Function of the PDZ-domain containing protein family of PSD-MAGUKs in AMPA receptor targeting to excitatory synapses

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Note of Collaboration

Electrophysiological recordings presented in this thesis were generated in collaboration with Dr. Roger Nicoll's lab by GM Elias. Due to the interwoven nature of our research, presentation of this data is necessary to clarify the full scope of the findings.

List of related Publications
(* indicates equal contribution)

“Synapse-specific and developmentally regulated targeting of AMPA receptors by a family of MAGUK scaffolding proteins.”
Elias GM*, Funke L*, Stein V, Grant SG, Bredt DS, Nicoll RA
Neuron, 2006 Oct 19, 52(2):307-20

“Membrane-associated guanylate kinases regulate adhesion and plasticity at cell junctions.”
Funke L, Dakoji S, Bredt DS
Annu Rev Biochem. 2005; 74:219-45. Review

Summary 3

Zusammenfassung 5

Introduction 7

The glutamatergic synapse 9
The postsynaptic density 10
Ionotrophic Glutamate Receptors subdivide into two families 11
PSD-MAGUKs 12
Regulating Synaptogenesis 15
Organizing Signal Transduction Pathways 17
Clustering Receptors at Synapses 18
Modulating Synaptic Plasticity 20

Results 25

PSD-95 shRNA 25
PSD-95 knock-down in neurons 27
Loss of PSD-95 reduces surface glutamate receptor 2 (GluR2) 29
Function of PSD-MAGUK family members 30
Identification of efficient shRNAs for all PSD-MAGUKs 30
Each PSD-MAGUK shRNA is target specific 31
Isoform specificity of shRNA PSD-MAGUKs 33
Knock-down in hippocampal cultures 33
High titer lentivirus particle 34
Infection of hippocampal neuronal cultures with shRNA lentiviruses 36
Surface GluR2 staining 39
Synaptic transmission of hippocampal neurons 39
Knock-down of PSD-95 or PSD-93 reduces AMPAR mediated synaptic transmission 40
PSD-95 and PSD-93 knock-out mice 42
Excitatory synaptic transmission is normal in PSD-93 and PSD-95 knock-out mice 42
Specific binding partners of PSD-95 and PSD-93 44

The Effects of Gene-Targeted Double Knockout (DKO) of PSD-95 and PSD-93 on Synaptic Transmission 47
Role of SAP102 in Synaptic Transmission 50
Discussion 55
Previous findings with overexpression of PSD-MAGUKs 56
Specificity of RNAi and role of SAP97 57
Identification of novel binding partners 59
shRNA mediated knock-down of PSD-MAGUKs 59
Studies in gene targeted deletions of PSD-MAGUKs 60
What happens to AMPARs not targeted to the synapse? 62
Developmental switch of PSD-MAGUKs 63
Loss of PSD-MAGUKs and NMDARs 64
Conclusion 66
Material and Methods 69
DNA Constructs 69
Antibodies 72
Knock-out mouse strains and genotyping 72
Overexpression in heterologous cells 73
Neuronal Culture and Transfection 74
Lentivirus Production and Neuronal Infection 76
Brain Lysates and Solubilization 77
Electrophysiology in Acute Slices 78
Electrophysiology in Slice Culture 79
Immunoprecipitations 81
Western blot analysis 82
References 83

Summary

The majority of excitatory transmission in the vertebrate central nervous system is communicated through synapses that use the amino acid glutamate as neurotransmitter. Glutamate is the ligand for a large number of receptor molecules that can be separated into metabotrophic and ionotrophic glutamate receptors, according to their ability to conduct ions. AMPA receptors (AMPAR), a subgroup of ionotrophic glutamate receptors, carry the majority of ion flux at theses synapses. Their number determines the strength of a given synapse. Changes in synaptic strength are viewed as a potential molecular mechanism of learning and memory. The proteins targeting and anchoring AMPAR and determining their number at a synapse are poorly understood.

This study focuses on a family of membrane associated guanylate kinase (MAGUK) proteins that are abundant at the post-synaptic densities (PSD) of excitatory synapses, named PSD-MAGUKs. The four PSD-MAGUKs, PSD-95, PSD-93, SAP97 and SAP102 are highly homologous. Overexpression of PSD-95, PSD-93 and SAP102 causes enhanced synaptic recruitment of AMPAR. Surprisingly, none of the PSD-MAGUK knock-out mice show a deficit in AMPAR transmission.

Through a combinational approach utilizing gene targeted deletion mouse mutants and acute loss of expression using RNA interference, this study establishes PSD-95 and PSD-93 as jointly responsible for AMPAR targeting to mature synapses of the hippocampus. Unexpectedly, they function at mostly

non-overlapping synapse populations. SAP102 is the dominant PSD-MAGUK during early development and can partially compensate for loss of PSD-95 and PSD-93. This study establishes PSD-MAGUKs as central factors maintaining synaptic strength.

Zusammenfassung

Der Grossteil der exzitatorischen Signalweiterleitung an Synapsen des zentralen Nervensystems von Säugetieren wird durch den Neurotransmitter Glutamat übermittelt. Glutamat wird von der Präsynapse ausgeschüttet und dient als Ligand für vornehmlich postsynaptische Glutamatrezeptoren. Glutamatrezeptoren werden anhand ihrer Fähigkeit Ionen zu leiten, in metabotrophe und ionotrophe Rezeptoren unterteilt. Eine Untergruppe der ionotrophen Glutamatrezeptoren sind die AMPA Rezeptoren. Da sie den grössten Anteil an liganden induziertem Ionenfluss in glutamatergen Synapsen leiten, bestimmt die AMPA Rezeptorenanzahl die Stärke einer Synapse. Veränderung der synaptischen Stärke wird als ein möglicher molekularer Mechanismus von Lernen und Gedächtnisbildung angesehen. Die Faktoren, die AMPA Rezeptoren in der Synapse verankern und dort ihre Anzahl bestimmen, sind unzureichend verstanden.

In dieser Arbeit wird eine Unterfamilie der Membran-assoziierten Guanylat Kinasen (MAGUK) und ihr Einfluss auf die Verankerung synaptischer AMPA Rezeptoren untersucht. Die vier hochgradig homologen MAGUKs, PSD-95, PSD-93, SAP97 und SAP102 sind in der sogenannten post-synaptischen Dichte (PSD) angereichert und werden im Weiteren PSD-MAGUKs genannt. Überexpression von PSD-95, PSD-93 und SAP102, jedoch nicht von SAP97, führt zu einer dramatischen Anreicherung von AMPA Rezeptoren in Synapsen. Im Gegensatz dazu zeigt keine der erzeugten PSD-MAGUK Knock-out Mäuse

ein Defizit der basalen AMPA Rezeptor vermittelten synaptischen Signalweiterleitung.

Durch Kombination mehrerer Mausmutanten und RNA Interferenz vermitteltem acutem Expressionsverlust wird gezeigt, dass PSD-95 und PSD-93 gemeinsam für die Verankerung von AMPA Rezeptoren in Synapsen des Hippocampus von adulten Mäusen verantwortlich sind. Interessanterweise nehmen PSD-95 und PSD-93 ihre Funktion an nicht überlappenden Subpopulationen von Synapsen wahr. Bevor PSD-95 und PSD-93 ausreichend exprimiert werden, füllt SAP102 ihre Funktion in der frühen postnatalen Entwicklung aus und kann für den Verlust von PSD-95 und PSD-93 teilweise kompensieren. Gemeinsam bestimmen PSD-MAGUKs somit die Stärke von Synapsen im Hippocampus.