippocampus-dependent tasks, and support the hypothesis that acute neuroinflammation impairs context discrimination memory via disruption of pattern separation processes in hippocampus.

1. Introduction

Cytokines, signaling molecules that mediate the immune response and are beneficial at basal or low levels, can produce sickness behaviors and impair cognition at pathophysiological levels (Dantzer et al., 2008; Yirmiya and Goshen, 2011). There is evidence of cognitive impairment in humans with a variety of disorders that result in elevated cytokine levels, including multiple sclerosis, Alzheimer's disease, AIDS-related dementia, cancer, and patients undergoing chemotherapy (Kaul et al., 2001; Huijbregts et al., 2004; Meyers et al., 2005; Ahles and Saykin, 2007; Guerreiro et al., 2007).

During an inflammatory response, microglia become activated, resulting in the release of cytokines, including interleukin-1 (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), in the brain (Hanisch, 2002). These pro-inflammatory cytokines have been demonstrated to directly affect neuronal function, including long-term potentiation (LTP), glutamate release, AMPA receptor trafficking, and activation of cell-signaling pathways (O'Connor and Coogan, 1999; Albensi and Mattson, 2000; D'Arcangelo et al., 2000; Tancredi et al., 2000; Vereker et al., 2000; Beattie et al., 2002; Lynch et al., 2004). Because these processes affect synaptic plasticity and neurotransmission, it is apparent that cytokines may impact neuronal processes pertinent to cognition.

There is a high density of cytokine receptors in the hippocampus, particularly the dentate gyrus (DG) (Lechan et al., 1990; Schöbitz et al., 1992), indicating that the hippocampus may be particularly vulnerable during neuroinflammation. Indeed, using animal

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models, researchers have observed that administration of cytokines or other immunogenic stimuli, including the bacterial endotoxin lipopolysaccharide (LPS), can disrupt hippocampus-dependent learning and memory processes (Oitzl et al., 1993; Gibertini et al., 1995; Pugh et al., 1998; Barrientos et al., 2002). Specifically, several studies have shown that acquisition of the Morris water maze and consolidation of contextual but not cued fear conditioning are disrupted during neuroinflammation (Gibertini et al., 1995; Pugh et al., 1998; Arai et al., 2001; Barrientos et al., 2002; Thomson and Sutherland, 2005). However, there have been mixed results across studies regarding the effect of neuroinflammation on the water maze, as well as observations that cytokines do not impair, and can even facilitate, learning and memory (Cunningham and Sanderson, 2008; Yirmiya and Goshen, 2011), making it difficult to ascertain the precise impact of neuroinflammation on cognition.

Importantly, patients with neuroimmune disorders have reported difficulty with memory retrieval (Thornton et al., 2002; Woods et al., 2007), which can be just as detrimental to daily function as encoding or consolidation deficits. Despite this, however, research to date has focused primarily on memory acquisition and consolidation processes. In a recent study, we examined the effect of acute neuroinflammation induced by systemic LPS injection on retrieval of a simple contextual fear task or a context discrimination fear task (Czerniawski and Guzowski, 2014). Although both tasks are hippocampus-dependent, LPS only impaired retrieval of context discrimination memory. In addition, analysis of neural circuit activity provided evidence that LPS-mediated neuroinflammation impaired pattern separation processes in CA3 and CA1. The behavioral and neural circuit data from this study are consistent with the hypothesis that acute neuroinflammation preferentially disrupts pattern separation functions necessary for context discrimination. In the present study we tested this working hypothesis by examining the effect of systemic LPS administration on retrieval of three additional tasks that vary with respect to hippocampal information processing: the spatial water maze task, context–object discrimination (COD), and novel object recognition (NOR). The water maze is a hippocampus-dependent task that tests navigation and spatial memory, while COD is a hippocampus-dependent task that tests context discrimination (Morris et al., 1982; Aggleton and Brown, 1999; Mumby et al., 2002; Barker and Warburton, 2011). NOR, although similar to COD in that it involves incidental encoding, does not typically require the hippocampus (Barker and Warburton, 2011). Of these three tasks, COD is the only one thought to require hippocampal pattern separation and, accordingly, is the only task predicted to be impaired by LPS treatment.

