Summary

Regulation of the vesicular monoamintransporter 2- Influence of heterotrimeric G-proteins and intracellular signalling pathways

Neurotransmitters are key molecules of neurotransmission. They are concentrated first in the cytosol and then in small synaptic vesicles by the activity of specific neurotransmitter transporters of the plasma and the vesicular membrane. Following an action potential, synaptic vesicles fuse with the plasma membrane and release their transmitter content into the synaptic cleft, where the transmitter interacts with receptors mostly at the postsynaptic site.

The quantity of neurotransmitter released per vesicle, which does not allways saturate all postsynaptic receptors influences the postsynaptic response. Furthermore the probability of exocytotic events and the number and density of postsynaptic recepors are essential, too.

Since vesicular quanta depend on transport and storage of neurotransmitter the accumulation of serotonin inside the vesicle by the transporter VMAT2 was the aim of this work. Main storage pools of serotonin are the CNS and the platelets. Heterotrimeric G-proteins are involved in the regulation of monoamine storage into the vesicles. The VMAT2 is differently regulated by $G_{\alpha o2}$ and $G_{\alpha q}$ in CNS and platelets, respectively.

In the first part of this study the influence of the electrochemical gradient ($\Delta\mu H^+$) on the VMAT2 activity was determined.There are no differences between wildtype- and $G\alpha_{O2}^{-/-}$-mice concerning the VMAT2 activity.

Furthermore it was verified that through the determination of synthesizing and degrading enzymes of monoamines and the expression of the VMAT2 in $G_{\alpha o2}^{-/-}$-mice the intra- and extravesicular neurotransmitter concentration is strict regulated.

In the second part it was pointed out that the VMAT2 is complexly regulated with respect to intracellular signal transduction molecules. For the first time it was shown that the second messengers cAMP and cGMP have different effects on vesicles of CNS and platelets.

Beside this different regulation the phospholipase C might be an important effector in both systems.

The modulation of VMAT2 activity through heterotrimeric G proteins and their affiliated downstream signals are important for a fast reuptake of the cytosolic toxic monoamines into the vesicle and hence connects the regulated signal transmission and the viability of the cell.