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The Microtubule Cytoskeleton Acts as a Key Downstream Effector of Neurotransmitter Signaling

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ABSTRACT Microtubules are well known to play a key role in the trafficking of neurotransmitters to the synapse. However, less attention has been paid to their role as downstream effectors of neurotransmitter signaling in the target neuron. Here, we show that neurotransmitter-based signaling to the microtubule cytoskeleton regulates downstream microtubule function through several mechanisms. These include tubulin posttranslational modification, binding of microtubule-associated proteins, release of microtubule-interacting second messenger molecules, and regulation of tubulin expression levels. We review the evidence for neurotransmitter regulation of the microtubule cytoskeleton, focusing on the neurotransmitters serotonin, melatonin, dopamine, glutamate, glycine, and acetylcholine. Some evidence suggests that microtubules may even play a more direct role in propagating action potentials through conductance of electric current. In turn, there is evidence for the regulation of neurotransmission by the microtubule cytoskeleton. **Synapse 65:249–256, 2011.**

INTRODUCTION

Microtubules in brain function

The neuronal microtubule cytoskeleton plays a key role in many cellular processes including protein transport, cell division, and neurotrophic support. Kinesin and dynein motor proteins transport cargoes along microtubules between the nucleus and cell extremities. Indeed, neurotrophic support is dependent on the trafficking of neurotrophic factors including brain-derived neurotrophic factor along microtubules to the cell nucleus after their binding to neurotrophin receptors. Microtubules also play key roles in the formation of the mitotic spindles involved in cell division. Not surprisingly, a number of diseases are associated with mutations in components of the microtubule cytoskeleton. These include Charcot-Marie-Tooth disease, which can be caused by mutations in dynamin (Tanabe and Takei 2009) or the kinesin KIF1B (Zhao et al. 2001) and epilepsy, which can be caused by mutations in a number of microtubule-associated proteins (MAP) (Gardiner and Marc 2010). Mutations in the MAP doublecortin (DCX) cause either classical lissencephaly or double cortex (Gleeson 2000). Mutations in the MAP disrupted in Schizophrenia 1 perturb cerebral cortex development (Kamiya et al. 2005) and mutations in a second MAP, neuregulin, also cause schizophrenia (Chen et al. 2010). Microtubules are also implicated in other neurological disorders including motor-neuron disease where there is a link to low levels of the α-tubulin acetylating protein ELP3 (Simpson et al. 2009) and Alzheimer's disease where abnormal hyperphosphorylation of the MAP Tau causes neurofibrillary tangles and dystrophic neurites (Iqbal et al. 2009).

Microtubule dynamic properties

Microtubules are composed of heterodimers of α- and β-tubulin with which both bind to a molecule of GTP. GTP bound to α-tubulin is stable, whereas GTP bound to β-tubulin may be hydrolyzed to GDP. GDP-tubulin is prone to depolymerization and there is generally a cap of GTP tubulin, protecting it from disassembly. When hydrolysis catches up with the tip of the microtubule, it undergoes rapid depolymerization and shrinkage, or "catastrophe." This property of microtubules is known as dynamic instability. GTP-

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bound tubulin can also begin adding to the end of the microtubule again, "rescuing" the microtubule. Many proteins interact with microtubules and are involved in critical functions such as microtubule growth, stabilization, destabilization, and interaction with other cellular organelles (Wade 2009). Other MAPs control tubulin availability and modulate microtubule dynamics to enable neuronal development in response to environmental cues (Poulain and Sobel 2010).

Microtubules in dendrites

The primary site of contact of downstream neurons with presynaptic axons on excitatory hippocampal and cortical neurons are dendritic spines (Hu et al. 2008). The role of actin in the structure of dendritic spines has been much studied. Actin makes a key contribution to dendritic spine morphogenesis and function, with the loss of the actin-binding protein debrin causing synaptic dysfunction (Sekino et al. 2007) and dendritic spines undergoing rapid actin-based changes in their morphology after excitatory synaptic transmission (Schubert and Dotti 2007). Relatively, little work has been done on the role of microtubules. However, microtubules are known to rapidly invade dendritic spines in mature central nervous system neurons. Only a small percentage of spines are targeted at any given time and only for a few minutes, but over time many spines are targeted. An increase in neuronal activity enhances both the number of spines invaded and the duration of these invasions (Hu et al. 2008). Thus, there is evidence for the interaction of microtubules with synapses from this study. Other work also shows that microtubules are important for dendritic function. The microtubule motor protein dynein steers cargo, including α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptors into dendrites (Kapitein et al. 2010) and growing microtubule ends regulate the localization of p140Cap, thus controlling the function of the actin-binding protein cortactin and modulating actin dynamics within dendritic spines (Jaworski et al. 2009).

