This Week in The Journal

How the Dopamine Transporter Gets to Axon Terminals

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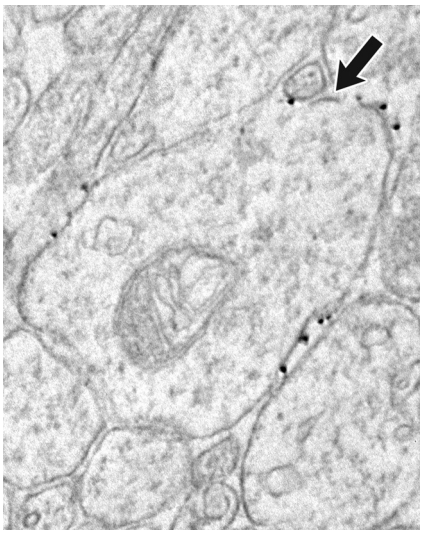
(see pages 234–250)

Most axonal proteins are synthesized in the soma and must be transported to their proper destination. Several decades ago, researchers discovered that proteins traveling toward distal axons move at different rates, centered around two peaks: slow and fast. Later work determined that microtubule, neurofilament, and cytosolic proteins move via slow transport, whereas transmembrane proteins move more than 10 times faster as they are carried in vesicles along microtubules by various motor proteins. It was assumed that all membrane-associated proteins are trafficked by this fast transport mechanism; but new work suggests this is not the case.

Bagalkot et al. were interested in trafficking of the dopamine transporter (DAT)—a protein that takes up synaptic dopamine—in axons that project from the midbrain through the medial forebrain bundle (MFB) to the striatum. Previous studies indicated that in the somata of midbrain dopaminergic neurons, a large fraction of DAT was associated with intracellular membranes, consistent with a high rate of synthesis and trafficking. Yet little DAT was associated with intracellular membranes in axonal terminals in the striatum, suggesting that transport to distal axons was minimal. How then could adequate levels of DAT be maintained at synapses to ensure precise regulation of dopaminergic signaling? To answer this question, Bagalkot et al. examined the distribution and movement of DAT tagged with hemagglutinin (HA) in axons in the MFB.

HA-DAT was present along the entire length of axons, but most of it was associated with the plasma membrane. This surprising finding was confirmed with both super-resolution microscopy and electron microscopy. Indeed, the latter showed that ~68% of HA-DAT in MFB axons was localized to the plasma membrane; intracellular labeling in vesicular or endosomal membranes was infrequent. Furthermore, fluorescence recovery after photobleaching suggested that much HA-DAT in MFB axons is immobile, and when it moved, it traveled at ~0.55 μm/s.

The authors conclude that most DAT in midbrain neurons is inserted into the plasma membrane near the base of the axon, and it diffuses from there to synaptic terminals, possibly in association with lipid rafts. They speculate that this mode of transport could help to minimize vesicle traffic jams where axons narrow and arborize in the striatum: such jams have been proposed to contribute to the degeneration of dopaminergic neurons in Parkinson's disease.



Immunogold labeling of DAT shows that it is most frequently localized to the plasma membrane of dopaminergic axons in the MFB. See Bagalkot et al. for details.

Role for the Entopeduncular Nucleus in Cocaine Aversion

Hao Li, Maya Eid, Dominika Pullmann, Ying S. Chao, Alen A. Thomas, et al.

(see pages 298–306)

Cocaine produces a euphoric state followed by a crash. The crash is thought to be driven by lateral habenula neurons that activate GABAergic neurons in the rostromedial tegmental nucleus; these, in turn, inhibit dopaminergic neurons in the ventral tegmental area. In rodents, this pathway is activated by several aversive stimuli and is inhibited by rewarding stimuli. Notably, the activity of habenula neurons increases 15–20 min after cocaine infusion, about the time when aversive effects set in. What activates habenula neurons has been unclear, but a likely candidate is the rostral entopeduncular nucleus (rEPN), the rodent homolog of the globus pallidus internus. Like habenula neurons, rEPN neurons are inhibited by rewarding stimuli and are activated by aversive stimuli. Moreover, inhibiting these projections attenuates evoked responses in the habenula.

Li et al. now provide direct evidence that rEPN projections to the habenula contribute to cocaine aversion in rats. First, intravenous cocaine infusion increased the activity of habenula-projecting rEPN neurons. In fact, many rEPN neurons had biphasic responses to cocaine, initially decreasing, then increasing after 15–30 min, paralleling the switch in cocaine valence. Second, excitotoxic lesion of the rEPN reduced cocaine-induced activation in the lateral habenula and rostromedial tegmental nucleus.

The aversive properties of cocaine can be demonstrated in a runway task, in which rats receive an infusion of cocaine after running down a corridor. Normally, rats take longer to traverse the corridor across trials, suggesting they acquire place aversion for the site of cocaine infusion. But Li et al. found that inhibiting the rEPN 10 min after peripheral cocaine infusion eliminated this aversion. Moreover, whereas rats normally develop conditioned place aversion when given cocaine in one chamber of a cage, cocaine produced conditioned place preference if habenula-projecting rEPN neurons were inhibited.

These results suggest that rEPN neurons contribute to the delayed activation of habenular neurons that underlies the aversive effect of cocaine. Intriguingly, previous work has shown that rEPN neurons release both GABA and glutamate and that GABA release is blunted during withdrawal from chronic cocaine administration. Future experiments should determine whether a similar mechanism occurs after acute cocaine treatment.

This Week in The Journal was written by Teresa Esch, Ph.D.
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