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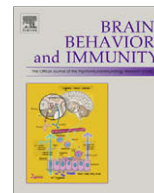

Sustained hippocampal IL-1β overexpression impairs contextual and spatial memory in transgenic mice

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ABSTRACT

Neuroinflammatory conditions such as traumatic brain injury, aging, Alzheimer's disease, and Down syndrome are often associated with cognitive dysfunction. Much research has targeted inflammation as a causative mediator of these deficits, although the diverse cellular and molecular changes that accompany these disorders obscure the link between inflammation and impaired memory. Therefore, we used a transgenic mouse model with a dormant human IL-1β excisional activation transgene to direct overexpression of IL-1β with temporal and regional control. Two weeks of hippocampal IL-1β overexpression impaired long-term contextual and spatial memory in both male and female mice, while hippocampal-independent and short-term memory remained intact. Human IL-1β overexpression activated glia, elevated murine IL-1β protein and PGE_2 levels, and increased pro-inflammatory cytokine and chemokine mRNAs specifically within the hippocampus, while having no detectable effect on inflammatory mRNAs in the liver. Sustained neuroinflammation also reduced basal and conditioning-induced levels of the plasticity-related gene Arc.

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1. Introduction

Neuroinflammatory conditions such as traumatic brain injury, aging, Alzheimer's disease, and Down syndrome are often associated with cognitive dysfunction, including memory deficits (Casadesus et al., 2007; Griffin et al., 1989; Montine et al., 1999). Much research has focused on anti-inflammatory treatments to try and prevent these memory deficits with mixed results (ADAPT Research Group et al., 2007; Hurley et al., 2002; Rogers et al., 1993). It is clear that acute inflammation, caused by injection of lipopolysaccharide or interleukin-1β (IL-1β) itself, impairs memory (Gibertini et al., 1995; Hein et al., 2007; Oitzl et al., 1993; Pugh et al., 1998, 2001; Thomson and Sutherland, 2005). However, a lack of experimental models has made the study of the effects of chronic neuroinflammation on memory difficult, especially when trying to parse the potential influences of resulting sickness or neurodegeneration on memory. Therefore, we utilized a recently developed mouse model, which can maintain sustained IL-1β overexpression with temporal and regional control, to study the effects of prolonged IL-1β overexpression and ensuing neuroinflammation on learning and memory processes.

This mouse model retains a dormant human IL-1β excisional activation transgene (IL-1β^{XAT}). When activated by microinjection of a virus expressing Cre, astrocytes local to the injection site express human IL-1β (Shaftel et al., 2007b). Human IL-1β binds to the murine IL-1 receptor and signals downstream pathways to induce inflammation. Research in this model has shown that a single microinjection of virus expressing Cre into the hippocampus causes sustained IL-1β overexpression for up to nearly a year after injection (Shaftel et al., 2007b). Within 2 weeks of transgene activation, IL-1β overexpression within the hippocampus leads to glial activation, elevated cytokines, elevated chemokines, leukocyte infiltration, and increased vascular permeability (Moore et al., 2009; Shaftel et al., 2007a,b). However, after 2 weeks or 2 months of IL-1β overexpression, no overt loss of neurons or neuronal integrity is apparent within the hippocampus as measured by apoptotic stains and neuronal, synaptophysin, and acetylcholinesterase labeling (Moore et al., 2009; Shaftel et al., 2007a). Therefore, this model allows us to study the role of chronic IL-1β driven neuroinflammation on learning and memory processes.

Initial behavioral studies in this mouse model revealed spatial learning deficits in the Morris water maze 2 weeks following transgene activation (Moore et al., 2009). Here we further characterize

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these deficits by testing hippocampal-dependent and -independent, as well as short- and long-term, fear memory and potential gender differences in fear conditioning and the Morris water maze. We also further characterize the central and peripheral inflammatory responses to sustained hippocampal IL-1β overexpression and find changes in one plasticity-related gene, activity-regulated cytoskeleton-associated protein (Arc; also Arg 3.1).

2. Materials

2.1. hIL-1β^{XAT} construct

Creation and genotyping of IL-1β^{XAT} mice on a C57BL/6 background has been described previously (Shaftel et al., 2007b). Briefly, a construct with a murine GFAP promoter, loxP flanked transcriptional stop, and downstream signal sequence for the human IL-1RA was fused to the cDNA of human mature IL-1β to allow extracellular release of IL-1β.

2.2. Feline immunodeficiency virus (FIV)

The construction and packaging of FIV-Cre has been described previously (Lai et al., 2006). Briefly, the FIV-Cre virus encodes a modified Cre recombinase protein with a nuclear localization sequence, and V5 epitope tag under the control of a cytomegalovirus promoter. FIV-Cre mediated excision of the transcriptional stop activates the IL-1β^{XAT} transgene. FIV-Cre and FIV-green fluorescent protein (GFP) (System Biosciences, Mountain View, CA) used in these studies had final titers of $\sim 1 \times 10^7$ infectious viral particles per milliliter.