Here, we discuss the role of microtubules in the propagation of neurotransmitter-mediated signaling to dendritic spines. Many of the receptors affected by microtubules relate to brain functions associated with mood, sleep, and memory. The microtubule cytoskeleton is regulated in various ways to ensure its correct cellular function. These are tubulin posttranslational modification, binding of MAPs, interaction with second-messenger molecules including Ca^{2+}, and regulation of tubulin expression levels. Neurotransmitters act on the microtubule cytoskeleton through all these pathways. Drug studies also suggest functional interaction between neurotransmitters and microtubules, as does the direct binding of neurotransmitter receptors to scaffolding proteins and the microtubule cytoskeleton.

Abbreviations

5-HT(3A)	serotonin receptor 3A
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
DAergic	dopaminergic
GlyR	glycine receptor
HDAC6	histone deacetylase 6
MAP	microtubule-associated protein
NMDA	*N*-methyl-d-aspartic acid
Rac1	Ras-related C3 botulinum toxin substrate 1
SCN	suprachiasmatic nucleus
STOP	stable tubule only polypeptides
TTLL7	tubulin-tyrosine ligase like 7

Microtubule dynamics and mediators thereof

Posttranslational modification of tubulin

Tubulin undergoes various posttranslation modifications including acetylation, polyglutamylation, glycosylation, and detyrosination. The elongator complex acetylates tubulin and this controls the migration and differentiation of cortical neurons (Gardiner et al. 2007; Creppe et al. 2009). Tubulin-modifying enzymes also interact with MAPs. Tau protein binds to the tubulin deacetylase histone deacetylase 6 (HDAC6) and decreases its activity, leading to an increase in neuronal acetylated tubulin (Perez et al. 2009). Microtubule acetylation promotes the binding of MAPs to microtubules and promotes kinesin-1 binding and transport (Reed et al. 2006). β-tubulin is also polyglutamylated by the enzyme tubulin-tyrosine ligase like 7 (TTLL7). Knockdown of TTLL7 represses NGF-stimulated MAP2-positive neurite growth (Ikegami et al. 2006). α-Tubulin undergoes cycles of detyrosination/tyrosination at its carboxy terminus, with detyrosination impairing microtubule disassembly in neurons and inhibiting the activity of the neuronal depolymerising motor kinesin 2A in vitro (Peris et al. 2009). In addition, tubulin tyrosination enables kinesin-1 to discriminate between axons and dendrites (Konishi and Setou 2009).

The serotonin-reuptake inhibitor fluoxetine alters the posttranslational modification of microtubules in rats (Bianchi et al. 2009). In rats raised in isolation, fluoxetine increased the Tyr/detyrosinated (deTyr)-tubulin ratio, whereas in grouped rats it decreased acetylated tubulin, suggesting that serotonin is important in the remodeling of the microtubule cytoskeleton during development. The increase in Tyr/deTyr-tubulin ratio also indicates that neurotransmitters may act to regulate dendritic transport along microtubules, as increased tyrosination in dendrites is associated with a decrease in axon-specific kinesin transport (Konishi and Setou 2009). Increased neuronal activity induced by blocking glycine receptor (GlyR) activity facilitates tubulin polyglutamylation (Maas et al. 2009), and this polyglutamylation facilitates the mobility of proteins including gephyrin and KIF5C, as well as increasing the binding of MAP2 to microtubules. Again, this demonstrates that increased neuro-

nal activity in dendritic spines may act to create functional differences between the axonal and dendritic microtubule cytoskeletons.

