This Week in The Journal

● Cellular/Molecular

Intracellular Accumulation of Aβ Kills Neurons

Ning Cheng, Huaibin Cai, and Leonardo Belluscio

(see pages 13699–13704)

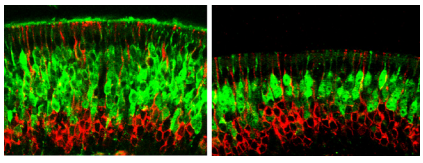
Olfactory impairment is common in people with Alzheimer's (AD) and other neurodegenerative diseases. β-Amyloid (Aβ) aggregates within olfactory epithelium (OE) neurons in AD patients, and the prevalence of these aggregates correlates with that of cortical Aβ plaques. Because the OE is easily accessible for biopsy, detection of intracellular Aβ aggregates in OE could be an effective diagnostic tool for AD. The OE might also facilitate studies of how Aβ accumulation leads to neurodegeneration. Cheng et al. found that expressing AD-linked human amyloid precursor protein (APP) selectively in immature or mature olfactory sensory neurons increased levels of toxic Aβ species in mouse OE. APP expression promoted apoptosis, but only of neurons expressing the mutant protein: nonexpressing neurons were spared, and no extracellular plaques were detected. Turning off mutant APP expression increased survival of immature neurons. Although mature neurons were not similarly rescued, the results indicate that the effects of toxic Aβ production can be halted.

▲ Development/Plasticity/Repair

Vitamin D Deficiency Stimulates Nociceptor Growth

Sarah E. Tague, Gwenaëlle L. Clarke, Michelle K. Winter, Kenneth E. McCarson, Douglas E. Wright, et al.

(see pages 13728–13738)



Expression of human APP (right) reduces the number of mature olfactory sensory neurons (green), without affecting immature neurons (red). See the article by Cheng et al. for details.

Receptors for vitamin D, which is produced in the skin upon UVB irradiation, are present in nearly all tissues, suggesting the vitamin is more important than once realized. Estimates of vitamin D requirements have risen recently, and most people are now thought to have insufficient levels. Vitamin D insufficiency has been linked to many conditions, including cancer, multiple sclerosis, depression, and musculoskeletal pain; but because vitamin D insufficiency is widespread and is often confounded by sedentary lifestyle and calcium insufficiency, causative links have rarely been established. Therefore, Tague et al. studied vitamin D deficiency in rats. Animals deprived of vitamin D for 4 weeks exhibited reduced pain thresholds for muscle compression and increased muscle innervation by nociceptors, without significant changes in cutaneous pain sensitivity, skin innervation, or muscle and bone structure. Growth of cultured sensory neurons was inversely correlated with vitamin D concentration, indicating that vitamin D deficiency may induce muscle pain by stimulating nociceptor growth.

■ Behavioral/Systems/Cognitive

Lack of FGFR1a Causes Aggression-Boldness Syndrome

William H. J. Norton, Katharina Stumpenhorst, Theresa Faus-Kessler, Anja Folchert, Nicolas Rohner, et al.

(see pages 13796–13807)

In many vertebrate species, aggressive individuals are less likely than their conspecifics to avoid frightening environments, and they explore new objects and environments more quickly. Behavioral tendencies that co-occur across individuals like this are called behavioral syndromes. Behavioral syndromes have been hypothesized to occur when several behaviors are regulated by the same factor, but their genetic bases remain largely unexplored. Norton et al. found that zebrafish lacking fibroblast growth factor receptor 1a (FgfR1a) exhibited the aggression-boldness syndrome described above, demonstrating that allelic variation in a single gene can underlie behavioral syndromes. Downregulation of FgfR1 targets was particularly pronounced in the periventricular nucleus of mutant fish, and brain histamine levels were reduced. Inhibiting a histamine-metabolizing enzyme that was slightly upregulated in mutant fish reduced aggression and boldness in mutant, but not wild-type fish, as did a histamine agonist. Thus, reduced FGF signaling likely produces aggression-boldness syndrome in part by decreasing histamine levels.

♦ Neurobiology of Disease

Extrasynaptic NMDARs Boost Prostaglandin Production

David T. Stark and Nicolas G. Bazan

(see pages 13710–13721)

Activation of synaptic NMDA receptors (NMDARs) not only promotes synaptic plasticity, but also is required for neuron survival. In contrast, activation of extrasynaptic NMDARs leads to excitotoxic cell death. These opposing effects result from differential regulation of transcription factors, including cAMP response element-binding protein (CREB): synaptic NMDARs activate, whereas extrasynaptic NMDARs inhibit CREB-dependent transcription. Cyclooxygenase 2 (COX-2), a CREB-regulated protein involved in long-term plasticity, catalyzes synthesis of prostaglandins and thus also contributes to inflammation associated with neurotoxicity. Stark and Bazan hypothesized that extrasynaptic NMDARs promote pathological effects of COX-2. Activation of synaptic NMDARs greatly increased levels of COX-2, but not of its substrate, arachidonic acid; conversely, extrasynaptic NMDAR activation increased the latter, but not the former. In both cases, prostaglandin synthesis remained low. When synaptic and extrasynaptic NMDARs were sequentially activated, however, both enzyme and substrate levels increased, as did prostaglandin synthesis. Nonetheless, COX-2 inhibitors did not limit apoptosis, suggesting that prostaglandin did not exacerbate excitotoxicity.