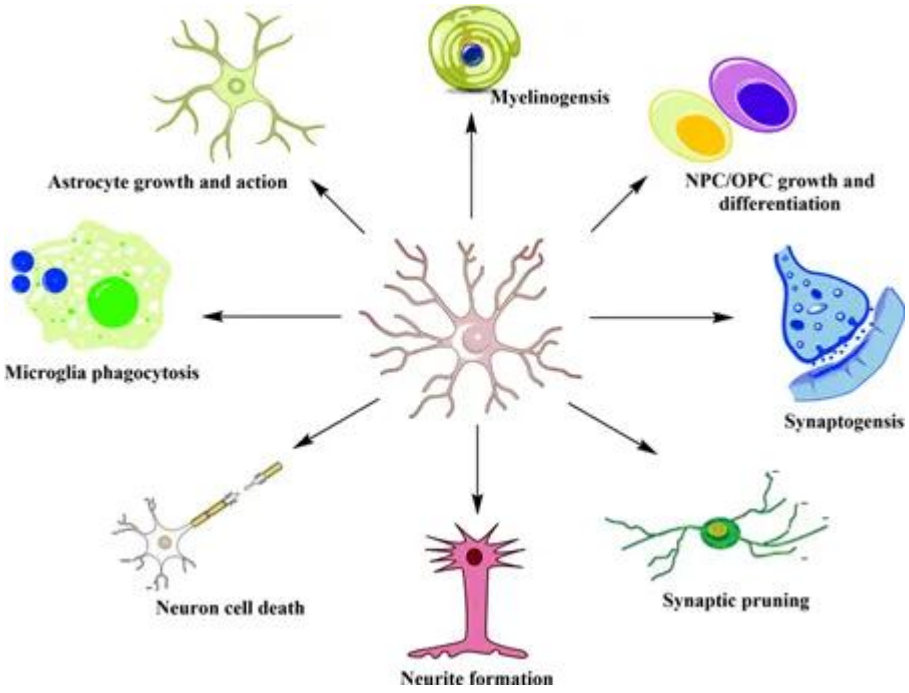
[et_pb_section fb_built="1" admin_label="section" _builder_version="4.16" global_colors_info="{}"][et_pb_row admin_label="row" _builder_version="4.23" background_size="initial" background_position="top_left" background_repeat="repeat" width="90%" max_width="none" hover_enabled="0" global_colors_info="{}" sticky_enabled="0"][et_pb_column type="4_4" _builder_version="4.16" custom_padding="|||" global_colors_info="{}" custom_padding__hover="|||"][et_pb_text admin_label="Text" _builder_version="4.16" background_size="initial" background_position="top_left" background_repeat="repeat" global_colors_info="{}"]

Neuroinflammation is defined as an inflammatory response mediated by astrocytes, microglia, and endothelial cells within the central nervous system (CNS), initiated by various stimuli, such as infection, traumatic brain injury, toxic metabolites, and autoimmunity. The primary responders are microglia, the resident macrophages in the brain that play critical roles in the onset and progression of neuroinflammation. The hippocampus is a part of the brain's limbic system, embedded deep into the temporal lobe, and is important for cognition, learning, and affective brain functions. It is a vulnerable structure that gets damaged by a variety of stimuli. Hippocampal γ-aminobutyric acid (GABA)-ergic synaptic deficit, induced by an altered excitation-to-inhibition balance, results in cognitive and memory impairments, anxiety, and depression. In this study, Korean researchers used several methods to investigate the brain pathology associated with hippocampal inflammation resulting from systemic inflammation induced by lipopolysaccharide (LPS) in C57BL/6J mice.

Synapses are fundamental information-processing units of neuronal circuits. They form the basis for all brain functions by controlling the excitation-to-inhibition balance. Various cellular and molecular mechanisms underlie synapse formation. Microglia shape the number, morphology, and/or connections of synapses under neuroinflammatory conditions. It was initially reported that microglia contribute to the reconstruction of neuronal circuits by eliminating excess neuronal synapses and newborn neurons during brain development. According to recent data, however, microglia are actively involved in synapse dynamics in healthy adult brains.

The authors stressed that their previous work has shown that two daily intraperitoneal injections of 0.5 mg/kg LPS activated microglia throughout the brain, including the hippocampus. Also, a recent study demonstrated that intraperitoneal administration of the LPS markedly reduced the expression of calbindin, a marker of GABAergic neurons in the mouse brain.
https://discovermednews.com/s1-protein-causes-brain-inflammation-and-decreases-the-acetylcholine-levels/



Multiple physiological roles of microglia in the CNS. Original figure from the article of Wang H et al. Journal of Neuroinflammation, 2022; 19(1).

About the study

The scientists used several methods to investigate the temporal sequences of brain pathology associated with hippocampal neuroinflammation, such as microglial activation, synaptic dysfunction, and memory-related behavioral changes. They focused on changes in the CA1 region, the dominant histological region of the hippocampus, known for its role in memory.