Microtubule-associated proteins

MAP2

The MAP2 contributes to the acquisition and maintenance of dendritic microtubules through promoting microtubule assembly and stability. Recent work also shows that it has a role in anchoring membranous organelles and signaling proteins to dendritic microtubules and is a receptor for neurosteroids (Farah and Leclerc 2008). The phosphorylation status of MAP2 controls its association with the cytoskeleton, with phosphorylation leading to dissociation of MAP2 from microtubules and a marked increase in their dynamic instability (Illenberger et al. 1996).

A number of neurotransmitters affect the phosphorylation status of MAP2. The SSRI fluvoxamine increases phosphate incorporation into MAP2 after 5 days of administration, suggesting that changes in the protein phosphorylation system associated with microtubules could be an early modification associated with the drug (Perez et al. 1995). Dopamine receptor 1 antagonists cause a decrease in dendritic extension corresponding with an elevation in MAP2 phosphorylation (Song et al. 2002). Activation of glutamate receptors 1 and 5 also increases MAP2 phosphorylation (Llansola et al. 2005) and MAP2a is an metabotropic glutamate receptor 5-interacting protein (Farr et al. 2004). Glutamate produces a biphasic change in MAP2; a rapid, transient increase in phosphorylation mediated by metabotropic receptors followed by a persistent dephosphorylation mediated by *N*-methyl-D-aspartic acid (NMDA) receptors (Quinlan and Halpain 1996).

Neurotransmitters are also known to affect the expression levels of MAPs. Serotonin depletion in rats leads to a significant decrease in the MAP2 (Whitaker-Azmitia et al. 1995). Melatonin increases MAP2 expression and attenuates its decay in the adult aging hippocampus. This effect seems specific because melatonin does not affect MAP2 levels in the primary somatosensory cortex (Prieto-Gómez et al. 2008). Conversely, glutamate antagonists inhibit calpain-mediated proteolysis of MAP2 (Minger et al. 1998). Thus increased neuronal activity causes an increase in the stabilization of microtubules in dendrites by MAP2. The action of neurotransmitters may be reflected in the high levels of MAP2 found in dendrites as opposed to axons (Kosik and Finch 1987).

Neurotransmitters play a key role in modulating MAP2 function at a cellular level. Transformation of insect MG-1 cells with MAP2c causes the formation of processes, and coinfection with the phosphoinositide-linked mGluR1a or mGluR1b receptor subtypes inhibits the formation of these processes. Inhibitors of phospholipase C reverses the effect of mGluR1 on process formation, suggesting that one or more metabolites in the PI pathway are responsible for the inhibitory effect (Huang and Hampson 2000). GlyR blockade alters the binding of MAP2 to microtubules and reduces motor protein motility and cargo delivery into neurites (Maas et al. 2009).

Tau protein

Tau protein is another important neuronal MAP. Alzheimer's disease and related tauopathies are characterized by neurodegeneration involving hyperphosphorylation of tau, which is accompanied by the formation of neurofibrillary tangles and dystrophic neurites. Normal tau promotes microtubule assembly and stabilizes microtubules whereas hyperphosphorylated tau sequesters normal tau, MAP1 and MAP2 and disrupts microtubules (Iqbal et al. 2009).

High serotonin concentration reduced the levels of tau protein in neuroblastoma cells, whereas lower serotonin concentrations increased tau protein in the cytoplasmic fraction but decreased its presence in the membrane fraction (John et al. 1991). Melatonin and acetycholine seem to have a neuroprotective effect, with melatonin preventing isoproterenol-induced tau hyperphosphorylation (Wang et al. 2005.) In addition, inhibition of melatonin biosynthesis with haloperidol increases tau hyperphosphorylation (Zhu et al. 2004). Two acetylcholine agonists were shown to reduce tau phosphorylation in PC12 cells transfected with the gene for the rat m1 muscarinic acetylcholine receptor (Sadot et al. 1996).

There is a possibility that neurotransmitters could contribute to neurodegeneration. Thus, activation of dopamine receptor caused hyperphosphorylation of tau protein through a protein kinase A, cyclin-dependent kinase 5 and glycogen synthase kinase 3 beta-dependent pathway (Lebel et al. 2009). Tau mRNA was also upregulated after a 15 min exposure to toxic levels of glutamate and this appeared to occur through a transcriptional mechanism (Esclaire et al. 1997). Glutamate increased tau phosphorylation in primary neuronal cultures from fetal rat cerebral cortex (Sindou et al. 1994), again suggesting a role for glutamate in tau neurotoxicity.

