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Microtubule Motor Proteins and the Mechanisms of Synaptic Plasticity

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Microtubule motor proteins – kinesins and dyneins – play an important role in intracellular transport. Impairments to axon transport can influence neurotransmitter release and short-term presynaptic plasticity. Impairments to dendritic transport, particularly recycling of synaptic receptors, affect postsynaptic plasticity. This review seeks to follow the link between microtubule motor proteins and the mechanisms of synaptic plasticity from the point of view of their involvement in transporting proteins and organelles, where their role in the mechanisms of synaptic plasticity has been demonstrated.

Keywords: kinesins, dyneins, neurotransmitter release, receptor recycling, synaptic plasticity.

Introduction. The neuron is the structural-functional unit of the nervous system. Individual neurons are connected to each other to form neural networks by means of special formations – chemical or electrical synapses. Morphological and biochemical changes in synapses affecting response magnitude are regarded as the basis of synaptic plasticity. The phenomena in which increases in responses are seen are termed potentiation, while those decreasing responses are termed depression. These phenomena are classified on the basis of their duration into short-term and long-term. Long-term synaptic plasticity, in contrast to short-term, can last hours and days, and requires gene expression and de novo protein synthesis [Bear and Malenka, 1994].

Most proteins are synthesized in the cell body and then transported into axons and dendrites. Disruption of intracellular transport leads to impairment to the growth and development of nerve endings in growing neurons, while in mature neurons it produces impairment to receptor recycling, altering synaptic plasticity [Kennedy et al., 2006; Santos et al., 2009].

Motor proteins play a key role in intracellular transport, taking part in the transfer of organelles, membrane proteins, ion channels, synaptic vesicle precursors, endosomes, mRNA, signal molecules, and cytoskeletal elements from one compartment of the cell to another [Hirokawa, 1998; Vale and Milligan, 2000]. Transport direction can be anterograde, from the center of the cell body to nerve endings, or retrograde, from nerve endings to the center of the body. Anterograde transport is mediated by motor proteins of the kinesins superfamily and retrograde transport by dyneins. Movement of motor proteins in both directions is along microtubules oriented longitudinally to nerve endings [Shea and Flanagan, 2001].

Transport speed can be fast or slow. In mammalian neurons there are at least two speed ranges for fast anterograde transport: ~100–400 mm/day and ~20–70 mm/day, both involving transport of organelles [Vallee and Bloom, 1991]. Retrograde axonal transport has been shown by radiolabeling studies to have speeds in the range 130–230 mm/day [Bisby and Bulger, 1977; Mitsumoto et al., 1990]. Signals received from cells from outside have been shown to be mediated by neurotrophins. These maintain cell viability, stimulating the growth and development of neurons. By means of retrograde transport, neurotrophins reach the cell body, where they trigger signal cascades [DiStefano et al., 1992]. In addition, retrograde transport returns damaged mitochondria to the neuron body, where they are degraded [Miller and Sheetz, 2004].

Slow axonal transport has two components: A and B. The A component relates to microtubule and neurofilament

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transport occurring at a rate of ~0.1–1 mm/day. The B component transports soluble proteins, clathrin, actin monomers, glycolytic enzymes, and Cu–Zn superoxide dismutase at a rate of ~5–10 mm/day [Shah and Cleveland, 2002].

According to the "stop and go" theory proposed by Brown [2000], motor proteins of the kinesin and dynein superfamilies are involved not only in fast axonal transport, but also in slow axonal transport of neurofilaments (A) [Brown, 2000]. Thus, despite the fact that there are several types of axonal transport discriminated by speed, they nonetheless involve the same motor proteins.

Microtubules, neurofilaments, and actin filaments are components of the cytoskeleton. Microtubules consist of heterodimers of α- and β-tubulin, which, undergoing polarization using GTP hydrolysis energy, form hollow cylinders 25 nm in diameter [Desai et al., 1997]. The direction of transport is determined by microtubule polarity. Assembly of tubulin heterodimers occurs at the "plus" end, with disassembly taking place at the "minus" end. Microtubules in axons and distal dendrites always have the plus end towards the end of the nerve fiber and the minus end towards the cell body, while in proximal dendrites the polarity is reversed [Hirokawa et al., 2010].

History of the discovery of kinesin. Data on the involvement of a molecular weight 130 kDa protein [Brady et al., 1985] in fast axonal transport were first published in 1985 by two independent groups [Brady et al., 1985; Vale et al., 1985]. By this time, the existence of two other motor proteins – dynein and myosin – were already known, though the new protein differed from these in terms of its properties and molecular weight. Vale [1985] suggested terming this protein "kinesin" from the Greek for "mover." Since then this protein has been known as kinesin in the literature. This is now the best-studied protein of the kinesin superfamily of motor proteins (KIFs). On the contemporary classification, it belongs to the kinesin-1 family (KIF5s), which is also termed "conventional kinesin."

