

Japan-US Brain Research Cooperation Program
The Report of Information Exchange Seminar in 2004 fiscal year

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1. The Seminar Title: Workshop on Molecular Basis of Synaptic Plasticity

2. The Term: From 2004.06.27 To 2004.06.30

3. The Location:

Room 815, Meyer Complex, New York University, New York, NY, USA

4. The Representative's Name, Title and Affiliation:

Japanese Coordinator:

Tomoaki Shirao, Professor, Dept. of Neurobiology and Behavior, Director of Institute of Experimental Animal Research, Gunma University School of Medicine

US Coordinator:

Chiye Aoki, Professor, Center for Neural Science, New York University

5. The Participants:

Japan: The Invited participants _13_ people The others ___ people

Name, Title and Affiliation of the Invited participants

Teiichi Furuichi

Laboratory for Molecular Neurogenesis, RIKEN Brain Science Institute

Kenji Hanamura, Research Associate, Department of Neurobiology and Behavior, Gunma University Graduate School of Medicine

Kensuke Hayashi, Professor, Life Science Institute, Sophia University

Ryoki Ishikawa,

Dept. of Molecular and Cellular Pharmacology, Gunma University Graduate School of Medicine

Takuji Iwasato

Behavioral Genetics Lab, RIKEN Brain Science Institute

Haruo Kasai, Professor, Department of Cell Physiology, National Institute for Physiological Sciences

Masanori Matsuzaki, Post-doctorial fellow, Department of Cell Physiology, National Institute for Physiological Sciences

Shigeo Okabe, Professor, Department of Cell Biology, Tokyo Medical and Dental University

Makoto Saji, Professor, Department of Physiology, School of Allied Health Sciences, Kitasato

University

Yuko Sekino, Associate professor, Department of Neurobiology and Behavior, Gunma University Graduate School of Medicine

Tomoaki Shirao, Professor and Chairman, Department of Neurobiology and Behavior, Gunma University Graduate School of Medicine

Tadaharu Tsumoto, Professor, Department of Neurophysiology, Osaka Univ. Graduate School of Medicine

Sachiko Yoshida, Professor, Department of Materials Science, Toyohashi University of Technology

US: The Invited participants 7 people The others Approx. 25 people
Name, Title and Affiliation of the Invited participants

Chiye Aoki, Professor, Center for Neural Science, New York University

Barbara Calabrese, Post-doctorial fellow, Department of Cell Biology, The Scripps Research Institute

Shelley Halpain, Associate Professor, Department of Cell Biology, The Scripps Research Institute

Venkatesh Murthy, Associate Professor, Dept. of Molecular & Cellular Biology, Harvard University

Yasunori Hayashi, Professor, The Picower Center for Learning and Memory, Department of Brain and Cognitive Science, RIKEN-MIT Neuroscience Research Center

Kenichi Okamoto, Post-doctorial fellow, Picower Center for Learning and Memory, Department of Brain and Cognitive Science, RIKEN-MIT Neuroscience Research Center

Peter Penzes, Professor, Department of Physiology, Northwestern University

Shasta Sabo, Post-doctorial fellow, Center for Neuroscience, University of California, Davis

Dan Sanes,
Center for Neural Science, New York University

Peter Scheiffele
Physiology and Cellular Biophysics, Columbia University

William J. Tyler
Dept. of Molecular & Cellular Biology, Harvard University

A number of discussants from the American sides were affiliated with the hosting institution, the CNS, but many more from New York University Medical School (Skirball Institute), Columbia University and Cornell University. Many of the local discussants stayed for only limited portions of the Workshop, but greatly enriched the discussions over these portions of the meetings.

6. The Abstract and the Significance of this seminar (300 words):

Search for the molecular mechanisms underlying synaptic plasticity has led many neuroscientists

