Time-dependent effects of LPS-induced chronic neuroinflammation and aging upon glutamate transporter GLT1 and SNAP25 expression correspond with spatial memory deficit in the rat hippocampus

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Introduction

Neuroinflammation may contribute to synapse loss, neurodegeneration and cognitive impairment in Alzheimer’s disease.

- Activated microglia are concentrated in vulnerable regions prior to the onset of cognitive deficits (Cagnin et al., 2001 & 2006; Edison et al., 2008).

Cognitive deficits may be due to an increase extracellular glutamate.

- Decreasing glutamate function in a model of inflammation and in natural aging is protective. ↓ release of glutamate by cannabinoids or caffeine (Marchalant et al., 2007b; Brothers et al., 2010).
- ↓ NMDAR function with menopause (Rui et al., 2006).

- Lipopolysaccharide (LPS) decreases NMDARs and increases calbindin (unpublished data), suggesting compensatory protection of neurons from increased calcium entry through NMDARs.

- Glutamate is increased in a model of diffuse brain injury (Hitzeman et al., 2010) and middle-aged rats, but aged rats show a compensatory protection through increased clearance (Stephens et al., 2009).

- Glutamate may be elevated in part due to changes in glutamate clearance by the glutamate transporter GLT1 (excitatory amino acid transporter 2, EAAT2) responsible for 80%-90% of clearance (Maragakis et al., 2004; Seltik et al., 2005).

- Glutamate transporter GLT1 deficiency accelerated onset of cognitive deficit in AβPPswe/2nd mice.

Neuroinflammation → ↑ Glutamate

Methods

- Subjects: F-344 male rats, 4 and 24 months.
- Surgical procedures: Infused either lipopolysaccharide (LPS, E. coli, 0.25 μg/ hr) or aCSF over 4, 2 or 8 weeks into ivth ventricle of young rats through cannula connected to an Alzet osmotic minipump (model 2006, 0.15 μl/ hr).
- Behavioral testing: Morris water maze (hippocampal-dependent spatial memory).
- Histology and Western blot analysis:
  - MHCII expression by microglia
  - SNAP25, a synaptic vesicle docking protein
  - GLT-1, glutamate transporter (EAAT2)
- Data are presented as mean ± SEM. Significant differences marked as: * treatment (aCSF vs LPS vs age) and † infusion duration (2w, 4w or 8w).

Water Maze Results

- All groups found the hidden platform more quickly on successive days except for Aged (p < 0.007*).
- Aged rats took longer to find the platform than aCSF and LPS 8w on day 1, and longer than all groups on days 2, 3 and 4 (p < 0.032*).
- LPS 4w took longer to find the hidden platform than LPS 8w on day 1 and longer than aCSF or LPS on days 2 & 4 (p < 0.028).
- Aged rats spent the least time in the vicinity of the missing platform during probe trials (p < 0.05†).
- Aged rats spent more time circling the perimeter of the WM pool than all groups on days 2, 3 and 4 (p < 0.002*).
- LPS 4w spent more time circling the perimeter of the WM pool than aCSF or LPS on days 3 & 4 (p < 0.001). Aged rats spent more than all groups on days 2 and 4 (p < 0.05†).
- Aged rats swam more slowly than all groups on days 2 & 4 (p < 0.05†).

Immunohistochemical Results

- aCSF 4w, LPS 2w, LPS 8w, Aged
- MHCII microglia in DG>CA3>CA1. LPS 4w and LPS 8w DG and CA3 > aCSF controls and LPS 2w (p < 0.002*). LPS 8w > LPS 4w in CA3 (p < 0.001†). Aged animals have more MHCII+ microglia in CA3 and DG than young controls. Aged data for MHCII is borrowed from Marchalant et al., 2008.
- GLT-1 is generally more highly expressed after LPS infusion as compared to controls and significantly increases with age.
- SNAP25 is generally more highly expressed after LPS infusion as compared to controls and significantly increases with age. LPS 4w CA3 > aCSF 4w CA3 (p < 0.006). LPS 8w CA3 > aCSF, LPS 2w and LPS 4w (p < 0.004†).

Conclusions

- LPS 4w and LPS 8w produced elevated numbers of ‘activated’ microglia in DG and CA3.
- LPS 4w induced spatial memory deficit, but not LPS 8w, indicating that animals were able to recover from the effects of chronic neuroinflammation.
- Rats may compensate for an age-related or LPS-induced chronic neuroinflammation by increasing expression of GLT1 and SNAP25.
- Increased SNAP25 (a synaptic vesicle docking protein) may contribute to the release of more event-related glutamate vesicles, and increased GLT1 (glutamate transporter) may lead to improved clearance of extracellular glutamate. If so, then these events may work synergistically to increase signal and reduce noise.

Neuroinflammation induces time-dependent changes in the hippocampus and a spatial memory deficit that can be attenuated through mechanisms that regulate glutamate.

References


