This Week in The Journal

● Cellular/Molecular

Sorting Out Membrane-Initiated Estrogen Effects

Marissa I. Boulware, Holly Kordasiewicz, and Paul G. Mermelstein

(see pages 9941–9950)

The caveolins (CAV1–3) are, not surprisingly, integral components of caveolae, pockets within the plasma membrane capable of signal transduction. In this week's *Journal*, Boulware et al. describe two distinct estrogen receptor signaling pathways that require caveolins, thus providing a potential mechanism for the membrane effects of estrogens. In the first, activation of membrane-localized estrogen receptor α (ERα) led to activation of metabotropic glutamate receptor 1a (mGluR1a). That signal culminated in mitogen-activated protein kinase (MAPK)-dependent phosphorylation of the cAMP response element-binding protein (CREB). In cultured hippocampal neurons, a point mutation in ERα that disrupted its association with CAV1 impaired estradiol activation of mGluR1a and CREB phosphorylation. Signaling was also abolished by a dominant-negative CAV1. In a second estradiol-activated pathway, binding at ERα or ERβ triggered mGluR2/3 activation, which attenuated L-type calcium channel-dependent CREB phosphorylation. This independent signaling process was not affected by the loss of ERα or CAV1 but was eradicated by loss of CAV3.

▲ Development/Plasticity/Repair

A SUMO E3 Ligase and Dendritic Morphogenesis

Aryaman Shalizi, Parizad Bilimoria, Judith Stegmüller, Brice Gaudillière, Yue Yang, Ke Shuai, and Azad Bonni

(see pages 10037–10046)

The terminal dendrites of cerebellar granule cells mature from smooth "cups" into the serrated dendritic "claws," which receive input from mossy fiber terminals and Golgi cell axons. This week, Shalizi et al. examined the underlying signaling mechanisms in dendritic morphogenesis. Claw differentiation requires the transcription factor myocyte enhancer factor 2A (MEF2A) in a form that was modified by linkage of a small ubiquitin-related modifier (SUMO). The final step in sumoylation is carried out by a SUMO E3 ligase. The authors demonstrated that the E3 ligase PIASx (protein inhibitors of activated STAT) led to SUMO modification of MEF2A and repression of MEF2-dependent transcription. After knockdown of PIASx expression with RNA interference, claw structures were reduced in dendrites of developing rat cerebellar cortex, whereas overexpression of PIASx increased claws. Expression of sumoylated MEF2A rescued claw differentiation in the absence of PIASx.

■ Behavioral/Systems/Cognitive

Getting at the Itch

Steve Davidson, Xijing Zhang, Chul H. Yoon, Sergey G. Khasabov, Donald A. Simone, and Glenn J. Giesler Jr

(see pages 10007–10014)

You don't need to be a neuroscientist to know that antihistamines can block itch. However, this week Davidson et al. examined cowhage, the lesser-known, nonhistaminergic itch producer. The authors report that it activated a different set of sensory-processing neurons than histamine. Cowhage is contained in tiny spicules, or hairs, covering the pods of the aptly named tropical legume *Mucuna pruriens*. The authors compared responses of primate ascending spinothalamic tract (STT) neurons to histamine and cowhage applied to receptive fields on the hairy skin. Units were classified as either wide dynamic range (WDR) or high threshold (HT), based on their responses to nonnoxious mechanical stimuli, pinching, and noxious heat. The pruritogens activated two nonoverlapping STT neuron populations of recorded cells. Histamine and cowhage activated WDR and HT neurons, but all neurons activated by either one also responded to the noxious chemical compound capsaicin. The data indicate two independent itch pathways, both of which also convey pain sensation.

Cowhage is contained in tiny spicules, or hairs, covering the pods of the tropical legume *Mucuna pruriens*. See the article by Davidson et al. for details.

♦ Neurobiology of Disease

Sleep Apnea and Hypoxic Neuronal Loss in Mice

Yan Zhu, Polina Fenik, Guanxia Zhan, Emilio Mazza, Max Kelz, Gary Aston-Jones, and Sigrid C. Veasey

(see pages 10060–10071)

One of every 100 readers of this paragraph likely has sleep apnea. The immediate concern with sleep apnea is daytime sleepiness because of frequent nighttime sleep disruption. However, some studies have suggested that the resulting cycles of hypoxia and reoxygenation may cause long-lasting neuronal damage. This week, Zhu et al. tested this idea in rodents. The authors exposed adult male mice to long-term intermittent hypoxia (LTIH) for 8 weeks. This treatment consisted of O_2 reduction from 21 to 10% for 5 s every 90 s, which caused desaturation of oxyhemoglobin, not unlike obstructive sleep apnea. Six months later, wakefulness was irreversibly impaired compared with control mice. There was also impaired activation of the immediate early gene *c-fos* upon waking in dopamine neurons in the periaqueductal gray and noradrenergic neurons in the locus ceruleus. Among wake-active neurons, only catecholamine neurons were diminished by LTIH. The NADPH oxidase inhibitor apocynin prevented the loss.