This Week in The Journal

Serotonin-Independent Actions of SSRIs in the Hypothalamus

David J. Lyons, Rachida Ammari, Arash Hellysaz, and Christian Broberger

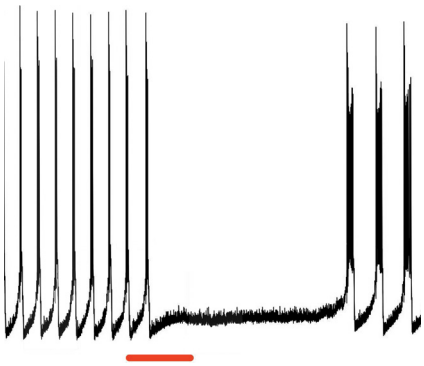
(see pages 7392–7406)

Prolactin is a pituitary hormone best known for its role in stimulating milk production in the mammary gland. Nonetheless, it also influences other physiological processes, including appetite, glucose metabolism, fertility, and sexual desire. Unlike other pituitary hormones whose release is triggered by hypothalamic releasing factors, prolactin is under tonic inhibitory control, which keeps its levels in the blood low most of the time. This inhibition is mediated primarily by tuberinfundibular dopamine (TIDA) neurons in the hypothalamic arcuate nucleus. Blocking dopamine production, release, or activation of D2 dopamine receptors removes tonic inhibition from pituitary lactotrophs, leading to hyperprolactinemia, which impairs sexual function and fertility. Serotonin also increases prolactin release, and selective serotonin reuptake inhibitors (SSRIs) can cause hyperprolactinemia. This may contribute to the sexual side effects commonly associated with SSRI use.

How serotonin promotes prolactin release has been unclear, but Lyons et al. now show that serotonin inhibits TIDA neurons. Application of serotonin hyperpolarized TIDA neurons, and thus eliminated the normal oscillatory activity of these neurons in rat brain slices. Hyperpolarization persisted in the presence of tetrodotoxin, indicating that serotonin acted directly on TIDA neurons. Serotonin-evoked hyperpolarization was mediated by 5-HT_{1A} receptors and downstream activation of a g-protein-dependent outward potassium current, likely involving GIRK channels.

SSRIs also altered TIDA neuron activity. Although therapeutic concentrations of SSRIs only slightly reduced the amplitude and frequency of oscillations in TIDA neurons, they dramatically decreased the intrinsic excitability of these neurons, as assessed by the number of action potentials elicited during a square current injection. Spike amplitudes were also decreased, while spike thresholds were increased. At higher doses, prolonged SSRI treatment abolished TIDA oscillations. These results are surprising, because they occurred in slices which presumably lack endogenous serotonin release. Indeed, the effects of SSRIs persisted in the presence of a 5-HT_{1A} receptor antagonist, confirming that they occurred independently of serotonin.

SSRIs may therefore increase plasma prolactin levels by reducing activity in TIDA neurons. In the intact brain, this action likely stems not only from SSRI-mediated increases in serotonin levels in the arcuate nucleus, but also from a serotonin-independent action of SSRIs on TIDA neurons. Whether these effects alter prolactin levels sufficiently to produce sexual dysfunction remains to be tested.



Serotonin application (red line) hyperpolarizes TIDA neurons, stopping oscillatory activity. See Lyons et al. for details.

Reciprocal Effects of Stroke and Gut Microbiota

Vikramjeet Singh, Stefan Roth, Gemma Llovera, Rebecca Sadler, Debora Garzetti, et al.

(see pages 7428 –7440)

Arterial occlusion leads quickly to oxygen and glucose depletion in surrounding tissue, resulting in neuron death. Molecules released from damaged tissues activate local immune cells, which in turn release inflammatory cytokines. Cytokines increase the permeability of the blood–brain barrier, which eventually allows peripheral immune cells, including T lymphocytes, to infiltrate the brain. Many T cells are pro-inflammatory or cytotoxic, and thus exacerbate brain damage, but regulatory T cells (Treg) limit inflammation and improve stroke outcome.

How different classes of peripheral T cells are activated during stroke is unclear, but the gut microbiota, which regulates the development of lymphoid nodules in the lining of the gastrointestinal tract, might be involved. Different gut microbial species promote development of pro- or anti-inflammatory T cells, and altering the composition of the microbiota with antibiotics was recently shown to reduce the population of cytotoxic T cells, increase the population of anti-inflammatory cells, and reduce infarct volume and functional impairment in mice subjected to stroke (Benakis et al. 2016 Nat Med 22: 516).

Besides affecting stroke outcome, the gut microbiota is altered by stroke. Singh, Roth et al. found that severe stroke led to substantial changes in gut microbiota composition—including a significant reduction in species diversity—in mice. This dysbiosis altered stroke outcome in germ-free mice that received gut microbiota from stroke-treated mice: stroke damage and functional impairment was greater in recipients of post-stroke microbiota than in recipients of control microbiota. In addition, stroke-microbiota recipients had more pro-inflammatory T cells in intestinal lymphoid nodules and brain than recipients of control microbiota. Finally, fecal microbiota transplantation after severe stroke reduced dysbiosis, increased microbiota diversity, increased the number of anti-inflammatory T cells and reduced lesion volume. Fecal transplant did not affect lesion volume in lymphocyte-deficient mice, suggesting that T lymphocytes were responsible for these effects.

These results suggest that stroke causes changes in the gut microbiota, resulting in increased production of pro-inflammatory T cells, which in turn exacerbate brain damage. Importantly, external manipulations can reverse these changes and improve stroke outcome. Identifying ways to promote the production of neuroprotective T cells and limit production of pro-inflammatory T cells might thus help to limit stroke damage.

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