Structure of kinesin. We will consider the structure of kinesin molecules using kinesin-1 as an example. The characteristic feature of molecules of the KIF superfamily is a globular domain of 360 amino acid residues. This conserved domain, termed the "head" or motor domain, contains the catalytic center at which ATP is hydrolyzed and a microtubule binding site. The head is attached to a "stalk," which is a coil of two helically twisted heavy chains – the whole structure is called the kinesin heavy chain (KHC). The C-terminal end of the stalk terminates with a fan-shaped structure, connected to the light chains (KLC). This part is called the "tail." The head is responsible for movement, while the stalk-tail component binds the molecules being transported: proteins, lipids, or nucleic acids.

There is an additional fragment between the head and the stalk – the "neck." This part carries the characteristic features of the family. For some families, this part is responsible for the direction of movement and regulation of activity [Diefenbach et al., 1998; Miki et al., 2005]. For example, the molecular mechanism controlling the formation of the kinesin-3 dimer from KHC monomers is located in the neck region. In KIF13A and KIF13B, the critical part is the proline residue located between the neck and the first segment of the stalk [Soppina et al., 2014]. This latter study established a link between dimerization of kinesin-3 and its high processivity of movement at the intermediate speed of 1.5 μm/sec. Another recent study showed that the shape of the neck affects the navigation of obstacles when moving along microtubules [Hoeprich et al., 2014]. Kinesin-1 and kinesin-2 showed the same sensitivity for the two isoforms of "Tau" protein (3RS-tau and 4RL-Tau), which are microtubule-associated proteins. However, despite the fact that the processivity of kinesin-1 is higher than that of kinesin-2, the longer neck region of kinesin-2 provides it with better optimization of navigation across complex microtubule landscapes [Hoperich et al., 2014].

Mechanism of kinesin movement. We will consider the mechanism of movement of kinesin using conventional kinesin as an example. KIF5 has very high processivity: one kinesin can hydrolyze more than 100 ATP molecules, moving sequentially along the microtubule until movement stops. The "walking" model of kinesin movement – a hand-over-hand model – is currently widely accepted. When one hand makes a step, the other must be tightly fixed to the substrate. Thus, the motor protein continuously moves along the microtubule. There are other models, less widely accepted than the hand-over-hand model: the inchworm model, where one hand always leads and the other, following the first, makes the same movements as a caterpillar; the asymmetrical hand-over-hand model, in which a dimeric motor moves along the protofilament with alternating step lengths, as though the motor protein is limping.

The first argument supporting the hand-over-hand model was obtained in experiments using the fluorescent label Cy3, with measurements of the kinesin step length – which was 17.3 ± 3.3 nm. The second is a conformational change in the linker part of the neck, synchronized with ATP hydrolysis. The data led to the conclusion that the linker region of the neck at the moment of ATP binding faces the "plus" end and that it becomes motile simultaneously with release of the phosphate after ATP hydrolysis [Hirokawa and Noda, 2008].

Classification of kinesins. A total of 45 proteins are currently regarded as member of the KIF superfamily. The position of the motor domain distinguishes three types of KIF. Kinesins in which the motor domain is attached to the NH_2-terminal are called N-kinesins; those in which it is attached to the COOH-terminal are C-kinesins; M-kinesins (middle motor) have the motor domain in the middle of the molecule. Among the 45 kinesins, only three are M-kinesins and three are C-kinesins; the remainder are N-kinesins. Of the 39 N-kinesins, two are monomers and the other 37 consist of multiple subunits [Miki et al., 2011].

Miki et al. [2004] identified 14 classes of KIF. C-Kinesins were grouped into two classes. M-kinesins were placed in a single class. N-Kinesins were grouped into 11 families. Most classes consisted of a single family of kinesins, three classes forming exceptions: N-3, N-4, and N-8 [Miki et al., 2004]. Wickstead and Gull [2006], using more contemporary sequencing methods, suggested dividing the kinesin-12 family into kinesin-15 and kinesin-16 families, and also identified a further family – kinesin-17 [Wickstead and Gull, 2006].

Structure of dynein. The motor protein dynein was discovered before kinesin-1. Neurons contain cytoplasmic dynein [Ahmad et al., 1998]

Cytoplasmic dynein consists of several domains: a heavy chain and several noncatalytic subunits. The heavy chain of cytoplasmic dynein is a member of the ATPases associated with diverse cellular activities group of superfamily 3 (AAA + ATPase). Members of this family mostly function as chaperones, in contrast to standard AAA + ATPases, which self-assemble and function as a hexameric ring; the subunits in dynein are not identical and fold into a single polypeptide. Cytoplasmic dynein has two C-terminal "heads," containing the microtubule binding site. The N-terminal "tail" of the dynein heavy chain mediates dimerization and also contains the binding site for various noncatalytic subunits involved in forming complexes of cytoplasmic dynein. In vitro, these subunits have no effect on the ability of dynein to move – their role is seen in vivo. They are believed to regulate the binding of dynein with the "load" and adaptor proteins controlling the operation of dynein. In many species, the noncatalytic subunits exist as various isoforms, encoded by a multiplicity of genes. Different isoforms can assemble on the dynein heavy chain in different combinations, forming functionally diverse dynein complexes [Kardon and Vale, 2009].

