HIGHLIGHTS

NEUROPHYSIOLOGY

Cause for excitation

Levels of extracellular dopamine are regulated by the dopamine transporter (DAT), a Na^+/Cl^--dependent transporter that is found on dopamine neurons. But there is evidence that DAT might have another role, as described by Ingram *et al.* in *Nature Neuroscience*. They find that activation of DAT triggers a current that increases the excitability of midbrain dopamine neurons.

Interest in DAT is high because both amphetamine and cocaine increase extracellular dopamine by interfering with DAT's ability to clear dopamine from the intercellular space. This increase in dopamine is thought to contribute to the rewarding effects of these drugs. Cocaine is an inhibitor of DAT, whereas amphetamine is a DAT substrate that competes with dopamine for occupancy of the transporter. Previous studies showed that amphetamine could have an excitatory effect on dopamine neurons that is independent of dopamine receptor activation; the new work looked for a potential mechanism of this action.

Ingram and colleagues investigated the effects of low concentrations of dopamine or amphetamine on cultured rat midbrain dopamine neurons. Normally, extracellular dopamine acts on D2 autoreceptors to inhibit the firing of dopamine neurons. But both dopamine and amphetamine increased the firing rate of the neurons in the presence of inhibitors of dopamine D1, D2 or adrenergic receptors. This excitation was caused by a DAT-mediated inward chloride current.

When they analysed the kinetics of the DAT-mediated currents, the authors found that the dopamine affinity of the currents was tenfold higher than the affinity for dopamine uptake by DAT. In other words, the DAT currents were uncoupled from the uptake of dopamine and did not result simply from ionic movements associated with dopamine transport.

An important question is whether this conductance is physiologically relevant. Dopamine neurons *in vivo* are tonically active with complex firing patterns, and regulation of these patterns is likely to be important for the modulation of dopamine release. Neurons contain tightly regulated concentrations of chloride ions, and the chloride equilibrium potential is generally close to the resting potential. This means that small changes in membrane potential that result from the DAT chloride current could have important effects on neuronal excitability and dopamine release.

The DAT-mediated conductance might be important in the somatodendritic release of dopamine from midbrain neurons. According to the authors, depolarization of the neurons by this mechanism provides an alternative to a previous theory — that somatodendritic release results from the reversal of DAT transport and subsequent dopamine efflux. Much more work will be needed to establish the physiological functions of DAT-mediated conductances *in vivo*.

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References and links

ORIGINAL RESEARCH PAPER Ingram, S. L. Dopamine transporter-mediated conductances increase excitability of midbrain dopamine neurons. *Nature Neurosci.* **5**, 971–978 (2002)

WEB SITES

Encyclopedia of Life Sciences:
http://www.els.net/dopamine