Neuronal CXCL10/CXCR3 Axis Mediates the Induction of Cerebral Hyperexcitability by Peripheral Viral Challenge

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While peripheral viral infections have been shown to increase the risk for seizures, the cellular/molecular mechanisms of infection-induced seizure hypersusceptibility are poorly understood. We have developed a preclinical murine model to study mechanisms by which peripheral infection exerts its effects on the brain by using an intraperitoneal injection of the epitomic viral mimetic, polyinosinic-polycytidylic acid (PIC). We have demonstrated that PIC challenge induces hyperexcitability of neuronal networks as seen from a profound increase in the basal synaptic transmission (a measure of neuronal communication) and long-term potentiation (a long-lasting increase in signal transmission between two neurons) in hippocampal slices, as well as from hypersusceptibility to kainic acid-induced status epilepticus. Because neuronal hyperexcitability is an invariable feature of seizures, it might provide a mechanistic link for the exacerbating effects of peripheral inflammation on disease progression.

To determine the molecular link between PIC challenge and neuronal hyperexcitability, we previously examined numerous cytokines, chemokines, and inflammatory mediators after PIC challenge. We demonstrated that in the hippocampus (an ictal site of seizures), only the chemokine CXCL10 was robustly increased, whereas other major inflammatory mediators were either only slightly elevated or unchanged. Because CXCL10 is a potent modulator of neuronal activity, it seems plausible that it might be a putative molecule, which acting through its cognate receptor, CXCR3, drives the development of hyperexcitability.

The present study was undertaken to determine the role of CXCL10 in mediating the development of hyperexcitability in response to PIC challenge. Briefly, young female C57BL/6 mice received an intracerebroventricular infusion of the CXCR3 antagonist, AMG 487 (3 mg/kg) and two hours later were given an intraperitoneal injection of the viral mimetic, PIC (12 mg/kg). Mice underwent examination 24 hours after PIC challenge. Blocking cerebral CXCR3 through intracerebroventricular injection of a specific inhibitor, AMG487, abrogated PIC challenge-induced increase in basal synaptic transmission and long-term potentiation, as well as the reduction of paired-pulse facilitation (a measure of glutamate release). The PIC-mediated abolishment of long-term depression (a long-lasting reduction in the efficacy of neuronal synapses) was also restored after application of AMG487. Moreover, CXCR3 inhibition attenuated seizure hypersensitivity induced by PIC challenge. The efficacy of AMG487 strongly strengthens the notion that CXCL10/CXCR3 axis mediates the induction of cerebral hyperexcitability by PIC challenge.

Statement of Research Advisor

Allison's work strongly indicates that the CXCL10/CXCR3 axis governs the induction of neuronal hyperexcitability and suggests that the CXCL10/CXCR3 axis may play a critical role in the comorbid effect of peripheral viral infections on the progression of major neuropathological diseases, including seizure hypersusceptibility. Future work will identify the how CXCL10/CXCR3 axis signaling mediates the development of hyperexcitability.

– Miranda Reed, Drug Discovery and Development

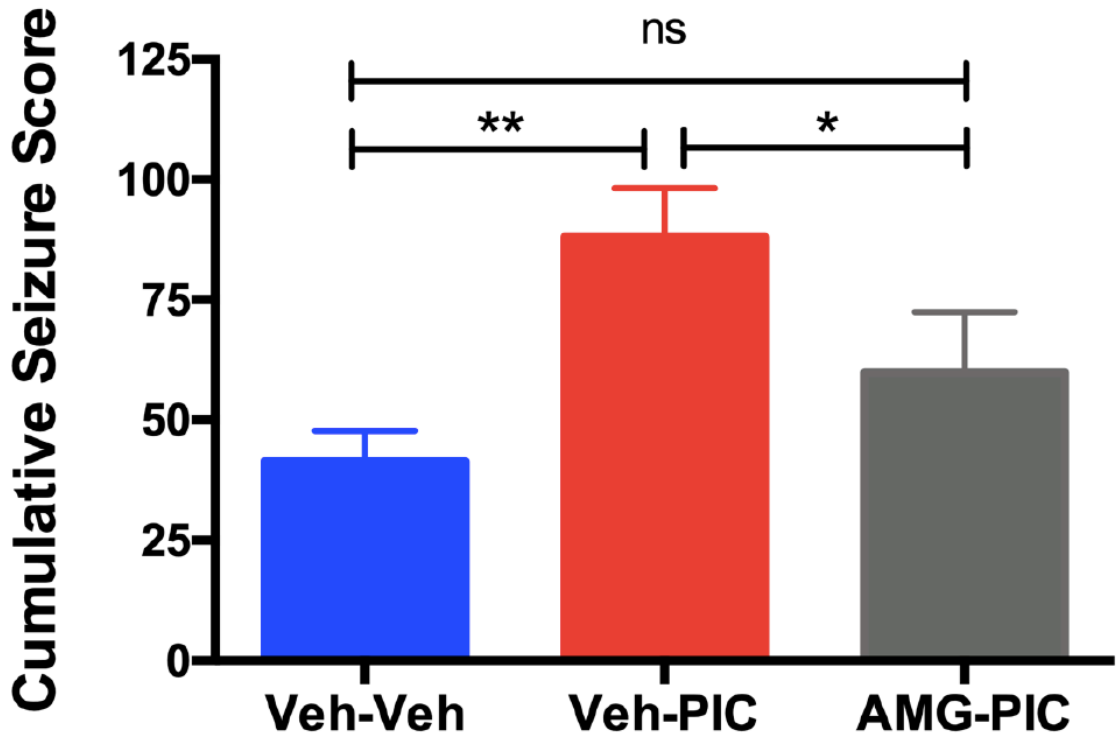

Figure 1: PCXCR3 inhibition attenuates seizure hypersensitivity induced by PIC challenge. Mice received a bolus of intracerebroventricular injection of AMG 487 (3 mg/kg) or vehicle (VEH). Two hours later, the acute antiviral response was induced by intraperitoneal injection of 12 mg/kg of PIC in saline. Mice injected with 100 μL of saline served as vehicle controls. Twenty-four hours after PIC injection, status epilepticus (SE) was induced by subcutaneous injection of 12 mg/kg of kainic acid. Mice injected with saline in lieu of PIC served as controls (VEH). Seizures were expressed as cumulative seizure score using a 6-step scale where 0 is no seizure and 6 is a severe, tonic-clonic seizure. Symbols represent means ± SEM from 3 to 6 mice per group. *$p \leq 0.05$, **$p \leq 0.01$; ns = not significantly different.