Mechanism of dynein movement. Dynein performs continuous processive movement, like kinesin motor proteins. This movement is mediated by dimerization of the two "heads." The principle of the movement of one dynein motor protein is the same as the hand-over-hand mechanism for kinesin: dynein moves along microtubules making alternative steps with the head domains. Studies of the strength of dynein using the optic trap method showed that movement coordination depends on the tension transmitted through the linkage of the two heads [Kardon and Vale, 2009].

Dynein step length, in contrast to kinesin, is variable. For the most part, dynein makes steps of length 8 nm towards the minus end, though from time to time the step increases to 32 nm and it makes one or several steps in the reverse direction. Dynein frequently makes a sideways step to the adjacent protofilament, which the kinesin motor protein rarely does. This motility allows dynein to navigate obstacles better, though how the mechanism of movements is regulated remains unclear [Kardon and Vale, 2009].

Motor proteins in the transport of presynaptic vesicle proteins and the mechanisms of presynaptic plasticity. Transient presynaptic plasticity associated with neurotransmitter release determines the shape of the response of the postsynaptic neuron and plays a key role in in encoding information in the nervous system. Regulation of presynaptic Ca^{2+} channels can facilitate or inactivate influx Ca^{2+} ion currents. This strong dependence of neurotransmitter release on the presynaptic Ca^{2+} current may predict the regulatory mechanisms acting on transient presynaptic plasticity [Catterall and Few, 2018].

Presynaptic vesicle proteins play an important role in neurotransmitter release. These form the so-called SNARE complex, which includes vesicle-associated v-SNARE protein (VAMP) or synaptobrevin, which interacts with membrane-associated t-SNARE proteins and syntaxin-1. Full functioning of the SNARE complex in the transmitter release process requires attachment of the protein synaptotagmin. Synaptotagmin is a calcium-binding presynaptic vesicle protein mediating calcium regulation of the fusion of vesicles with the plasmalemma. Ions entering the Ca^{2+} channel in the presynaptic bouton bind with synaptotagmin protein. The SNARE complex changes from the trans to the cis conformation, resulting in fusion of the vesicle membrane with the membranes of the presynaptic terminal and resultant neurotransmitter release [Catterall and Few, 2008].

The proteins synaptophysin and synaptogyrin are required for the effective endocytosis kinetics of presynaptic vesicles [Sugita et al., 1999; Kwon and Chapman, 2011]. Mice with knockout of synaptogyrin and synaptophysin showed significant impairments to short-term and long-term synaptic plasticity in hippocampal field CA1 [Janz et al., 1999].

Members of the KIF superfamily are involved in the transport of presynaptic vesicle proteins.

Mutations in the KIF1A gene lead to a deficiency of presynaptic vesicles in axons in *Caenorhabditis elegans* [Hall and Hedgecock, 1991]. KIF1A is regarded as a CNS-specific microtubule protein. Neonatal mice with lesions to the KIF1A gene died in the first day of life. These mice showed motor and sensory disorders induced by impairment to the transport of presynaptic vesicle precursors and their resultant accumulation in the neuron body. Neuron cultures from mutant mice showed the same symptoms in terms of cell degeneration and death. Addition of wild-type neurons or low-concentration glutamate to cultures prevented neuron death. It seems most likely that mutant neurons in cultures receive insufficient afferent stimulation [Yonekawa et al., 1998]. Results obtained in experiments using immunocytochemical and immunoprecipitation methods showed that KIF1A is involved in transporting vesicles containing synaptic vesicle precursors: synaptophysin, synaptotagmin, and Rab-3A [Okada et al., 1995].

The functions of KIF1A partially overlap those of another monomeric kinesin, KIF1Bβ. KIF1Bβ, like KIF1A, is involved in transporting presynaptic vesicle precursors synaptotagmin and synaptophysin [Zhao et al., 2001]. Further-

more, a recent study by Niwa et al. [2008] showed that KIF1Bβ and KIF1A have roles in the transport of DENN/MADD and Rab3. Both kinesins have been shown to bind DENN/MADD directly, via the tail domain. DENN/MADD in turn forms a bond with GTP-Rab3 [Niwa et al., 2008]. Thus, DENN/MADD is an adaptor protein for GTP-Rab3.

