Title: Postnatal inflammation increases seizure susceptibility in adult rats

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Abstract: There are critical postnatal periods during which even subtle interventions can have long-lasting effects on adult physiology. We have asked whether an immune challenge during early postnatal development can alter neuronal excitability and seizure susceptibility in adults. Postnatal day (P)14 male Sprague-Dawley rats were injected with the bacterial endotoxin lipopolysaccharide (LPS), while control animals receive sterile saline. Three weeks later, extracellular recordings from hippocampal slices revealed enhanced field excitatory postsynaptic potential slopes after Schaffer collateral stimulation and increased epileptiform burst-firing activity in CA1 following 4-aminopyridine application. Six to eight weeks after postnatal LPS injection, seizure susceptibility was assessed in response to lithium-pilocarpine, kainic acid, and pentylentetrazol. Rats treated with LPS showed significantly greater adult seizure susceptibility to all convulsants, as well as increased cytokine release and enhanced neuronal degeneration within the hippocampus following limbic seizures. These persistent increases in seizure susceptibility occurred only when LPS was given during a critical postnatal period (P7 and P14) and not before (P1) or after (P20). This early effect of LPS on adult seizures was blocked by concurrent intracerebroventricular (ICV) administration of a tumor necrosis factor (TNF)α antibody and mimicked by ICV injection of rat recombinant TNFα. Postnatal LPS injection did not result in permanent changes in microglial (Iba1) activity or hippocampal cytokine (IL-1β and TNFα) levels, but caused a slight increase in astrocyte (GFAP) numbers. These novel results indicate that a single LPS injection during a critical postnatal period causes a long-lasting increase in seizure susceptibility that is strongly dependent on TNFα.

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