

SFB 35 Impromptu Seminar

Colloquia in Membrane Transport

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna,
"Leseraum".

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Wednesday 21.10.2015 14:00 s.t.

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"Putting the Brakes on Trafficking: Ack1 Controls Dopamine Transporter Membrane Stability and Rescues an ADHD Coding Variant"

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Abstract.

The presynaptic dopamine (DA) transporter (DAT) temporally and spatially constrains DA neurotransmission by rapidly recapturing released DA. Aberrant DAT function is implicated in attention-deficit hyperactivity disorder and autism spectrum disorder. DAT is a major psychostimulant target and the rewarding properties of addictive psychostimulants strictly require their binding to DAT. DAT function is acutely modulated by dynamic membrane trafficking at the presynaptic terminal and a PKC-sensitive negative endocytic mechanism, or "endocytic brake", controls DAT plasma membrane stability. However, the molecular basis for the DAT endocytic brake is not defined, nor is it known whether this braking mechanism is unique to DAT or common to monoamine transporters. We have discovered that the cdc42-activated, non-receptor tyrosine kinase, Ack1, is a DAT-specific endocytic brake that stabilizes DAT, but not SERT, at the plasma membrane and is released in response to PKC activation. Intriguingly, constitutive Ack1 activation rescues the gain-of-function endocytic phenotype exhibited by the ADHD DAT coding variant, R615C. These findings reveal a unique endocytic control switch that is highly specific for DAT. Moreover, the ability to rescue the DAT(R615C) coding variant suggests that manipulating DAT trafficking mechanisms may be a potential therapeutic approach to correct DAT mutants that exhibit trafficking dysregulation.