Rab-3s proteins play an important role in controlling the Ca^{2+} concentration required for exocytosis of presynaptic vesicles. Neurophysiological studies using patch clamp methods have shown that excitatory Rab-3s-deficient neurons have unique time- and frequency-dependent short-term plasticity, as recorded in experiments using stimulation with impulse volleys. Analysis of vesicle release and the kinetics of preparation of vesicles for exocytosis (repriming) and Ca^{2+}-dependent neurotransmitter release showed that Rab-3s influences the pool of filled vesicles, controlling their fusion with the presynaptic membrane. Rab-3s-induced modification of vesicles at the priming stage promotes short-term increases in action potential effectiveness [Schlüter et al., 2006].

KIF5s are involved in transporting SNARE complex proteins. The 25-kDa synaptosome-associated protein (SNAP-25) directly binds the load-binding domain of kinesin heavy chains via its N-terminal [Diefenbach et al., 2002]. Syntabulin is an adapter protein between the syntaxin-"load" complex and KIF5s. Kinesin light chains are believed not to be involved in the mechanism of syntabulin and syntaxin transport, as syntabulin has been shown to bind directly to the C-terminal of the KIF5 molecule [Su et al., 2004].

As regards dynein, there are no direct data on its involvement in synaptic plasticity. The dynein superfamily is much less well studied, so there are few data identifying which proteins it interacts with. Kimura et al. [2012] demonstrated the involvement of dynein not only in retrograde axonal transport, but also anterograde transport of presynaptic vesicles. It is interesting to note that impairment of the transport of presynaptic vesicles evoked by dynein dysfunction is accompanied by a concomitant increase in the level of Rab3 GTPase. Furthermore, vesicle docking was disrupted by impairment to endocytosis [Kimura et al., 2012].

Bassoon protein is known to interact with dynein light chains DLCs (DLC1 and DLC2), operating as an adapter protein for the Piccolo-Bassoon transport of presynaptic vesicles. Disruption of the bond between Bassoon and DLCs led to weakening of *Bassoon* transport in neurons but had no effect on the distribution of *Bassoon-Piccolo* in the presynapse [Fejtova et al., 2009]. *Bassoon* and *Piccolo* proteins have been sown to take part in the formation of clusters of presynaptic vesicles but not to have any direct role in their exocytosis [Mukherjee et al., 2010]. Data have appeared in the last few years clarifying the role of *Bassoon* in presynaptic terminals: the anchor protein *Bassoon* operates in positioning voltage-dependent Ca^{2+} channels ($Ca_V2.1$) in the active zone by means of interaction with RIM-binding protein (RBPs) [Davydova et al., 2014].

CRMP-2 protein (collapsin response mediator protein-2), which functions as a KIF5 adapter protein, also takes part in controlling presynaptic N-type Ca^{2+} channels ($Ca_V2.2$) in the hippocampus. CRMP-2 binds $Ca_V2.2$ in two regions: channel domain I–II of the intracellular loop and the distal C-terminus. Neurons overexpressing CRMP-2 showed significant increases in the Ca^{2+} current. This effect was eliminated in lentivirus-mediated CRMP-2-knockdown neurons. The Ca^{2+} current increased not because of changes in Ca^{2+} channel permeability, but because of an increase in the number of $Ca_V2.2$. These neurons responded to a depolarizing stimulus with increases in transmitter release [Brittain et al., 2009].

Considering the fact that neurotransmitter release is a calcium-dependent process, it can be suggested that an understanding of the mechanisms of recruitment of $Ca_V2.1$ in the active zone, which may also involve members of the KIF5 family, might throw light on the mechanisms of short-term presynaptic plasticity.

Motor proteins in the transport of excitatory receptors and the mechanisms of postsynaptic plasticity. It has now been clearly demonstrated that recycling endosomes in postsynaptic terminals contain a pool of AMPA receptors, serving as a resource for their rapid insertion into the postsynaptic membrane. Activation of NMDA receptors can regulate the kinetics of endosome recycling and have significant influences on the ratio of receptors between the intracellular pool and the number of receptors on the postsynaptic membrane. This has been partially demonstrated for long-term potentiation: triggering of recycling is associated with accumulation of recycling endosomes in dendritic spines [Song and Huganir, 2002].

AMPA receptors play a major role in rapid excitatory synaptic transmission in the CNS in mammals. Recent years have seen increasing amounts of data showing that changes in the functional properties of AMPA receptors are linked with their transport, cytoskeletal dynamics, and local protein synthesis. This is why it is important to understand the mechanisms mediating these processes [Derkach et al., 2007].

