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Signalling mechanisms

Editorial overview

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Erin Schuman works on synaptic transmission and information storage in the nervous system. In recent years, her group has focused on regulated protein synthesis and degradation as cell biological mechanisms to implement local synaptic changes.

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Peter H Seeburg's research focuses on glutamate receptor channels and their role in synaptic plasticity and learning and memory in the mouse. His work has identified RNA editing as a crucial post-transcriptional step in determining the functional properties of AMPA receptors in central synapses and has contributed to our present understanding of the role of LTP in hippocampal spatial learning paradigms.

Introduction

This issue on signaling mechanisms highlights new insight from diverse areas of neuroscience, ranging from acute and degenerative brain disease to novel presynaptic coincidence detectors involved in regulating synaptic strength and to an induced switch from cholinergic to glutamatergic muscle innervation in rodents. The wide range of topics reflects the remarkable interest in the neuroscience community in elucidating the mechanistic underpinnings of the diverse signaling pathways, which are crucial for our understanding of the diseased and healthy brain.

Brain dysfunction

The discovery of the immediate early gene *Homer1a* by Worley's laboratory [1] led to the description of the Homer family of proteins, which are constitutively expressed in many, if not all, tissues, and the activities of which in the brain can be antagonized by Homer1a induced by neuronal activity. We know that Homer proteins are part of the postsynaptic density, where they interact with key synaptic players, such as metabotropic glutamate receptors (mGluRs), N-methyl-D-aspartate (NMDA) receptors and endoplasmic reticulum (ER) calcium channels. Thus, it comes as no surprise that Homer proteins might also be implicated in neuropsychiatric disorders. Szumlinski, Kalivas and Worley discuss current evidence for the roles of Homer proteins in behavior and in the *in vivo* regulation of glutamatergic neurotransmission that is relevant to the etiology and treatment of certain neuropsychiatric disorders.

Acute brain injury, such as trauma and ischemia, can lead to functional impairments, and any recovery results from the inherent mechanisms of brain plasticity. In the postgenomic era, scientists in both academia and industry are attempting to exploit our knowledge of plasticity to find better therapeutic strategies for treating insults to the brain. In particular, although older concepts were directed at minimizing neuronal loss after, for example, stroke, by developing antagonists to channels such as NMDA receptors that flux Ca^{2+} into cells, the focus today is on identifying and exploiting existing plasticity mechanisms in support of functional recovery. The many aspects and nuances that need considering are expertly discussed by Wieloch and Nikolich in this issue.

Neurodegenerative disease

The localization of mRNAs and their regulated translation in axons and dendrites is emerging as an important phenomenon in both the development and the plasticity of the nervous system. Fragile X mental retardation protein (FMRP), the protein that underlies Fragile X syndrome, is an RNA-binding protein detected at neuronal synapses. Most cases of Fragile X syndrome are caused by a polyglutamine expansion in the 5'UTR leading to

transcriptional silencing. The absence or mutation of FMRP causes irregularities in dendritic spines and synaptic plasticity. The presence of FMRP near synapses and the fact that it binds RNA suggest a role in translational regulation. Zalfa, Achsel and Bagni discuss the different possibilities for a specific role of FMRP in translational regulation; they favor the idea that FMRP regulates the initiation of translation.

In their review, Malgaroli, Vallar and Zimarino focus on the regulation of protein folding and aggregation at the synapse as a potential causative force in neurodegenerative disease. The scope of the synaptic proteome embraces not only neurotransmitter receptors, signaling molecules, and scaffolding proteins but also regulators of protein synthesis, folding and degradation, together with ribosomes, proteasomes and lysosomes. The authors point out that, from the point of view of these synaptic proteins, the synapse is a stressful environment that is subject to changes in pH, intracellular Ca^{2+} and ATP levels, and redox state induced by electrical activity or the local glial microenvironment. Many neurodegenerative diseases are characterized by multi-protein depositions called amyloids. These depositions form once the density of misfolded or altered proteins reaches a threshold. Malgaroli *et al.* suggest that the small volume and dynamic intracellular environment of the synapse make it particularly susceptible to aggregate formation. The authors explore the normal and abnormal function of many of the proteins involved in neurodegenerative disease and speculate on the how protein misbehaviour at the synapse could be the root, rather than the cause, of some forms of neurodegeneration.

Ca^{2+} -permeable AMPA receptors and disease

AMPA receptors are the workhorses of fast excitatory neurotransmission in our brains. New insight into the regulation and composition of these important synaptic players, and functional considerations in normal and pathological neurophysiology, are summarized and discussed from different angles in three contributions in this issue.

