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

Dissertation zur Erlangung des akademischen Grades des Doktors der Naturwissenschaften (Dr. rer. nat.)

eingereicht im Fachbereich Biologie, Chemie, Pharmazie
der der Freien Universität Berlin

vorgelegt von

Lars Funke
aus Salzkotten

April, 2007
1. Gutachter: Prof. Dr. David Bredt, University of California San Francisco, USA
2. Gutachter: Prof. Dr. Fritz Rathjen, Freie Universität Berlin, Deutschland

Disputation am 12. Juni 2007
Acknowledgement / Danksagung

First I would like to thank Dr. David Bredt and Dr. Fritz Rathjen for the willingness to review my Ph.D. thesis and their support for my dissertation. I would also like to thank the additional committee members for taking their time to evaluate my work.

The time in Dr. Bredt’s lab has been an exciting and stimulating learning experience. Apart from being one of the most gifted and driven researchers I know, I would like to thank him for his very critical view of research conducted mixed with unwavering “can-do” optimism. Dr. Bredt assembled an extraordinary team that worked in a professional and at the same time supportive and helpful atmosphere. Being the only graduate student among eleven Post docs was challenging at times but they also tough me so much. Among them I would like to thank Masaki and Yuko “Team”-Fukata for letting me share their large knowledge of biochemistry and their kind words. Aki Kato is a powerhouse of research experience and was always willing to share it and a good laugh. Susumu Tomita probably is the most efficient, fastest and best organized scientist I have worked with. He also managed to break it to me fast if I missed a detail in my experimental planning with his trademark comments of: “It’s dead!!” or “STUPID !!!” Followed by an explanation, how it would work next time – and it would. Thanks for that and good luck in Yale – I am sure you won’t need it. Wim Vandenberghe and his three kids and wife are now back in Belgium starting his own lab. The FC Bruegge will be happy about that as much as we miss his witty comments. Maybe he will find the time to learn his eighth language. Keith Byrd I would like to thank for his endless pool of crazy stories to keep us laughing through many lunch hours. Guille Yudowski never rested in his attempt to get me to finish my thesis faster. I wish him, his wife Julietta and their soon to be born child the very best. Jessie for making the transition from shy girl to merciless heartbreaker. Good hunting in Harvard. Last but not least “Last man standing” Olav Olsen for hanging on together with me and for being a great colleague and friend.

The members of the Nicoll lab and foremost Dr. Roger Nicoll I would like to thank for the great collaborations and for the warm support when our numbers started to dwindle.

On a more private note, thanks to Barbara and Dirk for getting us out of the lab and on crazy tours and for being great friends in general. I have not forgiven that you left California behind though! We miss you. Dana and Bradley, our non-scientific social stronghold, it makes me happy that after knowing me for over four years now, you still don’t understand why anyone would work on a Sunday without overtime pay. Bradley endured three years of Air Force Academy just to gather great stories to entertain large crowds at parties. Determination that is! I am grateful for having you as friends. The Olsens, Kim and Olav and their “minime-s” Kaia and Olav, are our substitute family away from home. Thanks for all the dinners, holiday events, BBQs and everything else you did. I hope you will
find a great place to raise your kids and be happy – meaning no snow in the winter.

Further I thank the kids from the Julius lab, Pam, Puffski, Gunther and Jan for all the beers shared over soccer matches. All my friends from my time in Berlin and school who stayed in touch although I decided to move to the other side of the world. Thanks for sticking around.


**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

“Membrane-associated guanylate kinases regulate adhesion and plasticity at cell junctions.”
   Funke L, Dakoji S, Bredt DS
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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 these 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


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 Receptor vermittelten synaptischen Signalweiterleitung.