to focus upon the pivotal roles played by cytoskeletal proteins. It is widely accepted that synaptic plasticity during development and in adulthood involves pre- and post-synaptic modifications, including structural changes spanning across the synaptic cleft and extending into axon terminals and spines. All of these changes, transient or long-lasting, slow or rapid, are likely to involve re-organization of cytoskeletal proteins, but the molecular mechanisms allowing for the link between cytoskeletal changes and synaptic plasticity is not yet fully understood. The Workshop on the "Molecular Basis of Synaptic Plasticity: Synaptogenesis, Receptor Trafficking and Cytoskeletal Proteins" at the Center for Neural Science, NYU, on July 1-3, 2004 brought together neuroscientists from Japan and the US who had contributed significantly to the cell biological mechanisms underlying synaptic plasticity and, in the process, discovered new enzymatic cascades, new proteins and new links between synaptic activity and cytoskeletal proteins. The participants presented overviews and new findings. Each presentation was followed by discussions that consider ways in which their newly elucidated molecular pathways could interact competitively, antagonistically, synergistically or in parallel. Furthermore, we made available on the internet a publication of each speaker's presentation, so that participants could begin to plan fruitful collaborations for the future. Through such exchanges of views, some new collaborations emerged and the existing ones were strengthened, ultimately leading to better understanding of the molecular mechanisms underlying synaptic plasticity. Titles and abstracts of the speakers' talks, together with relevant recent publications by the speakers and list of participants were publicized using a CNS website (<http://www.cns.nyu.edu/events/workshops/2004/synaptic-plasticity.php>).

7. The Result of this seminar and the results expected(300 words):

In this seminar, Japanese participants reported the physiological function of rat barrel formation (Iwasato), trafficking of BDNF (Tsumoto), spine function analyzed with caged glutamate (Kasai), role of drebrin on accumulation of actin cytoskeleton and PSD95 (Shirao), behavioral analysis of drebrin A knock down mouse (Saji), function of Homer and PSD95 in the spine (Okabe), and the role of Homer in the spine formation (Furuichi). American participants reported role of actin cytoskeleton in spine formation (Hayashi), homeostatic and Hebbian synaptic plasticity (Murthy), immunoelectron microscopic analysis of drebrin's role in synapse formation (Aoki), synaptic strength mechanism during development (Sanes), role of neurexin and neuroligin in synapse formation (Scheiffele), vesicle transportation in newly developed synapses (Sabo), activity dependent morphological changes of spines (Penzes), and role of actin organization and membranes in spine morphogenesis. More detail of each talk can be found in attached abstracts. Research of synapses is divided into presynaptic and postsynaptic researches. Research of presynaptic event, such as neurotransmitter release, has been studied under the leadership of American researchers. On the other hand, many postsynaptic proteins, such as drebrin, cupidin (homer), and neurabin, were originally found by Japanese researchers. However, this issue has not been recognized internationally. After this seminar, American participants realized the high scientific level of Japan in this research field, and realized the necessity of collaboration in this research field between Japan and US. When Japanese researchers attend the meeting organized by American Researchers, it is actually difficult for Japanese researchers to attend actively in the discussion. However in this seminar, both Japanese and US researchers attended equally into hot discussion. I believe that the similar number of major participants from Japan to that from US was the key point of our success in this seminar. Furthermore, small size of seminar and long discussion time can deepen the interrelationships between Japanese and US participants. This is another key for our success.

After this seminar, new collaborations have actually started, and some collaborative works have been even published in some journals. In addition, one symposium in Winter Conference of Brain Research held at next January in USA, and another symposium in Asian Pacific Neurochemistry Meeting will be organized by a US participant and a Japanese participant in this seminar. Furthermore, Drs. Okabe and Penzes will organize the second year of this seminar this year.

Participants in this seminar are expected to organize more interdisciplinary information-exchange seminars in near future.

8. The Others (Practical Issues, Special Mention Matters):

The organizational help from Matt Burdetsky of the Capital Meeting Planning, Inc. (CMPI) was an essential ingredient of the Workshop's success. He made sure reservations to hotels and restaurants, audio-visual setups, meeting room arrangements, etc., all were in order PRIOR to the meeting. He became the person to contact for all participants. The questions posed to him ranged from transportation within New York City to successful presentation of PowerPoint files on PCs versus MACs, to having name badges and laser pointers ready for use. It was particularly helpful when Mr. Burdetsky was able to arrange for the coffee breaks and breakfasts to be prepaid by NIMH funds.

On the other hand, the necessity to pay for dinners on the site was very cumbersome, particularly since some of the dinner participants were junior scientists from Japan and the US with only limited funds, and some reservations requested down-payment of \$100 pre-paid by two weeks.

Welcoming Remarks and Overview: What neurons can do in vivo as their neurites trespass layers and columns

Chiye Aoki

Abstract

A short presentation will be made to cover the topic of plasticity in adulthood. Examples will be taken from the adult visual cortex of monocular primates, in which the synaptic molecules within neurons and astrocytes can be seen to abide by columnar and laminar boundaries, even though their neurites trespass multiple layers and columns. These observations suggest that the intracellular trafficking of synaptic molecules within dendrites (and axons?) is determined, at least in part, by afferent levels of activities that can occur segregated across the layers and columns.