Kinesins and dyneins also have roles in the transport of postsynaptic receptors. KIF1A was extracted along with liprin-α/SYD-2 and proteins associated with liprin-α/SYD-2: AMPA receptors, GRIP/ABP, RIM, GIT1, and βPIX [Shin et al., 2003]. Liprin-α/SYD-2 is known as a multidomain carcass protein required for presynapse differentiation. In addition, it plays an important role in the clustering of AMPA receptors in the postsynaptic terminals. Liprin-α/SYD-2 binds GRIP (glutamate receptor-interacting protein) via an interaction with LAR receptor protein tyrosine phosphatase (LAR-RPTPs) [Wyszynski et al., 2002]. KIF5 is also involved in receptor transport in dendrites. The AMPA receptor subunit-GluR2-interacting protein (GRIP1) directly binds kinesin heavy chains [Setou et al., 2002].

KIF1Bα C-terminal directly binds the PDZ domain of postsynaptic density proteins (PSD-95), including PSD-95/

synapse-associated protein-90 (SAP90), SAP97, and synaptic scaffolding molecule (S-SCAM)-90 (SAP-90) [Mok et al., 2002].

PSD-95 is an important protein involved in regulating glutamate receptor activity. Palmitoylation of PSD-95 associated with the protein stargazin, which is involved in transporting AMPA receptors, regulates synaptic plasticity [El-Husseini et al., 2002]. NMDA receptors have been shown to bind PSD-95 via the NR2B subunit [Kornau et al., 1995]. Increases in long-term potentiation in frontal-subcortical glutamatergic synapses correlated with decreased PSD-95 levels in synapses [Yao et al., 2004]. Overexpression of PSD-95 in pyramidal neurons in rat cortical slices was accompanied by an increase in the frequency but not the amplitude of AMPAR-mediated miniature excitatory postsynaptic currents (mEPSC). This phenomenon reflects an increase in the number of synapses expressing AMPA receptors but not an increase in the number or functional activity of AMPA receptors per synapse. The results of experiments addressing the role of these changes in synaptic plasticity demonstrated increases in the probability of long-term depression [Béïque and Andrade, 2003].

KIF17 is an NMDA receptor motor protein. It is mainly located in the bodies and dendrites of neurons. KIF17 interacts directly, via its tail part, with the PDZ domain of mLin-10 (Mint1/X11), which is a large protein complex including mLin-2 (CASK), mLin-7 (MALS/Velis), and the NR2B subunit [Setou et al., 2000]. The bond between KIF17 and Mint1 is regulated by CaMKII: phosphorylation at serine 1029 leads to breakup of the KIF17-Mint1 complex and resultant impaired transport [Guillaud et al., 2008]. Transgenic mice overexpressing KIF17 showed rapid learning in behavioral tests, with good recall. These mice displayed increased levels of transcription factor CREB and its phosphorylation [Wong et al., 2002].

KIF11 or Eg5 is traditionally regarded as a motor protein of the mitotic spindle [Blangy et al., 1995]. Recent studies have shown that it also takes part in the transport of neurotrophins and postsynaptic receptors. Inhibition of Eg5 by β-amyloid or monastrol, an Eg5 inhibitor, led to a decrease in the number of NGF/NTR(p75) and NMDA receptors on the cell surface. Monastrol, like β-amyloid, also inhibited long-term potentiation [Ari et al., 2004]. An additional unexpected role of KIF11 is facilitation of the delivery of PAUF (pancreatic adenocarcinoma up-regulated factor) from Golgi complexes to the surface of the cell body [Wakana et al., 2013]. This probably explains the involvement of KIF11 in the transport of acetylcholine receptors in the bodies of command neurons in *Helix lucorum* [Vasilyeva et al., 2015]. Eg5 kinesin inhibitors have been shown to slow the rate of depression of acetylcholine responses in a cellular analog of acclimation in *Helix lucorum* command motoneurons.

Thus, KIF1A and KIF5 can be regarded as motor proteins of AMPA receptors and KIF17 as motor proteins of NMDA receptors which may have roles in the mechanisms of receptor recycling. At the same time, the role of KIF1Bα in the mechanisms of recycling can only be assessed indirectly, on the basis of the fact that KIF1Bα binds PSD-95, which plays a key role in the mechanisms of postsynaptic plasticity. Could KIF1Bα also have a role in transporting AMPA and NMDA receptors, as it forms a bond with PSD-95? This question remains open.

Motor proteins in the transport of inhibitory receptors and the mechanisms of postsynaptic plasticity. KIF5 also takes part in the transport of $GABA_A$ receptors. HAP1 (huntingtin-associated protein 1) protein operates as an adapter protein. Studies of the inhibitory response mediated by $GABA_A$ receptors in *Kif5a*-knockout mice demonstrated a decrease in the expression of $GABA_A$ receptors. KIF5 interacts with $GABA_A$ receptors via $GABA_A$-associated protein. Electroencephalograms recorded from such mice showed epileptic activity [Nakajima et al., 2012]. Degradation of the HAP1-KIF5 complex decreased the number of postsynaptic $GABA_A$ receptors, leading to a decrease in the amplitude of the inhibitory postsynaptic current. It is interesting that HAP1 mutations, which cause Huntington's disease, show the same effects. Thus, HAP1-KIF5-dependent $GABA_A$ receptor transport is one of the fundamental mechanisms controlling the magnitude of the inhibitory postsynaptic response in the mammalian brain [Twelvetrees et al., 2010].

