

This Week in The Journal

● Cellular/Molecular

Surprise! Tarantula Toxin Blocks A-Type Potassium Current Too

Tilia Kimm and Bruce P. Bean

(see pages 9182–9189)

Dopaminergic cells of the substantia nigra pars compacta (SNc) exhibit substantial voltage-dependent A-type potassium currents. Recently, Kimm and Bean set out to study whether calcium-evoked potassium currents might contribute to the outward flux. Naturally, they used the tarantula venom toxin SNX-482, a known inhibitor of Cav2.3 calcium channels, to tease apart a calcium-dependent component using voltage-clamp recordings from acutely dissociated mouse SNc neurons. Much to their surprise, the toxin wiped out most of the potassium current altogether. When they replaced extracellular calcium with cobalt, the toxin still thwarted potassium currents, indicating that the inhibited flux did not depend on calcium. In heterologous HEK cells expressing Kv4.3, the channel that passes A-type current in SNc neurons, the toxin reduced potassium currents by half at only 3 nM. The authors offer one caveat: SNX-482 also reduced current through related Kv4.2 channels, albeit with lower potency. The findings bring fresh utility to an oft-used tool and offer new insights to the interplay between animal toxins and ion channels.

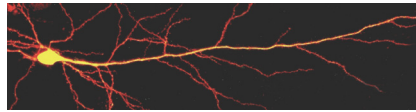
● Development/Plasticity/Repair

GluN3A NMDAR Subunit Promotes Developmental Synaptic Pruning

Laura A. Kehoe, Camilla Bellone, Mathias De Roo, Aitor Zandueta, Partha Narayan Dey, et al.

(see pages 9213–9221)

The postnatal brain is a tumultuous landscape of synapse formation, stabilization, and destruction. NMDA-type glutamate receptors (NMDARs) hold the key to activity-dependent plasticity, and their various subunits differentially contribute to the developmental process. The atypical GluN3A subunit reduces calcium permeability and voltage-dependent magnesium block and, according to Kehoe et al., it acts to reduce synaptic stability. Using confocal



A CA1 pyramidal neuron labeled with monomeric red fluorescent protein in which GluN3A has been silenced, resulting in increased spine protrusions compared to control. See the article by Kehoe et al. for more details.

time-lapse imaging, the researchers watched as synapses dynamically changed over time in mouse organotypic hippocampal slice cultures. When they overexpressed GluN3A in slices—keeping expression high past its normal developmental decline—CA1 neuron dendritic spines were significantly reduced compared to controls. Similarly, fewer protrusions appeared in cells with impaired endocytosis and in cells in which the GluN3A adapter protein PACSIN1 was silenced—which both effectively kept more GluN3A at the synapses. Conversely, spines proliferated abnormally when GluN3A expression was knocked down by short-hairpin interfering RNA. The findings cement the NMDAR subunit as a key regulator of synaptic stability during development.

● Behavioral/Cognitive

Dorsomedial Striatal Plasticity after Goal-Directed Learning

Qiang Shan, Miao Ge, MacDonald J. Christie, and Bernard W. Balleine

(see pages 9196–9201)

Goal-directed behaviors have long been associated with the frontal cortex, but in recent years the striatum has taken over the starring role. Shan and colleagues now delve further into the neural underpinnings of goal-directed learning in striatal medium spiny projection neurons (SPNs). The SPN population is split into cells expressing excitatory D1-type dopamine receptors (D1R) and projecting to the substantia nigra pars reticulata and others expressing inhibitory D2-type receptors (D2R) projecting to the external globus pallidus. The researchers used two transgenic lines of mice that expressed green fluorescent protein (GFP) coupled to either D1R or D2R and trained the mice in a task pairing reward with behavior or a

control task. Specifically within the posterior dorsomedial striatum (pDMS), staining for phosphorylated extracellular signal-regulated kinase increased, indicating heightened cellular activity, in D1R but not D2R neurons following learning. Electrophysiological recordings from pDMS SPNs in striatal slices indicated that D1R neurons expressed a higher ratio of AMPA-type compared to NMDA-type glutamate receptors after learning, whereas the ratio was reversed in D2R neurons. Together, the results suggest localized, bidirectional synaptic plasticity in neurons of the pDMS in goal-directed learning.

● Neurobiology of Disease

Calpain Inhibition Restores Tau Neuropathology, Lifespan

Mala V. Rao, Mary Kate McBrayer, Jabbar Campbell, Asok Kumar, Audrey Hashim, et al.

(see pages 9222–9234)

Tau contributes to neuropathology in Alzheimer's disease and other tauopathies, but how remains mostly mysterious. Calcium-activated cysteine proteases called calpains participate in tau hyperphosphorylation, truncation, and oligomerization, which contribute to tau's toxicity. Normally, calpains are kept in check by their endogenous inhibitor calpastatin, but in the JNPL3 mouse model of tauopathy, calpastatin is depleted and calpain activity runs rampant. Rao et al. sought to remedy that situation by transgenically overexpressing calpastatin in neurons and moderating calpain activity in the mice, with striking results. First, cleaved species of tau were reduced in the transgenic mice, as were multimeric complexes of the protein. Calpains contribute to toxicity by cleaving cyclin-dependent kinase 5 (cdk5) into a constitutively active form known to hyperphosphorylate tau. Boosting calpastatin normalized the high level of active cdk5 and hyperphosphorylation. Most importantly, calpain inhibition in JNPL3 mice delayed disease onset and extended life by about three months, restoring normal lifespan. The findings position calpastatin as a powerful brake on disease-related activity in tauopathies.