Other MAPs

MAPs can act to either stabilize or destabilize microtubules, and MAPs of both classes are implicated in signaling between neurotransmitter pathways and the microtubule cytoskeleton. The microtubule-stabilizing protein DCX is required in certain suprachiasmatic nucleus (SCN) neurons of the circadian clock nucleus, suggesting that it may play a key role in daily alteration in SCN neuronal signaling

(Geoghegan and Carter 2008). The microtubule-stabilizing protein adenomatous polyposis coli protein functions to localize alpha3nAChRs to postsynaptic sites and cooperates with another MAP, end-binding 1, in this process (Temburni et al. 2004). The phosphorylation of stathmin, a microtubule destabilising factor, is mediated by the activation of voltage-gated calcium channels and metabotropic glutamate receptor 1 (Ohkawa et al. 2007).

Other MAPs play different roles in the regulation of the microtubule cytoskeleton's functions in the cell and also interaction with neurotransmitter pathways. D1 receptor activation regulates the localization of MAP huntingtin, which plays a key role in regulating microtubule-based transport, by increasing the protein's association with endosomes (Kim et al. 1999).

Regulation of tubulin expression levels

Neurons carefully regulate their levels of tubulin expression and this is often related to neurogenesis. Different tubulin isoforms show different patterns of expression in developing neurons. For example, Talpha-1 tubulin promoter-driven EYFP expression decreases with age, indicating that Talpha-1 tubulin accurately identifies early-born postmitotic neurons (Coksaygan et al. 2006). Dibutryl cyclic adenosine monophosphate enables central branches to regenerate in the spinal cord, possibly in part by elevating tubulin expression (Han et al. 2004).

Physiological concentrations of melatonin were shown to induce an increase of microtubules in neuroblastoma NIE-115 cells but did not change levels of β-tubulin (Meléndez et al. 1996), whereas melatonin increased tubulin level in the pineal gland when applied exogenously (Freire and Cardinali 1975). Dopamine-induced changes in cytosolic Ca^{2+} levels may also modulate pituitary microtubules through changes in the expression of tubulin (Ravindra and Grosvenor 1990), and β-tubulin fragmentation is an early event in glutamate-induced apoptosis (Ankarcrona et al. 1996).

Regulation of microtubule dynamics by second messenger systems

Calcium

Second messenger molecules, such as Ca^{2+} are important regulators of the neuronal microtubule cytoskeleton. MAP are regulated by Ca^{2+} signals and Ca^{2+} may act in both adaptive and aberrant neuroarchitectural changes in the nervous system (Mattson 1992). A sustained increase in Ca^{2+} induced by glutamate in dendrites was correlated with calpain-induced dendrite retraction (Wilson et al. 2000). The small G protein Ras-related C3 botulinum toxin substrate 1 (Rac1) is a downstream target of serotonin signaling. Rac1 promotes Ca^{2+} release from endoplasmic reticulum stores, and Rac1 activity modulates Ca^{2+} by enhancing microtubule assembly which in turn promotes the spread of the endoplasmic reticulum into the growth cone periphery (Zhang and Forscher 2009).

CaMKII

The serotonin 5-HT1A receptor inhibits NMDA receptor-mediated ionic and synaptic currents through a microtubule-dependent mechanism. Activation of 5-HT1A reduces microtubule stability through a Ca2+/calmodulin-dependent protein kinase II and MAP kinase/extracellular signal-regulated kinase extracellular signal-regulated kinase dependent mechanism, potentially reducing the transport of NR2B-containing vesicles (Yuen et al. 2005).

MAP kinase

MAP kinase extracellular signal-regulated kinase is activated by D2 dopamine receptors through a G-protein and phosphoinositide 3-kinase dependent pathway (Welsh et al. 1998). The activation of group III metabotropic glutamate receptors appears to attenuate the selective toxicity of rotenone on dopamine neurons by activating the MAP kinase pathway to stabilize microtubules (Jiang et al. 2006).