2. Materials and methods

2.1. Subjects

Eighty-nine male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 250–275 g at the time of arrival served as subjects. All animals were individually housed in a temperature-controlled vivarium maintained on a 12 h light/dark cycle. All subjects had access to food and water *ad libitum* throughout the duration of the experiment and were handled 2 min/day for 5 days before the start of the experiment. On each day prior to training all animals were transported to a holding room and allowed to sit for 2 h undisturbed. All procedures complied with National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committee of the University of California, Irvine.

2.2. Apparatus

The water maze (Coulbourn Instruments, Allentown, PA) consisted of a blue circular pool (174 cm diameter and 97 cm high) filled with water (22–24 °C). An escape platform (15 cm diameter, 33 cm high) was placed in one of the quadrants (“Northeast”), 2.5 cm below water surface.

Two distinct environments in adjacent rooms were used for both COD and NOR. Environment A was an open box (60 × 60 cm) with 30 cm high walls. The box had Plexiglas walls with black paper attached on the outside, with white diagonal stripes on one of the walls. Clear Plexiglas covered a natural wood floor which was divided into nine squares with green tape. Environment B was a black cylinder (70 cm in diameter) with a height of 39 cm with a black floor. There were different visual cues in the different testing rooms.

The objects used were ceramic fish and frog toothbrush holders and open glass cubes. All the objects were ~11 cm in height, 11–12 cm width and placed 12 cm from the wall with 15 cm between the pair of objects. All objects were too heavy to be displaced by the rats. The environments and objects were cleaned thoroughly between subjects with 10% ethyl alcohol for environment A or 0.01% acetic acid solution for environment B. Cameras mounted above each environment were used to record the training and testing sessions.

2.3. Behavior

2.3.1. Spatial water maze training and testing

For training, each rat was placed in the water at one of the eight starting positions in a random order and was given 60 s to reach the platform. If the rat failed to locate the platform after 60 s, it was carefully guided to the platform and placed on it for 10 s. The rat was then taken out of the platform and allowed to rest in a holding chamber for 20 s. This was followed by another training trial. The latency to find the platform was measured for each trial. The rats were trained 5 trials each day, for 4 consecutive days. On the fifth day, the test for platform location consisted of a single probe trial, during which the platform was removed. The time spent in each quadrant of the maze and a zone (8% of the total tank area) around the target was measured. Immediately following the probe trial, the platform was placed in the quadrant opposite from the original location (“southwest”) for reversal learning. Each rat was placed on the platform in the new location for 10 s and immediately proceeded to training as before, and the latencies to reach the platform were measured. All data were collected and processed by Watermaze software (Actimetrics; Coulbourn Instruments), which includes the video equipment and a computer equipped with an analysis–management system.

2.3.2. NOR and COD training and testing

For both NOR and COD, subjects were placed into environments A and B for 5 min each for 2 days and allowed to freely explore. Subjects were returned to their home cage for a 20 min interval between these exploration sessions. The order of context presentation was counterbalanced between subjects and across days. There were pairs of different identical objects in each of the contexts. For NOR, these objects were ceramic fish in environment A and glass cubes in environment B (Fig. 1a). For COD, these objects were ceramic fish in environment A and ceramic frogs in environment B (Fig. 1b). The amount of time each subject explored each object (defined as nose pointed towards object within 2 cm of object) was collected using Limelight2 program (Actimetrics; Coulbourn Instruments).

The test session took place on Day 3 and consisted of 5 min in environment A′, which was A with one of the objects replaced by a different object. For NOR, one of the objects in A (fish) was replaced with a novel object (frog). For COD, one of the objects in A (fish) was replaced with one of the previously experienced objects in B (frog). Therefore, all subjects experienced the same