This Week in The Journal

● Cellular/Molecular

$GABA_A$ Upregulation Compensates for HCN1 Loss

Xiangdong Chen, Shaofang Shu, Lauren C. Schwartz, Chengsan Sun, Jaideep Kapur, and Douglas A. Bayliss

(see pages 2611–2622)

The hyperpolarization-activated cyclic-nucleotide-modulated channel HCN1 underlies an inward cation current, I_h, which is active at hyperpolarized membrane potentials and inactivated at depolarized potentials. I_h contributes to pacemaker activity in some neurons, but its presence in dendrites of hippocampal and neocortical pyramidal cells decreases input resistance at resting membrane potentials, thus acting as a shunt that limits synaptic summation. Consistent with this, knockout of HCN1 enhances summation-dependent hippocampal plasticity. Unlike HCN1 inhibitors, however, HCN1 knockout does not enhance recurrent cortical activity. The reason for this, as demonstrated by Chen et al., is that extrasynaptic $GABA_A$ α5 subunits are upregulated in cortical (but not hippocampal) neurons of HCN1-null mice. In wild-type mice, blocking I_h enhanced EPSP summation, whereas blocking $GABA_A$ currents had little effect. Conversely, in HCN1 knockouts, blocking tonic $GABA_A$ currents enhanced EPSP summation, whereas blocking I_h had no effect. Thus, upregulation of tonic $GABA_A$ currents compensated for the loss of I_h in cortical neurons.

▲ Development/Plasticity/Repair

Extracellular Cues Influence Centrosome Position

Shailesh Kumar Gupta, Karina Meiri, Kashif Mahfooz, Upasna Bharti, and Shyamala Mani

(see pages 2755–2766)

Where the axon emerges from the soma is determined largely by intrinsic factors, notably the position of the centrosome, which organizes microtubule extension. Centrosomes orient the mitotic spindle during the final cell division before neuronal differentiation, and the axon usually emerges from a nascent neuron perpendicular to the plane of the division. Extrinsic cues also influence the direction of axon emergence, however. Gupta et al. show that in mouse cerebellar granule cells plated on substrates patterned with the cerebellar extracellular matrix proteins laminin and vitronectin, centrosomes are positioned toward the matrix proteins. In cerebellar slices, antibodies against these proteins or their receptors disrupted the normal positioning of centrosomes. Positioning of centrosomes on patterned substrates required local activation of the membrane-associated proteins phosphoinositide-3 kinase (PI3K) and growth-associated protein GAP-43. In addition, knockout of GAP-43 prevented proper localization of several signaling proteins involved in neuronal polarization and disrupted the normal orientation of microtubules.

■ Behavioral/Systems/Cognitive

Basolateral Amygdalar Neurons Encode Unsigned Prediction Errors

Matthew R. Roesch, Donna J. Calu, Guillem R. Esber, and Geoffrey Schoenbaum

(see pages 2464–2471)

To optimize reward, animals must learn to associate cues with rewards and recognize when the value of the reward differs from what was expected. According to some learning models, if a reward is larger than expected, the association between the cue and reward will be strengthened, whereas if the reward is smaller than expected, the association will be weakened. Such models predict that the sign of the prediction error (i.e., whether the reward is bigger or smaller than expected) will be encoded in neural activity. This has been shown in midbrain dopamine neurons. Other learning models posit that prediction errors tell an animal that it must learn more about the cue–reward association and therefore serve to direct attention. These models predict that neural activity encoding prediction errors will be similar regardless of the sign of the error. This week, Roesch et al. show that this is true of neurons in the basolateral amygdala of rats.

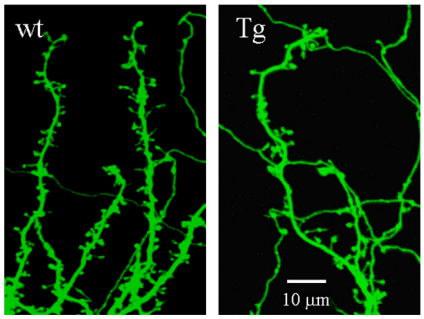
♦ Neurobiology of Disease

Calcium-Dependent Phosphatase Mediates Effects of β-Amyloid

Hai-Yan Wu, Eloise Hudry, Tadafumi Hashimoto, Kishore Kuchibhotla, Anete Rozkalne, et al.

(see pages 2636–2649)

Much evidence suggests that soluble β-amyloid (Aβ) peptides, rather than those accumulated in plaques, cause the synaptic dysfunction, spine loss, and dendritic dystrophy that underlie cognitive decline in Alzheimer's disease (AD). Wu et al. present evidence that these morphological changes result from excess activation of the calcium-dependent protein phosphatase CaN. Cultured cortical neurons from mice expressing mutant amyloid precursor protein (APP) had more dystrophic neurites, simpler dendritic arbors, and fewer spines than wild-type neurons. Medium from these cultures induced similar morphological changes in wild-type cultures. These effects were prevented if soluble Aβ was depleted from the culture medium or if CaN activity was blocked. Furthermore, a constitutively active form of CaN was elevated in cortical tissue from AD patients, and overexpression of this protein in wild-type cultures produced Aβ-related morphological changes. In contrast, viral expression of a CaN-inhibiting peptide in transgenic mice reduced neuritic dystrophy and spine loss without apparent effects on Aβ plaques.



Cultured neurons from wild-type mice (left) have more dendritic spines than neurons from mice expressing an AD-associated form of APP (right). See the article by Wu et al. for details.