It was recently discovered that AMPA receptors have auxiliary subunits that are crucial for the trafficking and gating of synaptic AMPA receptors in the brain. Starting with the seminal observation by Chen [2], who was working with Brecht and Nicoll at the time, that the stargazer mouse lacks synaptic AMPA receptors in cerebellar granule cells because of a mutation in stargazin, a protein related to a skeletal muscle Ca^{2+} channel subunit, the commendably fruitful collaboration of the Brecht and Nicoll laboratories has unravelled the role and diversity of the transmembrane AMPA receptor regulatory protein (TARP) family. In their elegant review, Osten and Stern-Bach summarize and discuss this important work and

identify issues that remain unanswered in spite of the remarkable progress made in TARP and AMPA receptor research.

AMPA receptors come in different flavors, particularly with respect to Ca^{2+} permeability. As a rule, AMPA receptors in glutamatergic neurons lack Ca^{2+} permeability, whereas those in GABAergic interneurons flux Ca^{2+} . The molecular determinant for this difference is the GluR2 (GluR-B) subunit, which participates in AMPA receptor assembly in glutamatergic principal neurons but is expressed at low levels relative to other AMPA receptor subunits in interneurons. GluR2 prevents Ca^{2+} permeability because of the presence of an arginine residue in a functionally crucial position of the pore-lining segment that it contributes to ion channel formation. Because this particular arginine residue results from a post-transcriptional RNA editing step within the primary GluR2 transcript, there are two ways of producing Ca^{2+} permeable AMPA receptors: insufficient GluR2 expression or even GluR2 knockout on one hand, and impaired RNA editing at the critical channel site (Q/R site) of GluR2 on the other. Kwak and Weiss discuss evidence for the involvement of Ca^{2+} permeable AMPA receptors in neurodegenerative diseases and ischemia. Intriguingly, the sporadic form (approximately 90% of all cases) of amyotrophic lateral sclerosis (ALS), a deadly motoneuron disease, might result from impaired RNA editing of GluR2 and the consequential increase of Ca^{2+} permeable AMPA channels in motoneurons. Ca^{2+} -permeable AMPA receptors also appear to contribute to neuronal death in ischemia, although different from the situation in motoneurons, the divalent permeability appears to result from downregulation of GluR2 rather than from impaired Q/R site editing. Although Ca^{2+} -permeable AMPA receptors were thought to either not exist in most glutamatergic forebrain neurons or to represent a very small fraction in these cells, recent work, lucidly summarized and discussed by Cull-Candy, Kelly and Farrant, implicates these receptors in synaptic function and plasticity, not only in disease but importantly also in normal function. Thus, understanding the mechanisms governing the regulation of Ca^{2+} -permeable AMPA channels in principal neurons and other neuronal types becomes an important mission.

Nerve terminal release and synaptic plasticity

The neurotransmitter that underlies the point-to-point communication at neuronal synapses is stored in small clear vesicles. Most nerve terminals possess about 100 vesicles but can fire at frequencies up to or exceeding 100 Hz. Clearly the recovery of vesicles by endocytosis is an important process. Schweizer and Ryan examine a moment in the lifetime of a neurotransmitter vesicle, describing work on the relationship between exocytosis and endocytosis of vesicles. Morphologically and

functionally distinct vesicle pools have been identified visually and electrophysiologically, but which vesicles will be released cannot be perfectly predicted by the originating pool. In addition, Schweizer and Ryan discuss the important potential mechanisms that couple exocytosis and endocytosis — current evidence suggests that calcium plays a key role.

Our textbook notion of synaptic transmission holds that a single action potential gives rise to the fusion of a single vesicle from a well-defined active zone. Matsui and Jahr revisit this dogma and review data suggesting that more than one vesicle can be released and that release can occur from 'ectopic' release sites. They describe evidence for multivesicular release from many central synapses, especially those with a high probability of release. In addition, they review data on release from non-conventional release sites and point out that, functionally, ectopic release could serve the purpose of activating extrasynaptic receptors in addition to synaptic receptors at non-releasing synapses. Interestingly, ectopic release has also been reported from dendrites.

Synaptic plasticity underlies most brain functions, and accordingly, is under intense mechanistic investigation, not only for postsynaptic aspects but also for presynaptic plasticity. The textbook example is the NMDA receptor with its coincidence detection of pre- and post-synaptic activity and the ensuing long-lasting change in synaptic strength upon paradigms triggering strong synaptic stimulation in hippocampal circuits. That there are numerous plasticity mechanisms that also function presynaptically is the topic of the excellent review by Duguid and Sjöström, who discuss recent advances in elucidating the contribution of presynaptic NMDA receptors and endocannabinoid signaling to synaptic plasticity.

