This Week in The Journal

● Cellular/Molecular

Cocaine-Responsive Neurons Can Be Isolated via FACS

Danielle Guez-Barber, Sanya Fanous, Sam A. Golden, Regina Schrama, Eisuke Koya, et al.

(see pages 4251–4259)

Addicts often take drugs habitually, rather than solely for enjoyment. This not only causes addicts to continue taking drugs when costs far outweigh benefits, but also makes quitting more difficult, because drug-associated cues trigger habitual responses. Plasticity in ventral striatum likely underlies initial learning about rewarding effects of drugs, but plasticity in dorsal striatum is thought to underlie habitual drug seeking. Studying the cellular mechanisms of this plasticity is difficult, however, because cocaine activates a small, widely dispersed population of striatal neurons. Therefore, Guez-Barber et al. used rats that expressed lacZ (which encodes β-galactosidase) under control of the cfos (a gene induced by neuronal activity) promoter. After cocaine injections, dissociated striatal neurons were labeled with fluorescent antibodies against β-galactosidase. This allowed separation of cocaine-activated and nonactivated neurons by fluorescence-activated cell sorting (FACS), and subsequent identification of genes differentially regulated across conditions. These included a marker of neurons expressing D_1 dopamine receptors, signaling molecules, and a potassium channel.

▲ Development/Plasticity/Repair

Stargazin Modifies Rectification of AMPA Receptors

Alexander C. Jackson and Roger A. Nicoll

(see pages 3939–3952)

AMPA receptor (AMPAR) properties are determined partly by which subunit types (GluRs) the receptor comprises. Receptors that include GluR2 are calcium impermeable and nonrectifying, whereas GluR2-lacking AMPARs are calcium permeable and—because they are blocked by polyamines at positive membrane potentials—they are inwardly rectifying (inward current at negative potentials is greater than outward current at positive potentials). Cerebellar stellate cells reportedly express GluR2-lacking AMPARs at synapses and GluR2-containing AMPARs extrasynaptically, and synaptic depression in these cells is accompanied by decreased rectification index (RI), which has been proposed to reflect replacement of GluR2-lacking with GluR2-containing AMPARs. But Jackson and Nicoll present evidence that similar proportions of GluR2-containing and GluR2-lacking AMPARs are present synaptically and extrasynaptically in mouse stellate cells. Furthermore, although knock-out of stargazin, an AMPAR regulatory protein, lowered RI, the sensitivity of AMPA currents to polyamines was unaffected, suggesting that AMPAR composition was unchanged and that RI is an inadequate measure of GluR2 content.

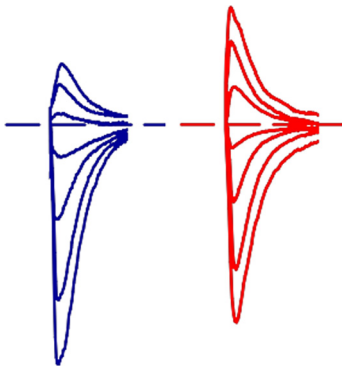
■ Behavioral/Systems/Cognitive

Sleep Rhythms Promote Removal of AMPA Receptors

Fabien Lanté, Juan-Carlos Toledo-Salas, Tomas Ondrejcak, Michael J. Rowan, and Daniel Ulrich

(see pages 3953–3961)

Trafficking of AMPA receptors (AMPARs) into and out of synapses contributes to long-term potentiation and long-term depression (LTD), which are thought to underlie learning. As discussed above, selective incorporation or removal of AMPARs that contain or lack GluR2 subunits has been proposed to underlie some forms of LTD. Sleep facilitates learning, but the cellular bases for this are unknown. To address this question, Lanté et al. examined the effects of sleep and sleep-associated electrical activity on AMPAR trafficking in rats. GluR2-lacking AMPARs were not detected at cortical synapses after several hours of sleep, but they were detected after a period of wakefulness. Stimulating neurons in cortical slices to mimic the asynchronous bursting that occurs during slow-wave sleep induced LTD and appeared to remove GluR2-lacking AMPARs regardless of whether synaptic inputs were active. In contrast, stimulation that mimicked synchronous bursting caused removal of both GluR2-lacking and GluR2-containing AMPARs, and induced LTD only at synapses whose inputs were activated.



In cortical slices taken at the end of the dark period (when rats had been awake), AMPA receptor currents (blue) showed inward rectification: the EPSCs at positive holding potentials were smaller than those at negative holding potentials. Inward rectification was not detected in slices taken during the light period (red) when rats had been sleeping. See the article by Lanté et al. for details.

♦ Neurobiology of Disease

Melanoma-Associated Antibodies Bind to TRPM1 in ON Bipolar Cells

Anuradha Dhingra, Marie E. Fina, Adam Neinstein, David J. Ramsey, Ying Xu, et al.

(see pages 3962–3967)

Paraneoplastic syndromes occur when antibodies generated in response to cancerous tumors attack healthy tissues. One example is melanoma-associated retinopathy (MAR), which is characterized by night blindness and photopsias. Electroretinograms of many MAR patients indicate that photoreceptor light responses are normal, but ON bipolar cell responses are greatly reduced. Furthermore, antibodies from MAR patients bind to rod bipolar cells. Dhingra et al. report that antibodies from some patients target the transient receptor potential channel TRPM1 in ON bipolar cells in rodents and primates. TRPM1, which is highly expressed in melanocytes, was recently identified as the cation channel responsible for the light response in ON bipolar cells. TRPM1 channels are inactivated by metabotropic glutamate receptor-mediated signaling in the dark, but when light reduces glutamate release from photoreceptors, this inhibition is removed, channels open, and ON bipolar cells depolarize. It is not yet clear how MAR antibodies interfere with this process.