This Week in The Journal

● Cellular/Molecular

CREB-Binding Protein Mediates Cocaine's Epigenetic Effects

Melissa Malvaez, Emanuela Mhillaj, Dina P. Matheos, Maura Palmery, and Marcelo A. Wood

(see pages 16941–16948)

Epigenetic modifications—such as histone acetylation—provide a molecular mechanism for long-lasting and powerful behavioral changes that accompany addiction. Some cocaine-induced behaviors have been linked to specific histone deacetylases (HDACs)—which negatively regulate gene transcription—in the nucleus accumbens (NAc). But the corresponding histone acetyltransferases (HATs) that promote gene transcription in response to cocaine had not been identified. Now, Malvaez et al. identify CREB-binding protein (CBP) as a critical mediator of cocaine-induced gene transcription. They cleared a previous hurdle by engineering a conditional homozygous knock-out of CBP specifically in the NAc. In wild-type mice, acute cocaine treatment induced expression of c-*fos* in the NAc, and chronic cocaine desensitized expression. In the knock-out mice, both effects were abolished, suggesting that CBP regulates cocaine-induced c-*fos* expression in the NAc. Importantly, CBP was also required for cocaine's acute and chronic locomotor effects and in a cocaine-associated memory task, which could underlie drug-seeking behaviors.

▲ Development/Plasticity/Repair

Bimodal mGluR1 Signaling Induces Plasticity

Shanti F. Frausto, Koichi Ito, William Marszalec, and Geoffrey T. Swanson

(see pages 16897–16906)

Frausto et al. describe a novel and rather sophisticated form of hippocampal mossy fiber synaptic plasticity. Whereas low-frequency stimulation (LFS) at these synapses is associated with long-term depression (LTD), and high-frequency stimulation induces classical long-term potentiation (LTP), the authors used a paired-pulse low-frequency stimulation protocol to evoke "mossy fiber low-frequency potentiation" (mf-LFP). The mf-LFP, which lasted about an hour, required both presynaptic and postsynaptic elements. Induction of the mf-LFP required postsynaptic calcium entry into CA3 pyramidal neurons through L-type (but not R-type) voltage-dependent calcium channels. Potentiation of EPSCs was independent of kainate-type glutamate receptors but required metabotropic glutamate receptor 1 (mGluR1). Bimodal mGluR1 signaling—through both conventional and non-G-protein-coupled cascades—was revealed by pharmacological experiments showing that tyrosine kinase activity as well as G-protein activation contributed to mf-LFP. Release probability from presynaptic granule cells increased with mf-LFP, apparently as a result of transsynaptic signaling.

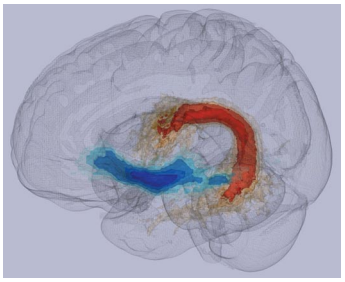
■ Behavioral/Systems/Cognitive

Language Processing by Two Tracts Is Synergistic

Tyler Rolheiser, Emmanuel A. Stamatakis, and Lorraine K. Tyler

(see pages 16949–16957)

Like the visual and auditory processing systems, different aspects of language are thought to be processed by two parallel white-matter tracts. Connecting the arcuate fascicle (AF) in the frontal region and the extreme capsule (EmC) in the temporal lobe, a dorsal tract is thought to convey phonological and syntax information while a ventral tract hypothetically carries semantic meaning. Now Rolheiser et al. show that language processing is likely not as functionally dichotomous as this simple system suggests. The authors examined subjects who had undergone left-hemisphere stroke with varying degrees of damage: to the dorsal, ventral, or both tracts. Whereas previous models were based largely on neuroimaging data, the current work also included an extensive battery of behavioral language tests to add more depth to the picture. While language tasks were biased toward one pathway or the other, a picture emerged of an overlapping, synergistic processing system between the two tracts.



Probabilistic region-of-interest masks representing two tracts involved in language processing: the arcuate fascicle (red/yellow) and the extreme capsule. See the article by Rolheiser et al. for details.

♦ Neurobiology of Disease

Vitamin C Transporter Helps Extracellular Matrix Mesh

Burkhard Gess, Dominik Röhr, Robert Fledrich, Michael W. Sereda, Ilka Kleffner, et al.

(see pages 17180–17192)

Despite the requirement for ascorbic acid (vitamin C) for myelination of Schwann cells *in vitro* and its benefits in an animal model of the demyelinating disorder Charcot-Marie-Tooth neuropathy 1A (CMT1A), clinical trials of vitamin C in CMT1A patients were disappointing. This week, the disconnect has been bridged by a study of the ascorbic acid transport mechanism. Mice heterozygous for expression of the sodium-dependent vitamin C transporter 2 (SVCT2$^{+/-}$) had decreased peripheral nerve ascorbic acid and reduced sciatic nerve myelin thickness. Nerve conduction velocity and sensorimotor performance were also impaired. Gess et al. traced the deficiencies to protein components of the extracellular matrix required for myelination and perhaps remyelination. Immunoreactivity for multiple collagens was reduced in the SVCT2$^{+/-}$ mice, indicating a critical deficiency. Quantitative real-time PCR revealed that the proteins were affected at the transcriptional level. Collagen proline hydroxylation, which precedes matrix incorporation and uses ascorbic acid as a cofactor, was not affected.