Systemic immune responses and neutrophil activation in the propagation of neuroinflammation after cerebral ischemia-reperfusion

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Post-ischemic neuroinflammation remains an elusive therapeutic target for patients suffering from global ischemia following cardiac arrest. While heightened inflammatory responses portend poor neurologic recovery, the lack of models that faithfully reproduce features of post-cardiac arrest syndrome (PCAS) remains a barrier to developing neuroprotective therapies. Here we demonstrate that serologically undetectable endotoxemia causes acute neutrophil activation and enhanced CNS inflammation when combined with global cerebral ischemia.

Transient global ischemia was induced in 5-8 week-old C57/B6 mice using 3-vessel occlusion (3VO), which involves basilar artery cauterization and 15-minute occlusion of the common carotid arteries. Mice were given saline or 50 µg/kg lipopolysaccharide (LPS) intraperitoneally to mimic enteric endotoxin leak and systemic inflammation observed during PCAS. Animals receiving saline or LPS served as controls.

Six hours after injury, upregulation of the neutrophil activation marker CD11b was observed in sham-treated animals, with greater activation in those also undergoing 3VO. Three days after ischemia-reperfusion, animals with concomitant inflammation experienced the greatest blood-brain barrier permeability, evidenced by upregulation of vascular PECAM-1, enhanced IgG deposition, and neutrophil migration into the CNS. Animals receiving 3VO and LPS exhibited microglial activation characterized by Iba1 upregulation and amoeboid morphology. These changes were specific to areas of dense neutrophil infiltration, suggesting the effects were likely cell-mediated and not a consequence of passive endotoxin transfer across the blood-brain barrier. While the role of neutrophils in cerebral ischemia reperfusion injury remains controversial, our data indicate that neutrophil activation and migration remain particularly relevant targets for mitigating neuroinflammation in the setting of cardiac arrest.