This Week in The Journal

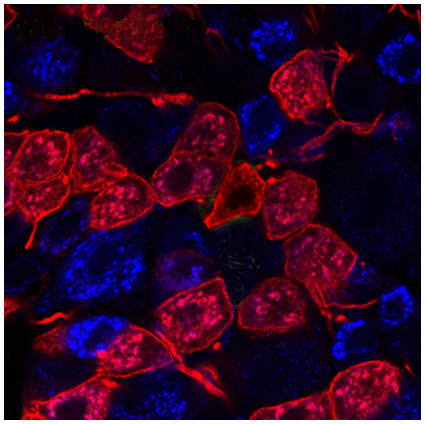
● Cellular/Molecular

Mrgprd Sensitizes Nociceptors

Kristofer K. Rau, Sabrina L. McIlwrath, Hong Wang, Jeffrey J. Lawson, Michael P. Jankowski, et al.

(see pages 8612–8619)

Most peripheral nociceptive neurons are polymodal, responding to noxious mechanical, chemical, heating, and/or cooling stimuli. They are classified by axonal diameter and myelination and subclassified by expression of specific molecules, such as substance P, isolectin B4, and various receptors. Unlike most nociceptor markers, Mas-related G-protein-coupled receptor D (Mrgprd) defines a subset of nonpeptidergic, unmyelinated nociceptors that innervate a single target type: the epidermis. Mrgprd is activated by β-alanine, but its contribution to nociception is not clear. Rau et al. report that Mrgprd increases sensitivity to mechanical and thermal stimulation. When Mrgprd was deleted, temperatures had to be lowered more during cooling and raised more during heating to evoke a response. Mrgprd deletion did not alter mechanical thresholds, but reduced the average spike rate of nociceptors during mechanical stimulation. Moreover, β-alanine reduced the current required to elicit spiking in nociceptors expressing Mrgprd, but not in deletion mutants.



Mrgprd is expressed in nonpeptidergic nociceptors (red). Blue, Calcitonin gene-related peptide. See the article by Rau et al. for details.

▲ Development/Plasticity/Repair

Pax6 Deletion Depletes Cortical Progenitors

Tran Cong Tuoc, Konstantin Radyushkin, Anton B. Tonchev, Maria Carmen Piñon, Ruth Ashery-Padan, et al.

(see pages 8335–8349)

Production of cortical projection neurons occurs through several rounds of division that expand the progenitor pool, followed by subsequent rounds in which the pool is diminished as postmitotic neurons are generated. Progressive changes in transcription factor expression during this period drive development of layer-specific characteristics and restrict cells' ability to differentiate into other neuronal types. Pax6 has been proposed to specify upper-layer neurons, because constitutive knock-out of this transcription factor nearly eliminated these layers. Because these mutant mice died before cortical neurogenesis was complete, however, Tuoc et al. restricted Pax6 knock-out to early or late progenitors of forebrain neurons. Early knock-out recapitulated the effects of constitutive knock-out on cortical layering: more deep-layer but almost no upper-layer neurons were present. Surprisingly, however, knock-out after the development of deep layers did not disrupt development of upper layers, suggesting that earlier knock-out causes premature cell-cycle exit that depletes the progenitor pool rather than preventing upper-layer specification.

■ Behavioral/Systems/Cognitive

Leucine Directly Activates Hypothalamus to Suppress Feeding

Clémence Blouet, Young-Hwan Jo, Xiaosong Li, and Gary J. Schwartz

(see pages 8302–8311)

The hypothalamus integrates peripheral and central signals to balance food consumption and energy expenditure. The arcuate nucleus (ARC) is central to this process. ARC neurons that release the appetite-stimulating hormone neuropeptide Y are activated by signals produced by the empty stomach, and they inhibit ARC neurons expressing proopiomelanocortin (POMC). In response to satiety signals, POMC neurons suppress feeding, in part via oxytocin neurons in the paraventricular nucleus (PVN), which project to the nucleus of the solitary tract (NTS) in the brainstem. Besides endogenous hormones, circulating nutrients can alter feeding. For example, increased protein (or leucine) consumption suppresses food intake. To examine the physiological basis of this effect, Blouet et al. injected leucine into the mediobasal hypothalamus of rodents. This reduced food intake, increased spiking of POMC neurons, and increased activity of PVN oxytocin neurons and NTS neurons. Melanocortin and oxytocin antagonists reversed leucine-induced suppression of food intake, implicating the ARC–PVN–NTS pathway in this effect.

◆ Neurobiology of Disease

Cognitive Defects Are Associated With Reduced Conduction Speed

Hisataka Tanaka, Jianmei Ma, Kenji F. Tanaka, Keizo Takao, Munekazu Komada, et al.

(see pages 8363–8371)

Myelination is a key determinant of axonal conduction speed. Because the conduction speed of individual axons influences whether they provide synchronous input to a shared postsynaptic cell and synchrony underlies synaptic integration, regulation of myelination could play a significant role in information processing in the brain. Indeed, myelination in the CNS parallels cognitive development in humans, and mutation and altered expression of myelin-associated genes have been linked to many psychiatric and developmental disorders, from schizophrenia to dyslexia. To study the role of myelin in cognitive functions, Tanaka et al. used mice that had extra copies of the myelin proteolipid protein 1 (*plp1*) gene. Conduction speed of CNS axons in mutant mice was decreased, possibly resulting from axonal thinning and paranode disruption, before demyelination or motor deficits were apparent. Performance on working and spatial memory tasks was impaired, and inhibition of the acoustic startle response by a quieter prepulse—a common measure of schizophrenic-like behavior—was reduced.