Nature Reviews Neuroscience | AOP, published online 9 April 2014; doi:10.1038/nrn3733

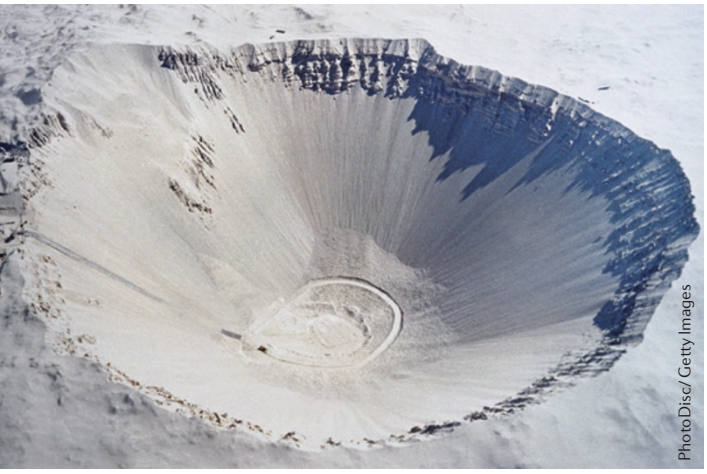
SYNAPTIC PLASTICITY

Microglial cell-mediated depression

> The authors recorded field potentials in hippocampal slices from wild-type rats and mice and CR3-knockout mice after exposure to LPS and/or hypoxic conditions.

Neuroinflammation and hypoxia are thought to interact synergistically to increase cognitive dysfunction in various brain disorders, including stroke and neurodegenerative diseases, but the mechanisms underlying these interactions remain unclear. MacVicar and colleagues now show that, in the presence of hypoxia, activation of microglial complement receptor 3 (CR3) by an inflammatory stimulus induces long-term depression (LTD) of synaptic transmission in the hippocampus, suggesting a means by which memory may be impaired in these disorders.

CR3 is only expressed in microglia in the brain and, probably through activation by complement 3, has a crucial role in synaptic pruning during brain development. However, CR3 can also be directly activated by various neuroinflammatory stimuli, including lipopolysaccharide (LPS). As microglia play a crucial part in CNS neuroinflammation in various brain disorders that are characterized by neuronal dysfunction, MacVicar and colleagues assessed the effects of LPS-mediated CR3 activation on synaptic transmission.



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The authors recorded field potentials in hippocampal slices from wild-type rats and mice and CR3-knockout mice after exposure to LPS and/or hypoxic conditions. In wild-type animals, LPS alone had no effect on basal synaptic transmission, but the hypoxic stimulus alone caused a transient depression in field excitatory postsynaptic potentials (fEPSPs). Strikingly, exposure to both stimuli (hypoxia–LPS) caused LTD of fEPSPs, indicating that these stimuli act synergistically to suppress synaptic transmission. No LTD could be induced in hippocampal slices from CR3-knockout mice, implying that LPS exerts its effects on synaptic transmission through microglial CR3.

LPS-mediated activation of CR3 stimulates microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which generates superoxide. The authors showed that apocynin, an NADPH oxidase inhibitor, blocked LTD in rat hippocampal slices if it was co-applied with LPS and hypoxia but had no effect on LTD if it was applied after the other stimuli. Moreover, ascorbic acid, which scavenges reactive oxygen species, could also block LPS–hypoxia-induced LTD. Thus, NADPH oxidase is necessary for LTD induction but is not required for its maintenance and exerts its effects through superoxide production.

The authors next examined the superoxide-mediated effects in neurons that are involved in LPS–hypoxia-induced LTD. Previous studies have revealed that superoxide can increase the activity of protein phosphatase 2A (PP2A). Here, the authors found that LPS–hypoxia-induced LTD was associated with increased PP2A activity and that okadaic acid-mediated blockade of PP2A prevented LTD induction. AMPA receptor endocytosis has a role in NMDA receptor-mediated LTD, and the authors found that interference with such endocytosis also prevented LPS–hypoxia-induced LTD. Thus, neuronal PP2A activity and AMPA receptor internalization are involved in microglial CR3-triggered LTD.

Together, these results provide a mechanism whereby activation of CR3 in microglia can depress synaptic transmission in neurons. This mechanism may, at least in part, contribute to the synaptic dysfunction and memory defects that are associated with a number of brain disorders that are characterized by neuroinflammation and hypoxia.

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ORIGINAL RESEARCH PAPER Zhang, J. *et al.* Microglial CR3 activation triggers long-term synaptic depression in the hippocampus via NADPH oxidase. *Neuron* http://dx.doi.org/10.1016/j.neuron.2014.01.043 (2014)