

# This Week in The Journal

## ● Cellular/Molecular

### *Putting the M in Pain Modulation*

KCNQ/M Currents in Sensory Neurons: Significance for Pain Therapy

Gayle M. Passmore, Alexander A. Selyanko, Mohini Mistry, Mona Al-Qatari, Stephen J. Marsh, Elizabeth A. Matthews, Anthony H. Dickenson, Terry A. Brown, Stephen A. Burbidge, Martin Main, and David A. Brown

(see pages 7227–7236)

The potassium current known as the M current [ $I_{K(M)}$ ] was first described more than 20 years ago in bullfrog sympathetic neurons by Paul Adams and David Brown. It drew immediate attention from biophysicists because of its slow kinetics and contribution to membrane excitability at subthreshold voltages. M channels (named for their sensitivity to block by muscarine) are primarily closed at rest potential but open (and stay open) with membrane potential depolarization. More recently, mutations of KCNQ2/3, the M current subunits underlying  $I_{K(M)}$ , have been linked to a familial epilepsy syndrome. This week, Passmore et al. add  $I_{K(M)}$  to the list of regulators of another condition with neuronal hyperexcitability, neuropathic pain. This hyperexcitability in primary afferents is characterized by increased sensitivity to noxious stimuli (hyperalgesia) and lowered threshold for pain (allodynia). The authors identified  $I_{K(M)}$  in rat nociceptors and confirmed the expression of KCNQ2/3. Retigabine enhanced M current in nociceptors, reduced responses of dorsal horn neurons to natural stimuli, and produced an analgesic effect in an animal model of chronic pain. Thus KCNQ2/3 channel activators may be novel analgesics. The M current has come a long way since the recognition of those odd, slow voltage-clamp relaxations.

## ▲ Development/Plasticity/Repair

### *Hibernation and Tau Hyperphosphorylation*

Reversible Paired Helical Filament-Like Phosphorylation of Tau Is an Adaptive Process Associated with Neuronal Plasticity in Hibernating Animals

Thomas Arendt, Jens Stieler, Arjen M. Strijkstra, Roelof A. Hut, Jan Rüdiger, Eddy A. Van der Zee, Tibor Harkany, Max Holzer, and Wolfgang Härtig

(see pages 6972–6981)

Ramón y Cajal first speculated about cytological similarities between Alzheimer's disease and synaptic plasticity in naturally occurring conditions such as starvation and hibernation. After all these years, the idea has resurfaced with recent findings indicating that hibernating animals in torpor, an inactive, hypothermic state, undergo dramatic, reversible changes in hippocampal neuronal connectivity. Torpor provides an incredible savings in energy but also comes at the price of memory impairment, albeit without overt brain damage. Now Arendt et al. have examined a molecular correlate of these synaptic alterations during hibernation in ground squirrels. Paired helical filaments (PHFs), a pathological hallmark of Alzheimer's disease, contain the microtubule-associated protein tau in a hyperphosphorylated state. However, the relationship of hyperphosphorylated tau to neuronal degeneration remains poorly understood. The current work describes an intriguingly reversible tau phosphorylation, particularly in CA3 neurons of the hippocampus, accompanied by cycles of synaptic regression and then reinnervation by mossy fibers. Neuronal connectivity and tau phosphorylation were correlated with the animal's arousal state. The results suggest a natural, nonpathological regulation of tau phosphorylation that is closely linked with synaptic plasticity, although neurofibrillary aggregation characteristic of PHFs was not observed. Thus studies of an unusual adaptive state, hibernation, may yet provide insights into neurodegenerative disease.

## ■ Behavioral/Systems/Cognitive

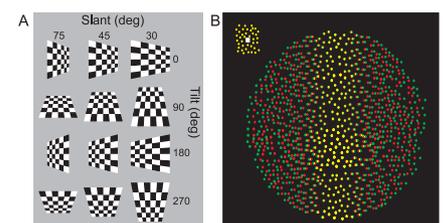
### *3-D-Sensing Neurons*

Disparity-Based Coding of Three-Dimensional Surface Orientation by Macaque Middle Temporal Neurons

Jerry D. Nguyenkim and Gregory C. DeAngelis

(see pages 7117–7128)

Hollywood filmmakers have long known that enhanced three-dimensional (3-D) images can lead to a powerful sensory experience. On a more mundane level, we need 3-D vision just to navigate in our complex environment. Although neurons in the parietal and temporal cortex have been identified recently as 3-D-sensitive, the origin of 3-D selectivity in visual pathways is not known. A neuronal prerequisite would seem to be large receptive fields, thus making the primary visual areas, V1 and V2, an unlikely site of origin. In this issue, Nguyenkim and DeAngelis now provide evidence that recognition of 3-D orientation of surfaces, defined by use of binocular disparity gradients, involves neurons in the middle temporal visual area (MT) with their large receptive fields, strong disparity signals, and known role in depth perception. They recorded from >200 MT neurons in two rhesus monkeys; many of the neurons were 3-D-sensitive in addition to their coding of retinal image velocities. MT receives direct input from V1 and V2, consistent with encoding of 3-D orientation early in the visual pathways.



**Schematic illustration of the 3-D orientation of planar surfaces.** Tilt refers to axis around which the plane is rotated away from frontoparallel; slant defines the rotation of the plane. See Nguyenkim and DeAngelis for details.