Karolinska Institutet

Department of Women's and Children's Health

Spatial control of postsynaptic proteins

A role in brain plasticity

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Nanna Svartz Auditorium, Karolinska Sjukhuset Solna

Tisdagen den 18 december, 2012, kl 14:00

av

Markus Kruusmägi

Huvudhandledare:
Professor Hjalmar Brismar
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Bihandledare:
Professor Anita Aperia
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Doktor Lena Scott
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Doktor Sergey Zelenin
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Fakultetsopponent:
Professor Daniel Choquet
Université Bordeaux 2
Institute for Interdisciplinary Neuroscience

Betygsnämnd:
Professor Gilberto Fisone
Karolinska Institutet
Institutionen för Neurovetenskap

Professor Abdel El Manira
Karolinska Institutet
Institutionen för Neurovetenskap

Docent Johan Elf
Uppsala Universitet
Institutionen för Cell och Molekylärbiologi

Stockholm 2012

ABSTRACT

Neurons communicate via synapses; the strength of each synapse is defined both pre and postsynaptically. Presynaptically, the strength of the synapse is defined by which neurotransmitter is being released and how much. On the postsynaptic membrane a corresponding receptor will receive the transmitter. Receptor abundance and availability determines the strength of the synaptic connection.

Protein function is as tightly linked to structure as it is to location. Due to the fluidic nature of the plasma membrane, any membrane protein will be highly mobile unless it is being anchored or confined within a compartment by an intracellular protein or cytoskeletal complex. High mobility facilitates interactions between proteins and ensures proper localization through free energy minimization without the need of directed transport. The dynamic regulation of protein mobility is fundamental in defining the function of the protein. The overall abundance and availability of postsynaptic proteins are dependent on many processes such as exocytosis/endocytosis, activation/inactivation, and lateral diffusion.

The aim of this thesis was to study how postsynaptic proteins can be regulated in the dendritic membrane by availability and mobility.

Dopamine is an important modulatory neurotransmitter that is involved in cognition, memory, motoric functions and reward-mechanisms.

Calcyon is an accessory protein that has been suggested to modulate dopamine receptor signaling. We show that calcyon is a neuron-specific vesicular protein with a high intracellular mobility. Furthermore we show that calcyon forms vesicular clusters located just beneath the plasma membrane. We propose a role for calcyon in the trafficking of proteins that are important for synaptic plasticity, to and from the dendritic plasma membrane.

Dopamine receptors are divided into two groups, the D_1-like and D_2-like group, each with distinct downstream signaling pathways. We show that the two isoforms of the D_1-like group, the D_1 and D_5 receptors have distinctly different subcellular localization in striatal neurons and interact differently with the NMDA receptors. We propose that the two isoforms, due to differences in localization and interactions with other receptors, have distinct roles in neuronal dopaminergic signaling.

Most G-protein coupled receptors are transported to the plasma membrane of the soma and are then transported via lateral diffusion to the site of action. We studied several GPCRs, involved in mood regulation and behavior, to elucidate whether GPCRs share a common mode of transport. We show that the 5-HT_{1B} receptor, in contrast to other GPCRs, is transported in vesicles in the lumen of the dendrites. We show that the vesicles release the receptors to the membrane close to inhibitory synapses, followed by subsequent lateral diffusion and confinement in inhibitory as well as excitatory synapses. We propose that this special mode of transport serves as an additional mode of regulation, which enables fine-tuning of serotonergic signaling.

The Na,K-ATPase is an essential ion transporting protein that is found in all cells where it is responsible for the generation of the plasma membrane ion gradient that is the driving force for many important cellular processes. Different isoforms of the catalytic, ion-pumping, α subunit are expressed in different cell types. We show that the neuron-specific α3 isoform is responsible for the sodium clearance in dendrites following synaptic signaling, which is essential for proper neuronal function. Furthermore we show that the α3 subunit is highly mobile in the postsynaptic membrane and that it is confined in excitatory synapses. We show that mobility is modulated by neuronal activity; excitatory stimulation results in an increased mobility in both the synaptic as well as the extrasynaptic region.

ISBN 978-91-7457-996-3