This Week in The Journal

● Cellular/Molecular

MrgprD Is an Itch Receptor

Qin Liu, Parul Sikand, Chao Ma, Zongxiang Tang, Liang Han, et al.

(see pages 14532–14537)

How itch is encoded and distinguished from other sensations transmitted by the same C-fibers is poorly understood. Histamine, which is secreted by mast cells in the skin, is the best-studied pruritic agent, and it activates a G-protein-coupled receptor that must interact with transient receptor potential channels to evoke itch responses. Many clinically relevant pruritic agents and chronic itch conditions are unaffected by antihistamines, however, prompting a search for histamine-independent itch pathways. One such pathway involves Mas-related G-protein-coupled receptors (Mrgprs). For example, Liu et al. show that β-alanine elicits scratching in wild-type but not MrgprD-null mice and only MrgprD-expressing dorsal root ganglion neurons are activated by β-alanine *in vitro*. Although no MrgprD-expressing neurons responded to histamine or chloroquine (a pruritic agent that activates MrgprA3), all responded to noxious mechanical stimulation of the skin. A subset of MrgprD-expressing neurons also responded to noxious heat, and only this subset responded to β-alanine. These data highlight the diversity of nociceptors and the complexity of somatosensory encoding.

▲ Development/Plasticity/Repair

Stress Hormone Reduces Caldesmon, Which Regulates Spine Size

Daisuke Tanokashira, Tsuyoshi Morita, Ken'ichiro Hayashi, Taira Mayanagi, Kentaro Fukumoto, et al.

(see pages 14583–14591)

Dendritic spines begin as motile filopodia that are stabilized by synaptic contacts and grow into mature, mushroom-shaped structures as synapses strengthen. The initial formation, motility, and remodeling of spines are driven by actin, and thus are regulated by proteins that promote stability or disassembly of actin filaments. Tanokashira et al. report that caldesmon—a ubiquitously expressed actin-binding protein that regulates neuronal migration and axon growth—has an essential role in shaping dendritic spines. As rat hippocampal neurons matured in culture, caldesmon expression increased and accumulated in spines. Overexpression of caldesmon increased actin stability in spines and enabled spine heads to grow larger, whereas caldesmon knockdown reduced spine head size. More importantly, of 25 actin-binding proteins examined, only caldesmon was substantially downregulated by corticosterone treatment in hippocampal cultures, and caldesmon overexpression attenuated corticosterone-induced reduction of spine size. Downregulation of caldesmon might therefore be a primary means by which stress leads to simplification of neuronal structure and impairs cognitive function.

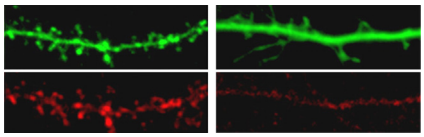
■ Behavioral/Systems/Cognitive

Sensory Substitution Underlies Recovery of Gaze Stability

Soroush G. Sadeghi, Lloyd B. Minor, and Kathleen E. Cullen

(see pages 14685–14695)

Head movements activate the vestibular ocular reflex, in which vestibular afferents activate neurons in the vestibular nucleus (VN), which in turn project to extraocular motor neurons that move the eyes in the opposite direction of head movement. This stabilizes gaze. In humans, damage to the vestibular system initially causes oscillopsia, but gaze stability recovers within 1–2 months. This recovery is thought to result from sensory substitution by neck proprioceptive afferents and, in the case of planned movements, efferent copies of motor commands that turn the head. Sadeghi et al. provide support for this hypothesis, showing that single VN neurons in monkeys became more sensitive to such inputs after bilateral vestibular inputs were removed. After surgery, the sensitivity of VN neurons to neck rotation increased in parallel with improvements in gaze stabilization. Likewise, VN neurons began to respond when an active head movement was planned but prevented, suggesting they received efferent copies of motor commands. Together, these inputs were sufficient to explain improved gaze stabilization.



Corticosterone treatment (right) reduces spine size (revealed by green fluorescent protein expression) and caldesmon levels (red). See Tanokashira et al. for details.

♦ Neurobiology of Disease

Paraquat Increases α-Synuclein Aggregation via NOX1

Ana Clara Cristóvão, Subhrangshu Guhathakurta, Eugene Bok, Goun Je, Seung Don Yoo, et al.

(see pages 14465–14477)

Parkinson's disease (PD) is characterized by cytoplasmic inclusions containing aggregated α-synuclein in midbrain dopaminergic neurons. Although PD sometimes stems from inherited mutations in α-synuclein or other proteins, it more commonly occurs sporadically and can be triggered by exposure to toxins such as the herbicide Paraquat. How toxins induce α-synuclein aggregation is poorly understood, but one likely link is oxidative stress resulting from high levels of reactive oxygen species (ROS). Dysfunctional mitochondria are a common source of ROS, but evidence suggests that superoxide generated by NADPH oxidase (NOX) may be a critical contributor to neurotoxicity. Cristóvão et al. previously showed that Paraquat increases NOX1 levels in rodent dopaminergic neurons, and inhibiting NOX1 decreased Paraquat-induced neuron death. They now present evidence linking NOX1 to α-synuclein aggregation. Specifically, whereas Paraquat increased α-synuclein expression and aggregation, as well as NOX1 levels, in rat substantia nigra, NOX1 knockdown reduced Paraquat-induced α-synuclein aggregation while attenuating loss of dopaminergic neurons.