Dynein light chain-1 (Dlc-1), also known as dynein LC8, binds tubulin-binding protein gephyrin. Gephyrin protein is a member of the group of carcass proteins supporting the efficiency of neuron transmission by forming a highly organized rigid structure on the postsynaptic membrane. In the submembrane space it binds proteins triggering signal cascades. Gephyrin takes part in clustering glycine and $GABA_A$ receptors. Dlc motor protein binds gephyrin via the central linker domain. Endogenous Dlc protein in hippocampal neurons is located on postsynaptic terminals, along with proteins synaptophysin and gephyrin. Dlc-1 and Dlc-2 are present in stoichiometric quantities in cytoplasmic dynein, and appears able to take part in positioning gephyrin protein [Fuhrmann et al., 2002].

Phosphorylation of gephyrin at the serine 270 residue by glycogen synthase kinase 3β (GSK3β) modulates GABAergic transmission. Blockade of phosphorylation at serine 270 increases the density of gephyrin clusters and the frequency of miniature GABAergic postsynaptic currents in hippocampus neuron cultures. The gephyrin concentration in clusters on postsynaptic terminals is limited by the Ca^{2+}-dependent degradation of gephyrin by the cysteine protease calpain-1 [Tyagarajan et al., 2011].

Gephyrin also takes part in stabilizing glycine receptors (GlyR). GlyR and gephyrin have been shown to be transported together in neuron dendrites. They were coextracted and colocalized with the motor protein dynein. Inhibition of dynein or the dynein-gephyrin complex and

depolarization of membranes prevents recruitment of gephyrin. Thus, transport of the GlyR-gephyrin-dynein complex supports the suggestion that the interaction of gephyrin and the motor protein contributes to the dynamics and reorganization of postsynaptic Gly receptors – a process underlying regulation of the postsynaptic response [Maas et al., 2006].

KIF5, apart from being a motor protein for AMPA receptors, also has a role in transporting $GABA_A$ receptors. Dynein, along with gephyrin protein, operates in the clustering of glycine and $GABA_A$ receptors. Recycling and clustering of receptors in the postsynaptic area plays a not unimportant role in the mechanisms of synaptic plasticity.

Motor proteins in the transport of signal molecules and the mechanisms of postsynaptic plasticity. KIF5 binds via kinesin light chains with JIP proteins: JIP-1, JIP-2, and JIP-3 – carcass proteins of the JNK kinase signal cascade [Verhey et al., 2001]. Rap2-JNK kinases have been shown to take part in the recycling of AMPA receptors in the depotentiation process. Activation of NMDA receptor triggers Rap2 GTPase via the NR2A subunit. In turn, Rap2, rather than activating Erk1/2 or *p38* MAPK, suppresses AMPA receptor-mediated synaptic transmission via activation of JNK. In addition, Rap2 controls the decrease in the number of AMPA receptors in the postsynaptic area on depotentiation [Zhu et al., 2005].

Amyloid precursor protein (APP) binds KIF5B via the TPR domain of kinesin light chains [Kamal et al., 2001]. APP has been shown to have an important role in maintaining the normal architecture of the dendritic tree, spine density and morphology, and synaptic plasticity and cognitive functions [Hick et al., 2015]. Muresan and Muresan [2005] showed that JIP-1 mainly interacts with APP phosphorylated at threonine 668 (pAPP) but not with unphosphorylated APP. The accumulation of JIP-1 and pAPP in nerve processes occurs as a result of KIF5. Expression of a mutant phosphorylated APP increased JIP-1 transport. Regulation by top-down pathways using interfering RNA weakened APP transport but had no effect on the transport of unphosphorylated APP. APP phosphorylation appears to regulate the formation of pAPP-JIP-1 complexes, which are then transported by KIF5 to the processes independently of the concentration of unphosphorylated APP [Muresan and Muresan, 2005].

Thus, members of the KIF5 superfamily play a role in the mechanisms of synaptic plasticity not only because of their involvement in the recycling of postsynaptic receptors, but also via their interaction with postsynaptic terminal signal molecules and proteins, for which a role in the mechanisms of postsynaptic plasticity has been demonstrated.

Motor proteins in mitochondrial transport and the mechanisms of synaptic plasticity. As noted above, the mechanism of synaptic plasticity in pre- and postsynapses are calcium-dependent.

