This Week in The Journal

Role of P2X7 Receptors in Epilepsy

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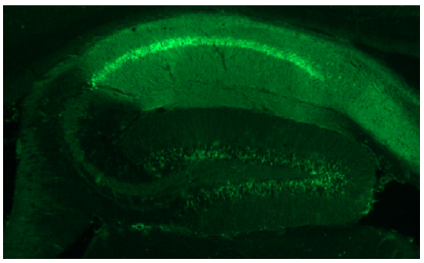
(see pages 5920 –5932)

Inflammation is an important contributor to seizure disorders. Infections, auto-immune diseases, and injuries that cause brain inflammation can trigger seizures, and seizures, in turn, prolong neuroimmune responses (Vezzani, et al. 2013 Exper Neurol 244:11). Inflammatory mediators can increase seizure susceptibility by reducing the ability of astrocytes to regulate extracellular potassium and glutamate levels. Moreover, interleukin-1ß (IL-1ß), which is released from activated astrocytes and microglia during neuroimmune responses, can promote phosphorylation of neuronal NMDA receptors, leading to increased calcium influx and heightened neuronal excitability. Importantly, inhibiting pro-inflammatory signaling by IL-1ß reduces seizure frequency in experimental animals. Therefore, inflammatory pathways may be good therapeutic targets in epilepsy.

An early step in neuroinflammation is activation of low-affinity ATP-gated P2X7 receptors. When cells are damaged, a large amount of ATP is released into the extracellular space, where it can activate P2X7 receptors on microglia. This causes immunological activation, during which microglia release IL-1ß and other cytokines. Jimenez-Pacheco et al. found that transcription of the gene encoding P2X7 receptors (*P2rx7*) increased in mouse hippocampus after temporal-lobe epilepsy was induced by injecting kainic acid into the amygdala. *P2rx7* transcription was upregulated not only in microglia, but also in CA1 neurons, where its expression is normally low. P2X7 receptor protein levels were also increased in these neurons, as were currents evoked by a P2X7 agonist, indicating the receptors were functional. Most importantly, systemic injection of a selective P2X7 receptor antagonist (given twice daily for 5 days) reduced the rate of spontaneous seizures in epileptic mice. Seizure rates remained lower for at least 6 days after injections ceased. Finally, hippocampal slices from antagonist-treated mice had less microgliosis and astrocytosis than those from untreated epileptic mice.

These results indicate that P2X7 receptor antagonists may reduce seizure incidence in people with epilepsy. This is important, because existing antiepileptic drugs are ineffective in ~30% of patients. Moreover, existing drugs target neuronal excitability, often causing unwanted side effects, and discontinuing their use typically results in renewed seizure activity. The fact that the effects of P2X7 receptor antagonists persisted after treatment ceased suggests that P2X7 receptor antagonists reduce the pathology underlying seizure susceptibility, possibly making life-long treatment unnecessary.



P2rx7 transcription is elevated in hippocampal CA1 neurons and microglia in epileptic mice. See Jimenez-Pacheco et al. for details.

Effects of D2-Expressing Striatal Neurons on Motivation

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(see pages 5988 – 6001)

To obtain a goal, one must think the goal is desirable at the present time, choose an appropriate goal-directed action, initiate that action, and maintain the action until the goal is reached. These processes are considered different facets of motivation, and they are driven by dopaminergic inputs to multiple brain areas, including the striatum. How dopaminergic inputs to different neuronal populations affect specific aspects of motivation remains unclear, however.

Previous work found that overexpressing D2 dopamine receptors, which are expressed in indirect-pathway striatal medium spiny neurons (MSNs), caused motivation deficits in mice. But interpreting these results is difficult, because the receptors were overexpressed throughout development, causing compensatory changes. For example, although activation of D2 receptors inhibits indirect-pathway MSNs, overexpression of D2 receptors made these neurons more excitable than normal.

To get a clearer picture of the role of D2-expressing MSNs in motivation, Carvalho Poyraz et al. inhibited the neurons in adult mice using designer receptors activated by designer drugs. In a progressive ratio task—in which the number of times mice are required to press a lever to obtain a reward increases after every trial—acute suppression of D2-MSN activity in either the dorsal or ventral striatum increased the number of lever presses and the number of rewards received in both D2-overexpressing and control mice. Suppressing D2-MSN activity also increased the number of lever presses in a progressive hold-down task, which requires mice to hold a lever down for a longer duration on each successive trial. Importantly, however, suppressing D2-MSN activity reduced the duration of lever holding in this task, so mice earned fewer rewards. Thus, while reducing D2-MSN activity was beneficial in a task requiring repeated action, it was detrimental in a task requiring sustained action. These results suggest that D2-MSN activity reduces the motivation to initiate goal-directed actions, but it enhances the motivation to maintain effort over time.

These results may be relevant to Parkinson's disease, in which action initiation is impaired. Indeed, D2 receptor agonists have been reported to enhance motivation in Parkinson's disease patients. But the present results suggest that these drugs may reduce motivation to complete sustained-effort tasks, which might be a problematic side effect.

This Week in The Journal is written by Teresa Esch, Ph.D.