Genetic Dissection of Barrel Formation in the Rodent Somatosensory System

Takuji Iwasato

Abstract

In the rodent primary somatosensory cortex, the configuration of whiskers and sinus hairs on the snout is topographically represented as discrete modules of thalamocortical afferent (TCA) terminals and layer IV granule cells. Developed within the first week of life, these module (barrel) formations depend on neural activity from the peripheral sensory organs (e.g. whiskers). Although recognized as a good model of activity-dependent development of mammalian neuronal circuits, technical limitations have hindered our understanding of the underlying mechanisms of barrel formation.

We developed a conditional gene targeting system that can selectively manipulate specific genes in cortical excitatory neurons. Using this system, we generated cortex-restricted knockout mice (CxNR1KO) for NR1, an essential subunit of NMDA receptor. Patterning of TCAs (pre-synaptic pattern) in CxNR1KO mice is present but less distinct than in wild-type mice. Aggregates of layer IV neurons (post-synaptic

pattern) do not develop. A detailed morphological analysis showed that the dendritic field of layer IV neurons failed to orient toward TCA terminal patches in these knockout mice. These results indicate that cortical NMDA receptor is a key player in both pre-synaptic and post-synaptic patterning in barrel formation.

Intra- and inter-neuronal trafficking of BDNF and its role in synaptogenesis

Tadaharu Tsumoto

Abstract

Neurotrophins such as brain-derived neurotrophic factor (BDNF) are suggested to play a role in synaptogenesis and synaptic plasticity. Important steps of processes for BDNF to exert such a role are assumed to be its trafficking in neurites to release sites, activity-dependent release and internalization with its receptors, TrkB in postsynaptic neurons or presynaptic terminals. Elucidation of mechanisms underlying such dynamic movements of BDNF is crucial for understanding of the function of BDNF. However, an actual movement of BDNF in neurites of living neurons has not fully been analyzed.

To address this issue, we developed molecular imaging techniques to demonstrate intra- and inter-cellular trafficking of BDNF tagged with green fluorescent protein (GFP) or other fluorescent proteins in living cortical neurons with the method of direct intranuclear injection of plasmid cDNAs. With this method we found that BDNF moves in presynaptic axons in the anterograde direction and transfers to postsynaptic neurons in an activity-dependent manner (Kohara et al., *Science* 291, 2419–2423, 2001). Then, we tested whether endogenous BDNF also transfers to postsynaptic neurons in the similar way to BDNF-GFP, using chimeric culture preparations of visual cortical neurons obtained from two types of transgenic mice, GFP mice and BDNF knockout mice. Neurons derived from the former mice have endogenous BDNF as well as GFP. We found that endogenous BDNF transfers to postsynaptic neurons and plays a role in development of dendrites of postsynaptic neurons (Kohara et al., *J. Neurosci.* 23, 6123–6131, 2003).

Rapid and persistent modulation of actin dynamics regulates postsynaptic

reorganization underlying bidirectional plasticity

Yasunori Hayashi

Abstract

The synapse is a highly organized cellular specialization, that reorganizes structure and composition according to input strength both positively and negatively. But the mechanisms orchestrating these changes remain elusive. Actin serves as both cytoskeleton and scaffold for various postsynaptic proteins and exists in a dynamic equilibrium between F-actin and G-actin, which is bidirectionally modulated by various cellular signals. This makes actin a plausible locus for bidirectional reorganization of structure and molecules. A newly innovated FRET-based live imaging technique that monitors F-actin/G-actin equilibrium revealed that a tetanic stimulation causes a rapid and persistent shift of actin equilibrium towards F-actin. This enlarges dendritic spines and increases the postsynaptic binding capacity. In contrast, prolonged low frequency stimulation shifts the equilibrium towards G-actin, resulting in a loss of postsynaptic actin and spine structure. This bidirectional regulation of actin is actively involved in postsynaptic assembly-disassembly and serves as a substrate for bidirectional synaptic plasticity.