Studies using mouse spinal cord preparations showed that increases in the intracellular Ca^{2+} concentration due to synaptic transmission were accompanied by uptake of free Ca^{2+} by mitochondria. This decreases long-term potentiation and blocks the induction of hyperalgesia in the spinal cord [Kim et al., 2011].

Deficiency of potential-dependent anion channels involved in regulating the permeability of the outer mitochondrial membrane degrades learning ability and synaptic plasticity in the hippocampus of mice [Levy et al., 2003]. Studies of milton protein deficiency in *Drosophila* photoreceptors showed that kinesin-mediated transport of mitochondria to presynaptic endings plays an important role in synaptic transmission [Stowers et al., 2002].

KIF1Bα has been shown to transport mitochondria at a speed of 0.5 μm/sec [Nangaku et al., 1994]. However, KIF1Bα is not alone in transporting mitochondria. Knockout of the KIF5B and KIF5C genes explained the compensation of mitochondrial transport in KIF1B knockout mice [Tanaka et al., 1998[Kanai et al., 2000]. Disruption of the kif5B gene led to accumulation of mitochondria in the neuron body [Tanaka et al., 1998].

Visualization studies of neuron cultures showed that a significant proportion of syntabulin colocated with mitochondria migrated along axons. Impaired syntabulin expression decreased the observed density of mitochondria along axons. Previous and new data led to the conclusion that syntabulin is involved as a KIF5 adaptor protein [Cai et al., 2005]. Syntabulin supports axonal transport of mitochondria, which produce ATP in presynaptic terminals. ATP molecules are in turn required for mobilization of presynaptic vesicles ready for exocytosis [Verhey et al., 2001]. Thus, KIF5B-syntabulin-mediated transport of mitochondria plays an important role in maintaining metabolism in the presynapse and in the regulation of presynaptic plasticity.

There is another mechanism regulating kinesin binding to mitochondria, this time at the postsynaptic terminal via mitochondrial protein Miro, involving the adapter protein milton. Displacement of mitochondria is known to be regulated by changes in the cytosolic Ca^{2+} concentration: opening of ionotropic glutamate receptor channels leads to an increase in the intracellular Ca^{2+} concentration. MacAskill et al. [2009] showed that Miro1 bound to mitochondria and KIF5 facilitates movement of mitochondria along microtubules. This binding is blocked by Ca^{2+} ions bound to Miro1 at micromolar concentrations. A mutation in the EF-hand domain of Miro1 prevents binding with Ca^{2+} ions. In these conditions, Miro1 facilitated the movement of transported mitochondria [MacAskill et al., 2009]. The same year saw the publication of similar results obtained for retrograde and anterograde axonal transport [Wang and Schwarz, 2009]. A year earlier, MacAskill et al., [2008] demonstrated the existence of another adapter protein operating as a mediator between Miro and KIF5 [MacAskill et al., 2008]. Expression of GRIF-1 stimulated anterograde mitochondrial transport. Increases in Miro expression increased the GRIF-1 level. Models proposed by the authors on the basis of these results are clearly presented in the review by Cai and Sheng [2009],

TABLE 1. Summary Table of Motor Proteins: Kinesins and Dyneins and the Proteins Transported by Them Involved in the Mechanisms of Synaptic Plasticity

Type of motor	Type of load	Adapter or carcass protein	Molecules transported
KIF1A or KIF1Bβ	Precursor of synaptic vesicles	DENN/MADD	Synaptophysin, synaptotagmin, SV2, and RAB3A
	Vesicles	Unknown	PtdIns(4,5)P2
KIF1Bα	Mitochondria	KBP	Mitochondrial proteins
KIF5	Mitochondria	Milton, Miro, syntabulin	Mitochondrial proteins
	Synaptic membrane precursors	Syntabulin	
	Unknown protein complex	DISC1	Syntaxin-1
	Vesicles	JIPs	SNAP25
		JIP1 (MAPK8IP1)	Phosphorylated APP
	Synaptic receptors	GRIP1	GluR2
		HAP1	$GABA_A$
	Neurotrophin receptors	CRMP2	TrkB
	Tubulin dimers	CRMP2	Tubulin
KIF17 (OSM3)	Synaptic receptors	LIN10 (MINT1)–LIN2–LIN7	NR2B
		Unknown	GluR5
KIF11 (Eg5)	Neurotrophic factors and NMDA receptors	Unknown	NGF/NTR(p75)
			NMDA
DLCs	Vesicular transport	Bassoon	Piccolo-Bassoon
Dlc-1	Transport of synaptic receptors	Gephyrin	$GABA_A$
			GlyR
Dynein	Mitochondria	VDAC1	Unknown

where the mechanisms of the movement and stopping of mitochondrial transport are dissected in detail. In the absence of Ca^{2+}, the tail C-terminal of KIF5 binds mitochondria by interacting with the milton-Miro complex. In the presence of Ca^{2+} ions, it interacts with the EFF-hand via the Miro motif, changing the conformation of the protein such that it binds the motor domain of KIF5, preventing interaction of KIF5 with microtubules. In the case of the adapter protein GRIF-1, the regulatory mechanism in conditions of a varying cytosolic Ca^{2+} concentration is similar to the mechanism involving milton protein. The only difference is that as the Ca^{2+} concentration increases, GRIF-1 detaches from KIF5, and with it the entire mitochondrion-Miro complex [Cai and Sheng, 2009].

