This Week in The Journal

● Cellular/Molecular

Increase in Readily Releasable Vesicles Occurs in Minutes

Annika Weyhersmüller, Stefan Hallermann, Nicole Wagner, and Jens Eilers

(see pages 6041–6052)

In *Drosophila* larvae that lack glutamate receptor subunit GluRIIA, miniature EPSCs at the neuromuscular junction are smaller than those in wild-type flies—i.e., the response to single quanta of neurotransmitter is reduced. Nonetheless, EPSCs evoked by action potentials are comparable to those in wild-type flies, indicating that presynaptic homeostatic plasticity compensates for reduced postsynaptic responses. Weyhersmüller et al. estimated that the number of vesicles released per action potential in GluRIIA-null larvae was double that in wild-type larvae. This could result from increases in either the number of readily releasable vesicles or the release probability. Analyses of paired-pulse ratio, cumulative postsynaptic current, and fluctuation in EPSC amplitude indicated that the release probability was unchanged, but the number of release-ready vesicles was elevated in GluRIIA-null larvae. This increase was accompanied by increases in the active zone protein Bruchpilot, which clusters calcium channels and vesicles. Similar changes in pool size and Bruchpilot occurred within minutes of pharmacological blockade of glutamate receptors.

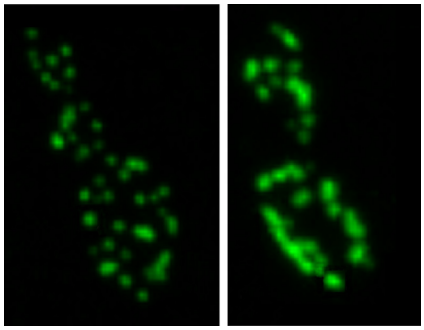
▲ Development/Plasticity/Repair

$GABA_A$ and Metabotropic Glutamate Receptors Regulate Gap Junctions

Won-Mee Park, Yongfu Wang, Soodong Park, Janna V. Denisova, Joseph D. Fontes, et al.

(see pages 5909–5920)

During development, neurons within many areas of the CNS are coupled by gap junctions. These junctions contribute to the generation of synchronous oscillations and are thought to be important in synaptogenesis and circuit formation, as well as neuronal survival and apoptosis. As the brain matures, increased activity of NMDA receptors triggers decoupling of gap junctions. Park et al. now report that gap junction coupling and expression of the gap junction protein connexin-36 (Cx36) are also regulated by type II metabotropic glutamate receptors (mGluRIIs) and $GABA_A$ receptors ($GABA_A$Rs) in rat hypothalamic and cortical neurons. Activating mGluRIIs or inhibiting $GABA_A$Rs enhanced developmental increases in coupling and Cx36 expression, whereas mGluRII antagonist or $GABA_A$R agonist reduced coupling and Cx36 expression. Increases in Cx36 expression involved a neuron-restrictive silencer element in its promoter, which represses transcription when occupied, whereas decreases in expression were mediated by a sequence in the 3′ untranslated region of the Cx36 mRNA.



Bruchpilot puncta (green) are bigger in GluRIIA-null larvae (right) than in wild-type larvae (left). See the article by Weyhersmüller et al. for details.

■ Behavioral/Systems/Cognitive

Antipsychotic Action Requires Muscarinic Receptors on MSNs

Ditte Dencker, Gitta Wörtwein, Pia Weikop, Jongrye Jeon, Morgane Thomsen, et al.

(see pages 5905–5908)

Schizophrenic hallucinations and delusions are probably caused by excessive dopamine, and therefore most antipsychotic drugs are dopamine D_2 receptor antagonists. Changes in neurotransmitter systems that interact with the dopamine system likely contribute to psychotic symptoms, however. Levels of muscarinic acetylcholine receptors (mAChRs), for example, are reduced in schizophrenics, and M_1/M_4 mAChR agonists, such as xanomeline, improve symptoms. M_4 is the main mAChR subtype in the striatum, where it is expressed on cholinergic interneurons and on striatonigral medium spiny neurons (MSNs) that express D_1 dopamine receptors. In transgenic mice lacking M_4 mAChRs in D_1-expressing neurons (D1-M4-KO mice), striatal dopamine release is elevated and the ability of mAChR agonists to counter D_1 receptor-mediated increases in cAMP is abolished. Dencker et al. report that amphetamine-induced hyperlocomotion—a behavior that is reduced by antipsychotic drugs—was reduced by xanomeline in wild-type, but not D1-M4-KO mice, suggesting that the antipsychotic effect requires activation of M_4 receptors in striatonigral MSNs.

♦ Neurobiology of Disease

Viral Expression of Orexin Reduces Cataplexy in Narcoleptic Mice

Meng Liu, Carlos Blanco-Centurion, RodaRani Konadhode, Suraiya Begum, Dheeraj Pelluru, et al.

(see pages 6028–6040)

The sleep–wake cycle is regulated by reciprocal inhibitory connections between sleep-active GABAergic neurons in the ventrolateral preoptic nucleus and wake-active monoaminergic neurons in the brainstem. Hypothalamic orexin neurons—which receive inputs from circadian, emotional, and energy control systems—inhibit sleep-active neurons and excite wake-active neurons, thus preventing inappropriate transitions between sleep and wake states. Loss of orexin neurons causes narcolepsy, characterized by sleep attacks and bouts of sudden muscle paralysis (cataplexy). Liu et al. used adeno-associated virus to express orexin in the zona incerta and lateral hypothalamus of mice in which orexin neurons had degenerated. This restored levels of orexin in the CSF to normal levels and reduced the number and duration of cataplexy bouts. It did not affect the number of sleep attacks, however, suggesting that cataplexy and sleep attacks involve distinct circuits. Orexin neurons express other neuropeptides besides orexin, so reducing sleep attacks might require restoration of another modulator.