Regulation of receptor or transporter function by microtubules

Microtubule polymerization status affects synaptic transmission, with more stable microtubules leading to a decrease in neural activity for various neurotransmitters and an increase for others. This tally with the findings of epilepsy studies in which depolymerization or stabilization of microtubules leading to an increase in uncontrolled synaptic transmission (Gardiner and Marc 2010). Microtubules seem to promote melatonin, AMPA, and dopamine neurotransmission and reduce serotonin and acetylcholine neurotransmission. They also decrease inhibitory glycine neurotransmission, which would lead to an increase in action potential propagation. A number of MAPs and scaffolding proteins may be involved in the interdependence of neurotransmission and microtubule polymerization status.

Melatonin receptor

Microtubule depolymerization prevents the loss of the high potency states of the human melatonin receptor 2 receptor and increases melatonin-induced protein kinase C activity. Both colcemid and nocodazole enhance the efficacy of melatonin to phase-shift the circadian activity rhythms of the Long Evans rat. Thus microtubules play a role in melatonin-induced

phase shifts of circadian activity rhythms, possibly explaining why circadian disturbances occur in diseases associated with microtubule disturbances (Jarzynka et al. 2009). Here, microtubule status governs neural activity, with an increase in the amount of polymerized tubulin decreasing activity.

Glycine receptor

Application of the microtubule-depolymerising agent colchicine by dialysis via a patch pipette reduced the quantal amplitude of spontaneous glycinergic miniature inhibitory postsynaptic currents, indicating that microtubules can regulate the function of GlyRs involved in inhibitory synaptic transmission (van Zundert et al. 2002). Disruption of microtubules reduced the amount of GlyR and the glycine-receptor anchoring protein gephyrin at synapses. This disruption increased GlyR exchanges between synaptic and extrasynaptic membranes and reduced receptor dwell-time at synapses (Charrier et al. 2006). It has been suggested that a complex is formed between GlyR, gephyrin, and dynein, and that this association contributes to the activity-dependent rearrangement of postsynaptic GlyRs (Maas et al. 2006). Here, microtubules increase neural activity through decreasing inhibitory receptor dwell-time at synapses.

Serotonin receptors

PSD-95, a postsynaptic density scaffolding protein, is connected to the microtubule cytoskeleton possibly through the proteins cysteine-rich PDZ-binding protein and dynein light chain (Valtschanoff and Weinberg 2001) both of which bind microtubules (Passafaro et al. 1999). PSD-95 is required for 5-HT(2A) inverse antagonists to normalize behavioral changes induced by antagonists of glutamate receptor, with both 5-HT(2A) and 5-HT(2C)-mediated downstream signaling being impaired in PSD-95 null mice (Abbas et al. 2009). Both MAP1A and MAP1B form complexes with neurotransmitter receptor-complex proteins, suggesting a functional interaction between the two. The light chain of MAP1B specifically interacts with 5-HT(3A) receptors and accelerates receptor desensitization time constants. MAP1A colocalises with 5-HT(2A) serotonin receptors in cortical dendrites of the adult rat, suggesting a possible functional relationship (Cornea-Hébert et al. 2002). Depolymerization of microtubules prolongs the desensitization of 5-HT receptors, suggesting a functional relationship between receptor and the microtubule cytoskeleton (Sun et al. 2008). Here, it seems that microtubules facilitate neural activity.

AMPA receptor

The microtubule-stabilizer taxol has been used to demonstrate the interconnectedness of microtubules and neurotransmission. Taxol-protected hippocampal neurons against glutamate excitotoxicity and suppressed Ca^{2+} influx through AMPA receptors (Furukawa and Mattson 1995). Thus, stabilization of microtubules reduces neural activity here.

Dopamine receptor

Stable tubule only polypeptides (STOPs) are MAPs that regulate microtubule stability and also interact with actin (Baratier et al. 2006) and golgi membranes (Gory-Fauré et al. 2006). An analysis of STOP interaction with neurotransmitter proteins suggested the presence of signaling from the microtubule cytoskeleton to proteins involved in neurotransmission. Mice deficient in STOP were hypersensitive to acute and subchronic locomotor effects of cocaine, showing that STOP deletion elicits alterations in dopaminergic (DAergic) neurotransmission (Bouvrais-Veret et al. 2008). Thus, less stable microtubules lead to a decrease in DAergic neurotransmission and neural activity.