Homeostasis and the single neuron

Venki Murthy

Abstract

Persistent changes in activity of individual neurons trigger adaptive responses in intrinsic excitability and synaptic transmission. By manipulating electrical activity or synaptic activity in individual neurons in an otherwise normal network, we have uncovered multiple forms of synaptic plasticity. We will discuss how these synaptic changes fit into current ideas about homeostatic and Hebbian synaptic plasticity

Single-spine functions studied with two-photon photolysis of caged-glutamate

Haruo Kasai

Abstract

Dendritic spines of pyramidal neurons in the cerebral cortex undergo an activity-dependent structural remodeling that has been proposed to be a cellular basis of learning and memory. It has remained unknown, however, how structural remodeling supports synaptic plasticity, such as long-term potentiation (LTP), and whether such plasticity is input specific at the level of the individual spine. We have now investigated the structural basis of LTP with the use of two-photon photolysis of caged glutamate at single spines of hippocampal CA1 pyramidal neurons⁸. Repetitive quantum-like uncaging of glutamate induced a rapid and selective enlargement of stimulated spines that was transient in large mushroom spines but persistent in small spines. Spine enlargement was associated with an increase in AMPA receptor-mediated currents at the stimulated synapse and was dependent on NMDA receptors, calmodulin, and actin polymerization. Long-lasting spine enlargement also required Ca²⁺/calmodulin-dependent protein kinase II. Our results thus indicate that spines individually follow Hebb's postulate for learning. They further suggest that small spines are preferential sites for LTP induction, while large spines might represent physical traces of long-term memory.

The emergence of drebrin A at newly forming synapses

Chiye Aoki

Abstract

Drebrin A is a neuron-specific, actin-binding protein. Evidence supporting the involvement of drebrin A in synaptogenesis is mounting, but this body of work relies mostly on in vitro assays. In order to determine whether drebrin A arrives at the plasma membrane of neurons, in vivo, in time to orchestrate synaptogenesis, a new

antibody was used to locate drebrin A in relation to electron microscopically imaged synapses. Western-blotting showed that drebrin A emerges at postnatal day (PNd) 6, and becomes progressively more associated with F-actin in the pellet fraction. Light microscopy showed high concentrations of drebrin A in the hippocampus and cortex. Electron microscopy revealed that drebrin A in these regions is located almost exclusively in dendrites both neonatally and in adulthood. In adulthood, nearly all of the synaptic drebrin A is within spines forming asymmetric, non-GABAergic, i.e., excitatory synapses. At PNd7, patches of drebrin A-immunoreactivity were discretely localized to the submembranous surfaces of dendrites forming slight protrusions. The drebrin A-sites exhibited only thin postsynaptic densities (PSD) but were already immunoreactive for the NR2B subunit of NMDA receptors. These drebrin A-sites lacked axonal associations or were contacted by axons that were immuno-negative for GABA and contained only a few vesicles. This, together with the selective association of drebrin A with asymmetric synapses in adulthood, indicates that the neonatal drebrin A-sites are precursors of excitatory synapses. Drebrin A may be involved in organizing the dendritic pool of actin for the formation of spines and of axo-spinous excitatory synapses.

Drebrin A plays a key role in cluster formation of F-actin and PSD-95 at postsynaptic site

Tomoaki Shirao

Abstract

Dendritic spines are the postsynaptic reception regions of most excitatory synapses, and spine formation is fundamental to the development of neuronal networks [1-3]. It has been reported that long thin protrusions from dendrites, dendritic filopodia, change into morphologically mature spines, such as mushroom-shaped or stubby spines. Previous studies suggested that the actin cytoskeleton mediated the morphology of both filopodia and spines. Drebrin A is a neuron-specific F-actin binding protein which is localized in dendritic spines. Immunocytochemical study showed that drebrin clustering in preceded PSD-95 clustering in dendritic filopodia. Suppression of drebrin A expression using antisense oligonucleotides inhibited the cluster formation of drebrin and PSD-95, and the spine formation. Replenishment of EGFP tagged drebrin A at postsynaptic site re-accumulate PSD-95. Over-expression of EGFP tagged drebrin A resulted in the enlargement of spines in mature neurons, but resulted in the formation of abnormal large protrusions in

immature neurons. These results indicate that drebrin A accumulates spine-resident proteins via protein-protein interaction, and that clustering of drebrin A plays a key role in the morphological change from dendritic filopodia into mature spines.

Is rat with antisense-induced in vivo knockdown of a spine protein drebrin A a model for schizophrenia?