2.3. Animals

2.3.1. Experiment 1

Male IL-1β^{XAT} B/b transgenic and wild-type (WT) littermate mice were used for experiment 1. Mice were housed in temperature (23 ± 3 °C) and light (12:12 light:dark) controlled rooms with free access to chow and water. All animal procedures were reviewed and approved by the University Committee on Animal Resources of the University of Rochester Medical Center for compliance with federal regulations prior to the initiation of the study. FIV-Cre injected WT and FIV-GFP injected IL-1β^{XAT} mice served as controls for both genotype and viral injection. Since no differences were found between these groups only FIV-Cre injected WT mice were used as controls in experiments 2 and 3.

2.3.2. Experiment 2

Male and female IL-1β^{XAT} B/b transgenic and WT littermate mice were used for experiment 2. Animal colonies were maintained as described above. After viral microinjections, mice were shipped to Denver, CO and allowed to recover for 7–10 days before behavioral experiments began. In Denver, animals were housed at the Center for Laboratory Animal Care at the University of Colorado Denver on a 12:12 h light/dark cycle with *ad libitum* access to food and water. Experiments were under the approval of the University of Colorado's Animal Care and Use Committee.

2.3.3. Experiment 3

Male and female IL-1β^{XAT} B/b transgenic mice were used for experiment 3 and maintained as in experiment 1.

2.4. Microinjections

Intrahippocampal microinjections were described previously (Shaftel et al., 2007b). At 8–16 weeks of age, mice received bilateral, hippocampal FIV-Cre or FIV-GFP injections in experiments 1 and 2. In experiment 3, mice were injected with FIV-Cre in one side of the hippocampus and FIV-GFP in the other to create a within subjects design. Under 1.75% isoflurane, in 30% oxygen and 70% nitrogen gas, mice were placed into a Kopf stereotaxic apparatus in a biosafety level 2 approved facility. A 0.5 mm burr hole was drilled at AP: −1.8 mm and ML: ±1.8 mm relative to bregma and a 33 gauge needle attached to a 10 μl syringe was lowered 1.8 mm over 2 min. A Micro-1 microsyringe pump controller (World Precision Instruments) injected 1.5 μl of virus at a constant rate over 10 min and 5 min was allowed for diffusion, resulting in delivery of approximately 1.5×10^4 infectious viral particles to the mouse hippocampus. The needle was raised over 2 min and burr hole sealed with bone wax. The procedure was then repeated on the opposite side to deliver virus bilaterally. Following both injections, the scalp incision was closed with tissue adhesive (Vetbond). Behavioral experiments began 2 weeks after FIV microinjections.

2.5. Behavioral procedures

2.5.1. Experiment 1

Mice underwent contextual and auditory fear conditioning to assess hippocampal-dependent and -independent memory processes (see Fig. 1A for timeline). For 3 days before fear conditioning, mice were transported from the colony room to the testing room, handled for 2 min each, and returned to the colony room to acclimate them to experimenter manipulation. On conditioning day, mice were allowed to explore the conditioning context, which consisted of a Plexiglas chamber and metal floor grid (model H10-11 M; Coulbourn Instruments, Whitehall, PA, USA). After 3 min, 15 s of white noise (80 dB) was presented co-terminating with a 2 s, 0.75 mA foot shock. This noise-shock pairing was repeated twice for a total of 3 shocks with an interval of 30 s between shocks. One or 24 h later to test short-term or long-term memory respectively, mice were re-exposed to the conditioning chamber for 6 min each. Mice that had been tested for long-term contextual fear memory were also tested for freezing to a novel context and the auditory stimulus 4 h after initial testing. Mice were placed in a novel context consisting of a 15 cm open-topped plastic cylinder with bedding on the floor for 3 min followed by re-exposure to the white noise for 3 min. All data were video recorded using FreezeFrame Video-Based Conditioned Fear System and analyzed by Actimetrics Software (Coulbourn Instruments). In a pilot study, automated scoring in this program showed greater than 95% concordance with human scoring.

2.5.2. Experiment 2

2.5.2.1. Fear conditioning. The protocol for these experiments was based on previous work with the Ts65Dn mouse model for Down syndrome (Costa et al., 2008). Mice were allowed to explore a novel conditioning chamber (Med Associates, St. Albans, VT, Modular Mouse Test Chamber) for 3 min before the onset of 15 s of white noise (80 dB) followed by a 2 s, 0.7 mA foot shock. Twenty-four h later, mice were re-exposed to the conditioning chamber and freezing measured every 9 s for 3 min by two observers blind to mouse genotype. Four hours later, mice were placed in a novel context for 3 min followed by re-exposure to the white noise for 3 min and freezing was assessed. All experiments were videotaped for archival purposes.

2.5.2.2. Morris water maze. The protocol for these experiments was also based on previous work with the Ts65Dn mouse model for Down syndrome (Stasko and Costa, 2004). After contextual and auditory fear testing, animals were allowed to rest for 2 days before water maze training began. A circular pool (95 × 17 cm) was filled with opaque water (24 ± 5 °C) and a platform (6.5 cm

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