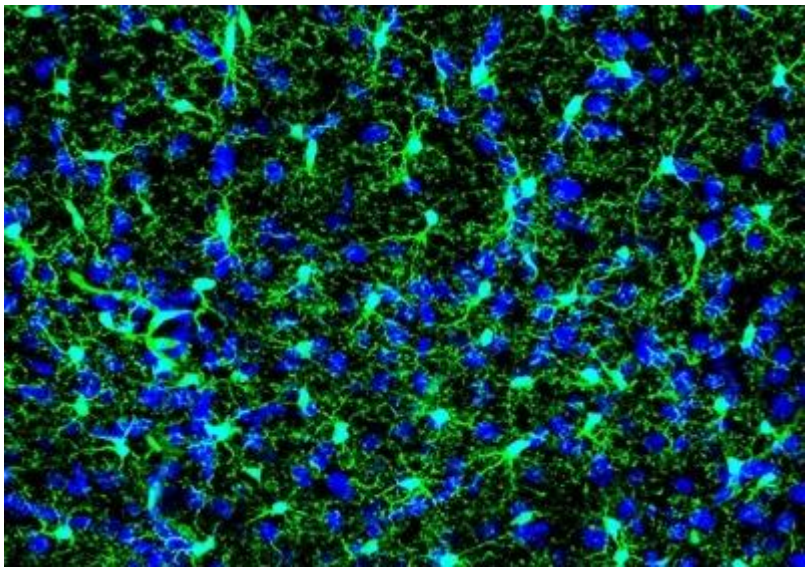
At the beginning of the study, to induce systemic inflammation, the researchers injected intraperitoneally 0.5 mg/kg LPS (from *Escherichia coli*) to eight-week-old C57BL/6J mice once a day for two days. Behavior in the acute phase of the disease, locomotor activity, and body weight were monitored daily until the mice were back in the normal range.

To investigate behavioral changes related to memory, the researchers use the open-field test that assesses general locomotor activity, the novel object-recognition test that assesses

memory deficit, and the light and dark transition test that assesses anxiety-related behavior.

At 3, 4, 6, and 8 days post-injection (dpi), the hippocampal slices were analyzed for the number of microglia positive for the microglial marker Iba-1 (ionized calcium-binding adapter molecule-1), and the expression level of CD68 (a lysosomal protein, frequently used as a marker for actively phagocytic microglia).

To assess whether microglial activation induced by LPS contributes to synaptic dynamics, scientists analyzed the excitatory and inhibitory synaptic puncta in various layers of the hippocampal CA1 region. In addition, they performed the whole-cell electrophysiological recording of spontaneous and evoked inhibitory postsynaptic currents (sIPSCs and eIPSCs) in hippocampal CA1 slices.



Results

The mice lost about 20% of their body weight after the intraperitoneal injection of LPS, but they returned to 90% of their body weight after four days.

At 3 dpi, immunohistochemical analysis demonstrated activation of hippocampal microglia in the LPS-injected mice according to microglial marker Iba-1, and marker of actively phagocytizing microglia, CD68. These findings were absent at 4–8 dpi. Also at 3 dpi, the morphological changes of microglia were seen, from ramified to bushy, but they returned to normal at 8 dpi. These results indicate microglial activation in the hippocampal CA1 region

3 days after the LPS injection with altered cellular morphology, microglial density, and expression of microglial markers. However, all of these changes gradually returned to normal at 8 dpi.

At 4-6 dpi, quantitative immunofluorescence revealed a significant decrease in density and the average size of VGAT puncta (GABA inhibitory presynaptic marker) in the hippocampal CA1 region. Minor changes were detected in the density and the average area of GABAARγ2 puncta (GABA inhibitory postsynaptic marker).

At 6 dpi, a semiquantitative immunohistochemical analysis using antibodies against VGAT (GABA inhibitory presynaptic marker) and gephyrin (scaffold responsible for organizing the inhibitory postsynaptic density) demonstrated that GABA-ergic synaptic components were reduced in all examined layers of hippocampal CA1 region in LPS-treated mice.

Importantly, there were no alterations in the density and average size of VGLUT1 (vesicular glutamate transporter 1; excitatory presynaptic marker) and PSD-95 (excitatory postsynaptic marker) puncta in all examined layers of hippocampal CA1 region in LPS-treated mice.

At 6 dpi, the overall locomotor activity measured by the open-field test and anxiety-related behavior, assessed by the light and dark transition, did not differ between LPS-treated and control mice. However, LPS-treated mice displayed a severe memory deficit, measured by the novel object-recognition test. This result implies that memory impairment lasted for 6 days.

These results show that transient hippocampal microglial activation preceded GABAergic synaptic deficit that was detected 4 days after systemic LPS administration. The persistence of GABAergic synaptic deficits up to 8 dpi, parallel with the memory impairment seen at 6 dpi, suggests long-lasting synaptic changes.

There was no difference in the whole-cell electrophysiological recording of spontaneous and evoked inhibitory postsynaptic currents (sIPSCs and eIPSCs) recorded from CA1 hippocampal neurons between LPS-treated mice and control mice.

Conclusion

This animal study has shown that systemic administration of LPS causes hippocampal microglial activation, GABA-ergic synaptic deficit, and memory impairment. Importantly, microglial activation induced by LPS specifically affected GABA-ergic synapses.

The authors believe that loss of GABA-ergic synapse in LPS-treated mice could be caused by synapse elimination mediated by microglia rather than by pro/anti-inflammatory cytokines released from activated microglia.

This research provides mechanistic insights that may explain the persistent cognitive deficit observed in individuals with neuroinflammation. The authors focused on hippocampal changes but emphasized that future investigations should examine the temporal sequence of biological events in other brain regions. Furthermore, future research is needed to explore why LPS-induced microglial activation specifically affects GABA-ergic synapses.

The article was published in Scientific Reports (Nature)

Journal Reference

Jung H, Lee D, You H et al. LPS induces microglial activation and GABAergic synaptic deficits in the hippocampus accompanied by prolonged cognitive impairment. Scientific Reports (2023) 13:6547. https://doi.org/10.1038/s41598-023-32798-9

[/et_pb_text][/et_pb_column][/et_pb_row][/et_pb_section]