This Week in The Journal

● Cellular/Molecular

PACAP Potentiates Synapses in the Amygdala

Jun-Hyeong Cho, Ko Zushida, Gleb P. Shumyatsky, William A. Carlezon Jr., Edward G. Meloni, et al.

(see pages XXX-XXX)

Pituitary adenylate cyclase-activating polypeptide (PACAP) and its receptors are expressed throughout the body and brain, and they regulate diverse processes including food intake, circadian rhythms, learning, stress responses, and anxiety. Furthermore, elevated PACAP levels and a mutation in a PACAP receptor have been linked to posttraumatic stress disorder in women. PACAP and its receptors are highly expressed in the amygdala, and Cho et al. report that PACAP enhances excitatory transmission between the basolateral (BLA) and the lateral division of the central (CeL) amygdalar nuclei. This effect was mediated by PACAP receptor VPAC1 and required postsynaptic increases in Ca^{2+}, activation of Ca^{2+}/calmodulin-dependent protein kinase II and protein kinase A, and synaptic delivery of AMPA receptors. PACAP-induced potentiation increased spiking in CeL neurons in response to a given intensity of BLA stimulation. The source of PACAP, which population of CeL neurons exhibit this potentiation, and the effect potentiation has on fear responses remain to be explored.

▲ Development/Plasticity/Repair

Contactins Guide Neurite Arborization in Retina

Masahito Yamagata and Joshua R. Sanes

(see pages XXX-XXX)

Parallel processing of visual information begins in the retina, where photoreceptors transmit information to ten different types of bipolar cells. Axons of bipolar cell subtypes terminate in specific sublaminae of the inner plexiform layer (IPL), where they synapse with different subtypes of amacrine and ganglion cell. Four closely related adhesion molecules of the immunoglobulin superfamily (IgSF) are expressed in non-overlapping populations of chicken amacrine and ganglion cells, and these molecules have been proposed to direct dendritic arborization in the correct sublamina of the IPL. But ~40% of cells do not express these proteins. Yamagata and Sanes suggest that the remaining cells are guided by another related group of molecules, contactins 1–5. Contactins were expressed in mostly non-overlapping sets of amacrine and ganglion cells, and cells expressing contactin-2 were generally distinct from those expressing other IgSF proteins. After contactin-2 knockdown, neurites arborized more broadly within the IPL, whereas ectopic expression of contactin-2 redirected processes to arborize in sublaminae that endogenously expressed contactin-2.

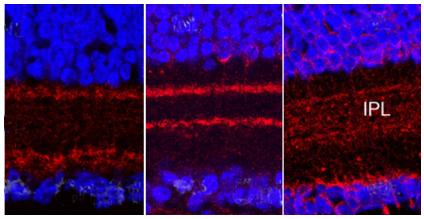
■ Behavioral/Systems/Cognitive

L-DOPA Improves Episodic Memory in Humans

Rumana Chowdhury, Marc Guitart-Masip, Nico Bunzeck, Raymond J. Dolan, and Emrah Düzel

(see pages XXX-XXX)

Long-term potentiation of hippocampal synapses encodes memories for events and places, but new proteins must be synthesized for potentiation to persist. Hippocampal dopamine release appears to be required for the induction of protein synthesis and thus for long-term memory retention. This might explain why rewarding, aversive, or novel events—all of which evoke dopamine release—are better remembered than neutral events. It may also help to explain declining episodic memory in older people, given that dopaminergic neurons often degenerate with age. If so, enhancing dopaminergic signaling might improve episodic memory in the elderly. Chowdhury et al. investigated this possibility by administering L-DOPA or placebo to subjects who viewed pictures of indoor and outdoor scenes. Consistent with a specific role for dopamine in memory persistence, L-DOPA improved memory for scenes after 6 h, but had no effect on memory after 2 h. This enhancement occurred only for doses within a narrow range, and it was absent if endogenous dopamine release was promoted by reward.



Contactin (red)-1 (left), -2 (middle), and -3 (right) are expressed in different sublaminar patterns in the IPL. See the article by Yamagata and Sanes for details.

♦ Neurobiology of Disease

PAR2 Mediates Orofacial Cancer Pain

David K. Lam, Dongmin Dang, Jianan Zhang, John C. Dolan, and Brian L. Schmidt

(see pages XXX-XXX)

Pain exacerbated by chewing is an early symptom of oral squamous cell carcinoma (SCC), and the pain worsens with cancer progression. Cancer pain might be induced by proteases, such as trypsin, which are secreted by malignant cells and have roles in tumor formation, survival, and metastasis. The targets of proteases include protease-activated receptors (PARs), which are present on both healthy and tumor cells. Notably, activation of PAR2 on nociceptors causes hypersensitivity. Lam et al. show that injecting supernatant from human SCC into mouse tongue caused acute orofacial pain, as indicated by latency to chew. Pain responses were attenuated by trypsin inhibitors, and were absent in PAR2-null mice. Persistent and chronic pain—produced by injecting SCC cells into the tongue or inducing tumors with carcinogens, respectively—were additionally associated with PAR2 upregulation in the trigeminal ganglion. The data suggest that trypsin-mediated activation of PAR2 causes orofacial cancer pain, and that upregulation of PAR2 in nociceptors leads to pain persistence.