Makoto Saji

Abstract

Drebrin A located in dendritic spines regulates their morphological changes and plays a role in the synaptic plasticity via spine function. Reduced drebrin A has been found in the brain of patients with Alzheimer's disease or Down's syndrome. To examine whether the down-regulation of drebrin A protein levels causes deficits in higher brain function, such as memory formation or cognition, we performed antisense-induced knockdown of drebrin A expression in rat brain by using an HVJ-liposome gene transfer technique. We investigated the effects of drebrin in vivo knockdown on acquisition of spatial memory in a hidden platform task in water maze, retention of spatial memory in a probe trial in water maze, sensorimotor gating including cognitive function in a pre-pulse-inhibition test, adaptive behaviors in an open-field test, and sensitivity to psychostimulant in an amphetamine-induced locomotor response. Rats with drebrin A in vivo knockdown displayed a stronger preference for a previous event due to perseverative behavior, impaired pre-pulse inhibition, increased locomotor activity, anxiety-like behavior, and an hypersensitivity to psychostimulant, suggesting modeling behaviors related to schizophrenia. These findings indicated that decreased drebrin A produces deficits in cognitive function but not in spatial memory formation, probably via hypofunction of dendritic spines. We conclude that the drebrin A in vivo knockdown rat may be a good animal model for positive symptom of schizophrenia.

Trafficking of vesicle precursors towards newly forming synapses

Shasta Sabo

Abstract

The formation of appropriate synaptic communication between cortical neurons is required for perception and behavior. In addition to the relevance of synaptogenesis to the initial establishment of synaptic connectivity, formation of new synapses appears to be an important mechanism for at least some forms of plasticity. Despite this importance, the mechanisms by which synapses are formed in the CNS remain relatively poorly understood. Importantly, both during development and in more mature neurons, it remains unclear how synaptic proteins are trafficked to the right place at the right time during synapse formation. Synaptic proteins appear to be transported to sites of synaptogenesis on at least two classes of precursor vesicles: one that carries active zone proteins and another that delivers synaptic vesicle proteins and, most likely, some active zone proteins, as well. Our research has been most concerned with the delivery of synaptic vesicle proteins to nascent synapses and has, therefore, focused on the latter. We use detailed, quantitative analysis of the transport of synaptic proteins using live, time-lapse confocal imaging of immature axons in cultured neurons derived from rat postnatal cortex to address these issues. I will address how synaptic vesicle proteins are transported to and accumulated at sites of synapse formation and address when immature CNS axons become competent for depolarization-dependent neurotransmitter release.

Turnover of PSD molecules in hippocampal neurons

Shigeo Okabe

Abstract

Remodeling of synaptic structure is important in both development of functional neural circuits and modulation of preexisting connections. A variety of proteins are recruited to the postsynaptic density (PSD), an electron dense thickening of the postsynaptic membrane, and are thought to play critical roles in the modulation of synaptic functions. We previously showed continual remodeling of postsynaptic structure containing PSD-95 in cultured hippocampal neurons (1) and synchronized accumulation of synaptic vesicle proteins and PSD-95 at synaptic junctional sites (2). Long-term observation of dissociated cultures of hippocampal neurons isolated from transgenic embryos expressing GFP-tagged PSD revealed synchronized assembly and disassembly of PSDs, which were regulated by cAMP-dependent signaling (4). These observations, together with imaging experiments performed in other laboratories, collectively indicated very rapid assembly/disassembly of PSD proteins

in the developing hippocampal network (5).

A variety of proteins, including membrane proteins, scaffolding proteins and cytoskeletal proteins, are recruited to the PSD and are thought to play distinct roles in organizing the complex molecular architecture. Although both PSD-95 and PSD-Zip45 (also known as Homer 1c) are PSD scaffolding proteins of excitatory synapses in the hippocampus, postsynaptic calcium increase selectively regulates the distribution of PSD-Zip45 (3). This result suggests that mechanism of assembly/disassembly of individual PSD scaffolding proteins is distinct and their turnover can be regulated independently. Our time-lapse analysis of multiple PSD proteins in hippocampal neurons revealed distinct kinetics of individual proteins. Transmembrane proteins, such as glutamate receptors, and lipid-anchored scaffolding proteins, such as PSD-95, are thought to function as linkers between the postsynaptic membrane and the cytoplasmic matrix and can potentially stabilize the PSD structure. Less dynamic behavior of PSD-95 at the postsynaptic sites is consistent with this notion. However, analyses of culture preparations from genetically manipulated mice and pharmacological treatments indicated that both glutamate receptors and PSD-95 are dispensable for the PSD stability. In contrast, manipulation that disrupts F-actin induced rapid disassembly of multiple PSD scaffolding proteins, including PSD-Zip45 (Homer 1c), GKAP, and cortactin-binding protein (Shank family proteins). These scaffolding proteins showed more dynamic behavior than PSD-95 and the fractions that showed actin-dependent dispersion were comparable with rapid-exchangeable fractions measured by fluorescence recovery after photobleaching analysis. In contrast, PSD-95 was resistant to pharmacological disruption of F-actin. Integrity of F-actin in dendritic spines is indispensable for the organization of PSD scaffolding proteins possibly through its interaction with the cytoplasmic surface of PSDs.