Syntaphilin has been shown to take part in immobilizing mitochondria in axons by binding to KIF5 [Chen and Sheng, 2013]. In vitro analysis showed that the interaction of syntaphilin with KIF5 inhibits the ATP binding site of KIF5, which is located in the motor domain [Chen and Sheng, 2013]. It may be that this mechanism detaches mitochondria from microtubules such that they acquire motility. Recent studies on the hippocampus reported by Sun et al. [2013] addressed the question: could mitochondrial motility contribute to the extent of variation in synaptic efficiency? Using brain slices from mice with knockout of syntaphilin, they showed that increases in mitochondrial motility increased the extent of variation in synaptic efficiency, while immobilization of mitochondria decreased it. Dual-color imaging studies showed that within a single nerve terminal, presynaptic vesicles were released as soon as mitochondria were present in the presynaptic bouton, as a result of a change in the ATP concentration in the axon [Sun et al., 2013].

Inhibition of the motor protein dynein changes the distribution of mitochondria in the axon, pointing to its role in the retrograde transport of mitochondria [Martin et al., 1999]. The dynein light chain Tctex-1 interacts with VDAC1 channels (voltage-dependent anion-selective channel 1) inserted into the outer mitochondrial membrane [Schwarzer et al., 2002]. VDAC1 channels have roles in various cellular processes, including in the control of mitochondrial ATP concen-

trations and Ca^{2+} currents. The results of behavioral experiments on mice with a deficiency of VDAC1 channels showed that these mice were unable to acquire a conditioned avoidance reaction or learn in a Morris maze. Results from electrophysiological experiments on brain slices from mice lacking VDAC1 channels also demonstrated the inability to acquire long-term and short-term synaptic plasticity. Inhibition of VDAC1 with cyclosporin A in brain slices from wild-type mice reproduced the results of the electrophysiological experiments in VDAC1-deficient mice. Thus, the normal functioning of mitochondrion outer membrane permeability, in which VDAC1 channels are involved, is important for learning and synaptic plasticity [Weeber et al., 2002].

In the light of existing data, it is unclear what contribution the motor protein dynein makes to these processes: whether it interacts with VDAC1 to trigger the process of mitochondrial mobilization or whether VDAC1 channels are those parts of mitochondria which bind to dynein for transportation of mitochondria along microtubules. It is also possible that this is not directly linked with its transport function but rather that via interaction with VDAC1 channels it has a role in controlling outer mitochondrial membrane permeability. These hypotheses remain to be verified.

Motor proteins in the transport of neurotrophins and the mechanisms of synaptic plasticity. KIF5s and CRMP-2, apart from their role in slow axon transport, are also involved in the transport of receptors for neurotrophins TrkA, TrkB, and TrkC, which are located on axon terminals. Neurotrophin receptors transmit signals from brain-derived neurotrophic factor (BDNF). The BDNF propeptide has been shown to produce direct facilitation of long-term depression in the hippocampus via GluN2B-containing NMDA receptors and the pan-neurotrophin receptor p75(NTR) [Mizui et al., 2015]. Arimura et al. [2008] showed that CRMP-2 complexed with Slp1 and Rab27B bind TrkB and KIF5. This binding is important for further anterograde transport of TrkB-containing receptors. The cytoplasmic tail of TrkB binds Slp1 via Rab27B, while CRMP-2 binds Slp1 with KIF5. Knockdown of these proteins using siRNA degrades the anterograde transport of TrkB, inhibiting BDNF-induced ERK1/2 phosphorylation in axons [Arimura et al., 2009].

Conclusions

Thus, despite the fact that there are currently few direct data on the role of kinesin and dynein in synaptic plasticity, their role in neuron transport as the only motor proteins of microtubules indirectly supports their involvement in the mechanisms of synaptic plasticity. Kinesin and dynein bind proteins in the pre- and postsynaptic density which have been shown to have roles in the mechanisms of synaptic plasticity [Yao et al., 2004; Zhu et al., 2005] (Table 1). There are direct data showing a correlation between inhibition of Eg5 kinesin by monastrol and the disappearance of long-term potentiation [Ari et al., 2004]. What determines the place of motor proteins in controlling biochemical cascades of the mechanisms of pre- and postsynaptic plasticity remains to be clarified.

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