This Week in The Journal

● Cellular/Molecular

Endosomal Markers Segregate Differently in Neurons

Zofia M. Lasiecka, Chan Choo Yap, Steven Caplan, and Bettina Winckler

(see pages 16485–16497)

Plasma membrane proteins that exhibit a polarized distribution follow a complex route from ribosome to cell surface: after passing through the endoplasmic reticulum and Golgi apparatus, many are sorted in the trans-Golgi network into vesicle populations destined for different locations. But some polarized proteins are initially trafficked throughout the cell. Achieving their proper distribution requires endocytosis from the initial insertion site, additional sorting in endosomes, and recycling to the appropriate domain. Endosomes are highly dynamic, often moving and merging, and their composition changes over time. The identification of protein markers of specific compartments has facilitated investigation of membrane trafficking in non-neuronal cells, and many of these markers also exist in neurons. By examining colocalization and movement of the axonal protein L1 and several endosomal markers, Lasiecka et al. have begun to unravel the path taken by L1 and discovered that some endosomal markers are distributed differently in neurons than in other cell types.

▲ Development/Plasticity/Repair

PICK1 Slows Recycling of AMPA Receptors during LTD

Ami Citri, Samarjit Bhattacharyya, Cong Ma, Wade Morishita, Scarlett Fang, et al.

(see pages 16437–16452)

Long-term potentiation (LTP) and long-term depression (LTD) result from changes in the expression, distribution, and interactions of many synaptic proteins. Perhaps the most striking of these changes is the movement of AMPA-type glutamate receptors (AMPARs) into or out of the synaptic membrane. This redistribution is mediated by calcium-dependent changes in other proteins, including PICK1 (protein interacting with C kinase 1). To elucidate the role of PICK1 in LTD, Citri et al. knocked down endogenous PICK1 in rat hippocampal neurons and simultaneously introduced full-length or mutated PICK1. PICK1 expression was required for induction of LTD via NMDA receptor activation, but it was not required for LTP. AMPAR endocytosis did not require PICK1, but without PICK1 the receptors quickly recycled back to the synaptic membrane, preventing LTD. Retention of AMPARs in endosomes depended on the calcium-, lipid-, and actin-binding domains of PICK1, but surprisingly, the domain that directly interacts with glutamate receptor subunits was not required.

■ Behavioral/Systems/Cognitive

Social Defeat Stress Increases Bursting in Dopaminergic Neurons

Jun-Li Cao, Herbert E. Covington III, Allyson K. Friedman, Matthew B. Wilkinson, Jessica J. Walsh, et al.

(see pages 16453–16458)

Depression is characterized by lack of motivation and failure to enjoy otherwise pleasurable activities. Because dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens have major roles in reward and motivation, they are likely to contribute to depressive phenotypes. Indeed, in VTA slices taken from mice that showed depression-like behaviors (i.e., reduced social interaction) after exposure to chronic social defeat stress, dopamine neurons were more active than those in VTA from unstressed animals. Cao et al. extend these findings with *in vivo* extracellular recordings, which showed that the firing rate of VTA dopamine neurons increased in mice susceptible to social defeat stress, and many cells shifted from tonic to burst firing mode. These changes were reversed by chronic (but not acute) treatment with an antidepressant selective serotonin reuptake inhibitor, and they did not occur in mice resilient to social defeat stress, suggesting that they are related to depression-like behavior.

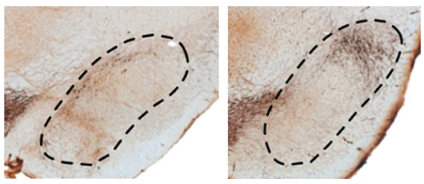
♦ Neurobiology of Disease

GDNF-Activating Transcription Factor Protects Nigrostriatal Neurons

Josee Laganiere, Adrian P. Kells, Jeffrey T. Lai, Dmitry Guschin, David E. Paschon, et al.

(see pages 16469 –16474)

A drop in neurotrophic factor levels is thought to contribute to Parkinson's disease (PD) and other age-related neurodegenerative diseases. Therefore, supplementing such factors might effectively slow, stop, or even reverse degeneration. Glial cell line-derived neurotrophic factor (GDNF), a target-derived factor required for dopaminergic neuron survival, is a particularly promising candidate for treating PD. In animal models of PD, GDNF increases survival of dopaminergic neurons *in vivo* and improves motor function. Unfortunately, attempts to replicate these results in PD patients have failed, probably because too little or too much GDNF was available to substantia nigral neurons. Reasoning that activation of the endogenous *GDNF* gene would be subject to regulation that would prevent overproduction, Laganiere et al. engineered a transcription factor to bind to the endogenous *GDNF* promoter and activate transcription. Virally mediated expression of this transcription factor in rat striatum attenuated toxin-induced loss of dopaminergic neurons and their striatal projections, and it reduced motor impairment.



Infusion of a toxin into rat striatum causes degeneration of dopamine fibers in the substantia nigra, as indicated by lack of tyrosine hydroxylase immunostaining (brown, left). Virally mediated expression of a transcription factor that activates GDNF expression reduces degeneration (right). See the article by Laganiere et al. for details.