Cupidin/Homer2 regulates postsynaptic molecular organization and dendritic spine morphology

Teiichi Furuichi

Abstract

Homer is a postsynaptic adaptor protein that binds various target proteins including the class I metabotropic glutamate receptors (mGluR1/5), IP3 receptors, Shank (a protein that binds to the GKAP/PSD-95/NMDAR complex and to an actin-binding

protein Cortactin), and Drebrin (a dendritic actin-binding protein) via the N-terminal EVH1 domain. In addition, Homer proteins self-assemble via the C-terminal coiled-coil domain and Leu zipper motifs. Thus, Homer is thought to generate physical and functional links among these target proteins in postsynapses. Three distinct genes of the Homer family (Homer1/Vesl-1/PSD-Zip45, Homer2/Vesl-2/Cupidin, and Homer3) and their alternative-splicing isoforms have been identified to date. The long Homer forms (Homer1b/c, Cupidin/Homer2a/b, and Homer3a/b) contain both N- and C-terminal domains. On the other hand, the activity-dependently expressed short Homer1a/Vesl-1S lacks the C-terminal self-assembly domain, and is suggested to act as a natural dominant negative regulator that intervenes with a physical link between multiple targets generated by self-assembled long Homer forms.

We analyzed the expression and function of Cupidin/Homer in synapse development. In the developing cerebellum, Cupidin/Homer2 is clustered in postsynapses of granule cells connecting mossy fiber terminals. The declustering of Cupidin was induced by Glu treatment within a minute via the NMDA receptor Ca^{2+} influx followed by MAPK/ERK cascades. Exogenous Cupidin overexpressed in granule cells increased NMDA currents, whereas overexpression of the N-terminal domain that resembles the short Homer1a had the opposite effect. These results suggest the involvement of Cupidin in synaptic transmission and its negative regulation by Homer1a in cerebellar granule cells. In hippocampal neurons, the clustering of Cupidin coincided with that of the NMDA receptor complex proteins NR2B and PSD-95 in the dendritic clustering and synaptic targeting. Overexpression of Cupidin increased the number of mushroom-like mature-type spines and enhanced the synaptic clustering of the NR2B, PSD-95, and N-cadherin. In contrast, overexpression of the N-terminal domain increased the number of long protrusions and decreased the synaptic clustering of PSD-95 and Drebrin.

In conclusion, these results indicate that Cupidin/Homer has two modes in regulating synaptic protein localizations and functions: 1) activity-dependent reversible declustering of long Homer proteins and 2) short-Homer (Homer1a)-mediated disruption of target links generated via self-assembled long Homers. The former regulatory mode appears to be fast response to synaptic activities, whereas the latter mode via the short Homer is slower response induced by strong stimulations such as sustained Glu treatment, electric convulsion, LTP, cocaine administration, etc. In addition, the long Homer is likely involved in the organization and links of postsynaptic proteins throughout dendritic and synaptic development, whereas the short Homer regulates the morphology of dendritic spines.

Regulation of dendritic spine activity-dependent structural plasticity

Peter Penzes

Abstract

Structural changes are a key aspect of synaptic plasticity, but the signaling mechanisms which regulate synaptic structural plasticity and coordinate it with functional synaptic plasticity are not well understood. We report that activation of synaptic NMDA receptors in cultured cortical neurons induces dramatic spine morphogenesis and activation of small GTPase Rap1. Rap1 regulates the PDZ domain-containing protein AF-6, which is recruited to the plasma membrane upon Rap1 and NMDA receptor activation. Rap1 and AF-6 regulate spine morphogenesis and mediate NMDA receptor-dependent spine morphogenesis. Rap1 and AF-6 also regulate synaptic localization and clustering of AMPA receptors. We identify a novel signaling pathway which regulates activity-dependent synaptic structural plasticity and coordinates it with functional plasticity.