The best-studied vertebrate synapses are arguably those at neuromuscular junctions, followed by the central synapses formed by Schaffer collaterals onto hippocampal CA1 pyramidal cells. The neuromuscular junctions are powered by the neurotransmitter acetylcholine, whereas L-glutamate drives most excitatory synapses in the brain including Schaffer–CA1 synapses. The differences between cholinergic and glutamatergic synapses are substantial, because of their distinct developmental and functional characteristics. It is thus a most remarkable finding that central neurons can form functional glutamatergic synapses onto muscle fibers. This discovery, put here into historical and evolutionary context by Pizzi and her co-workers, can perhaps be built upon in the future to treat spinal cord injuries.

Synapse to nucleus signaling

The unique morphology of neurons, in which synaptic compartments can be hundreds of microns from the cell

soma, can make the task of transcriptional regulation daunting. How are synaptic signals transported back to the nucleus to modify gene expression during development, plasticity and neuronal repair? Olofsdotter, Thompson and Martin discuss one mechanism, the active delivery of soluble signaling proteins via nuclear transport carriers called importins. Importins facilitate the energy-dependent importing of proteins at the nuclear pore. In neurons, importins can be detected in distal neuronal compartments. Synaptic stimulation causes the accumulation of importins in the nucleus. Moreover, injection of antibodies directed against nuclear pore proteins can block long-term synaptic plasticity. Martin and co-workers also highlight the important role that importins play in mediating distal injury-induced responses and recovery.

Wiring the brain

Brain functions require functional neural circuits, which get wired correctly during development. Numerous cell adhesion proteins are involved in this, prominently including those of the cadherin superfamily. Of this family, the three clustered protocadherin (Pcdh) subfamilies, pcdh- α , - β , - γ , contribute the largest number of members, with approximately 20 per subfamily. The particular gene arrangement and transcriptional organization of each cluster predicts unique expression control mechanisms. The first evidence of combinatorial expression of different protocadherins of the pcdh- α cluster in neurons, obtained several years ago by the Yagi laboratory [3], has spawned speculations on combinatorial protocadherin codes underlying the build-up of the many different connections between diverse types of neurons during development. Hirayama and Yagi summarize recent work on the expression, molecular evolution and allelic regulation of the Pcdh families.

Signaling during behavior

The influence of sex and reproduction on animal behavior and evolution cannot be underestimated. Hoffman discusses the important role of gonadotropin-releasing hormone (GnRH) in participating in the dialogue between brain and behavior. Recent studies have identified kisspeptins as the potential natural ligand that stimulates the GnRH release surge that accompanies puberty in mammals. Studies of natural behaviors have been particularly fruitful in delineating the role of GnRH in sex and reproduction. For example, studies in songbirds and cichlid fishes have elucidated a remarkable plasticity exhibited by the GnRH system in response to changing seasonal and social cues.

Major histocompatibility complex (MHC) molecules, which present pathogen-derived peptides in T cells, have been implicated in a number of non-immune roles in the central nervous system, particularly in synaptic development and plasticity. Olson, Dulac and Bjorkman focus on

a recent discovery that the non-classical I MHC molecule M10 is important for the delivery of a pheromonal receptor, V2R, to the surface of the vomeronasal organ (VNO). The VNO is a small sensory structure that is involved in pheromone detection; pheromones are small molecules that serve as social and sexual signals between animals. Individual neurons in the VNO express one (of ~60 possible) V2Rs and 9 M10s. In animals lacking M10s, V2Rs are not present on the surface. Olson *et al.* review data showing that classical MHC-binding peptides can activate V2R-expressing neurons, suggesting that M10 even participates in the recognition of pheromone ligands. Olson *et al.* carefully examine the recently solved crystal structure of M10.5, it possesses an open, but empty, groove big enough to accommodate a peptide or a polypeptide chain from another protein. In addition, it exhibits a thermal instability similar to other MHCs that are empty, but can bind to peptides. Taken together these data suggest the exciting possibility that this molecule participates in the binding and recognition of a currently unknown ligand.

Conclusions

We would like to note that the contributions in this issue represent a selection of the important work published in the area of signaling mechanisms of the past few years. The selection also had a subjective component and we apologize to those that we did not include here. Nevertheless, we hope that the readers enjoy this *Current Opinion in Neurobiology* issue as much as we enjoyed putting it together.

References

1. Brakeman PR, Lanahan AA, O'Brien R, Roche K, Barnes CA, Huganir RL, Worley PF: **Homer: a protein that selectively binds metabotropic glutamate receptors.** *Nature* 1997, **386**:284-288.
2. Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Brecht DS, Nicoll RA: **Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms.** *Nature* 2000, **408**:936-943.
3. Kohmura N, Senzaki K, Hamada S, Kai N, Yasuda R, Watanabe M, Ishii H, Yasuda M, Mishina M, Yagi T: **Diversity revealed by a novel family of cadherins expressed in neurons at a synaptic complex.** *Neuron* 1998, **20**:1137-1151.