SFB 35 Colloquia in Membrane Transport

15.09.2011, 14.00: Leseraum Pharmakologie

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"Integrins modulate the serotonin system through a three-fold interaction with the serotonin transporter"

Integrins are differentially expressed in the brain, where they modulate the assembly of synapses through the recruitment of scaffolding proteins that influence receptor localization and synaptic vesicle function. The integrin b3 gene (ITGB3) has been associated with autism, with a strong synergistic association with the serotonin transporter gene (SLC6A4, SERT). While SERTs have been extensively studied in the central nervous system, little is known on integrin b3 function in the brain. In the brain, integrin b3 binds to the integrin av subunit to form the vitronectin receptor (avb3). Here we utilize mouse models to determine the role of integrin avb3 on the modulation of the serotonergic system. Integrin b3 and SERT haploinsufficiency leads to several behaviors associated to altered serotonergic signaling. These behavioral modifications are correlated with reductions in av expression and integrin-linked signaling pathways due to the synergistic genetic interaction between these two genes. The genetic interaction also points to a functional interaction, where the activation of integrin avb3 signaling pathways are associated with increases in SERT reuptake activity. Increased adhesive properties in cells expressing avb3 also increase SERT uptake of serotonin in heterologous cells. Finally, some, but not all of the changes associated with avb3 activity may result from a direct interaction with the carboxyl-terminus of SERT. While we are still in the process of deciphering the multiple levels of interaction between integrin b3 and SERTs, we have discovered a complex mechanism by which cell adhesion may influence serotonin synaptic function and plasticity in vivo.