Acetylcholine receptors

Tenascins are extracellular glycoproteins that interact with the microtubule cytoskeleton. Incubation of tenascin-C negative cells with taxol restored total muscarinic acetylcholine receptors to normal levels, suggesting that agonist-induced downregulation of muscarinic acetylcholine receptors is functionally associated with tenascin-C-regulated microtubule structures in the developing cerebellum (Fukamauchi et al. 2000). The microtubule stabilizer epothilone D has a beneficial effect on synaptic function in STOP knockout mice (Andrieux et al. 2006). Mice deficient in the microtubule-stabilizing protein STOP show a decrease in alpha6nAChRs and an increase in alpha7-nAChRs (Bouvrais-Veret et al. 2007). Colchicine was shown to disrupt potentiation of cholinosensitivity of command neurons in edible snail. It was proposed that this occurs due to the dependence of cholinosensitivity on the incorporation of extra cholinoceptors into neuron plasmalemma with the participation of microtubules (Abramova et al. 2007). Here, microtubules promote synaptic activity.

Channel proteins, action potentials

Early literature has shown a correlation between conditions supporting membrane excitability and microtubule assembly, suggesting that microtubules associated with the internal surface of the plasma membrane regulate both the resting and the action potentials (Matsumoto and Sakai 1979). The drug NAPVSIPQ, which probably interacts with microtubules, was able to protect against kainic-acid excitotoxicity in hippocampal neuronal cultures, again suggesting that microtubules are a downstream target of synaptic signaling (Zemlyak et al. 2009). Sustained electrical activity in the sural nerve of the cat caused an increase in the number of microtubules and

reduced their sensitivity to the microtubule-depolymerising agent colchicine (Alvarez and Ramirez 1979).

The function of the $Na^{(+)}$ channel may also be dependent upon microtubules since there was a shift from slow onset-and-recovery to fast onset-and-recovery from inactivation in the presence of microtubule disruptors (Shcherbatko et al. 1999). Also, colchicine was found to disrupt the generation of sodium current in squid giant axons (Matsumoto et al. 1984) and the birefringence response to a brief depolarizing voltage pulse (Landowne et al. 1983).

The mec-12 (e1605) α-tubulin mutation in *Caenorhabditis elegans* results in a reduced mechanoreceptor current in sensory neurons without affecting distribution of the touch-transduction channel, indicating a specific role for microtubules in mechanotransduction (Bounoutas et al. 2009). Microtubules may act to transmit electric current, and thus information, through the propagation of soliton waves along the C-termini of microtubules, and it has been suggested that perturbations generated by C-termini tubulin interactions with counterions surrounding MAP2 may propagate over distances greater than those between adjacent microtubules. It has also been suggested that MAP2 is able to act as a biological wire transmitting local electrostatic perturbations arising from ionic concentration gradients from one microtubule to another (Priel et al. 2005).

CONCLUSIONS

The earlier literature survey shows that an intricate control is exerted over the neuronal microtubule cytoskeleton by various neurotransmitters. Through control of tubulin posttranslational modifications, modulation of MAP function, regulation of second messenger release and regulation of tubulin expression levels this control affects various microtubule-based functions including protein transport and neuronal survival or death. The interaction is bidirectional, with microtubules directly and indirectly influencing neurotransmission. As it has been suggested that microtubules may transmit electrical current directly the structure of the microtubule cytoskeleton, including its associated proteins, may be crucial to the propagation of action potentials through neurons. Dysfunction of the microtubule cytoskeleton in this model leads to aberrant neurotransmission.

Much further work needs to be done in order to elucidate the role of microtubules in neuronal neurotransmission. For example, we still do not have a complete list of proteins that interact with microtubules in neurons. A proteomic approach to identifying neuronal MAPs will likely reveal many associated proteins of crucial importance to synaptic function. Electroencephalography studies on knockout mice that lack important neuronal MAPs such as Lis1 and Ndel1 (Youn et al. 2009) or HDAC6 (Zhang et al. 2008) would provide interesting data on the role of microtubules in modulating electrical activity in the brain.

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