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Microtubule and Microtubule Associated Protein Anomalies in Psychiatric Disease

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Anomalies in neuronal cell architecture, in particular dendritic complexity and synaptic density changes, are widely observed in the brains of subjects with schizophrenia or mood disorders. The concept that a disturbed microtubule cytoskeleton underlies these abnormalities and disrupts synaptic connectivity is supported by evidence from clinical studies and animal models. Prominent changes in tubulin expression levels are commonly found in disease specific regions such as the hippocampus and prefrontal cortex of psychiatric patients. Genetic linkage studies associate tubulin-binding proteins such as the dihydropyrimidinase family with an increased risk to develop schizophrenia and bipolar disorder. For many years, altered immunoreactivity of microtubule associated protein-2 has been a hallmark found in the brains of individuals with schizophrenia. In this review, we present a growing body of evidence that connects a dysfunctional microtubule cytoskeleton with neuropsychiatric illnesses. Findings from animal models are discussed together with clinical data with a particular focus on tubulin post-translational modifications and on microtubule-binding proteins. © 2016 Wiley Periodicals, Inc.

Key Words: microtubule; depression; schizophrenia; MAP2; JNK

Introduction

It is almost 50 years since tubulin was identified as the globular protein that makes up microtubules [Mohri, 1968]. Tubulin polymers, or microtubules, along with actin microfilaments and intermediate filaments, make up the cytoskeletal framework, which provides structure and dynamics to cells [Wells, 2005]. Neuronal cells are exceptional in their usage of microtubules to generate a highly polarized morphology consisting of long axons and dendritic arbors that form the receptive field for electrochemical input. Axonal microtubules are polarized and confer the rigidity that is necessary for long distance transport, whereas dendritic microtubules show mixed polarity and influence processes such as arborization and signaling to dendritic spines [Kapitein and Hoogenraad, 2011].

In cells, α and β tubulin exist as heterodimers. They are structurally homologous, comprising two β-strands surrounded by α-helices. Each subunit is divided into three functional domains: the N-terminal domain that incorporates a nucleotide-binding region (i.e., GTP), an intermediate domain comprising the taxol-binding site, and a C-terminal domain which provides the binding surface for motor proteins [Nogales et al., 1998]. α/β heterodimers interact in a head-to-tail conformation giving rise to linear polymers with inherent polarity known as protofilaments [Black and Baas, 1989]. Typically, a microtubule consists of a cylindrical assembly of 13 protofilaments with a diameter of 25 nm, and highly variable length. Microtubules actively modify their structure through dynamic cycles of assembly and disassembly. The plus end where β-tubulin is exposed elongates more rapidly than the α-tubulin exposed, minus end [Horio et al., 2014]. The process of rapid growth and collapse of microtubules is known as dynamic instability and it is regulated by the local abundance of free tubulin dimers, microtubule-associated proteins, plus-end tracking proteins, post-translational modifications (PTMs) of tubulin, and motor proteins [Garnham and Roll-Mecak, 2012; Kevenaar and Hoogenraad, 2015]. Microtubule polarity ensures directional transport of molecules in neurons and helps establish the compartmental specification of the neuron into axon and dendrite, an organization that is essential for synaptic transmission [Hoogenraad and Bradke, 2009; Tischfield and Engle, 2010].

Currently, cytoskeleton dysfunction has been inferred in the pathology of several neuropsychiatric diseases such as schizophrenia, major depressive disorder (MDD) and bipolar disorder [Wong et al. 2013; Brown et al., 2014]. Specific features of depressive disorders include a persistent sad

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mood, the absence of ability to feel pleasure in daily situations (anhedonia), and suicidal tendencies. Bipolar subjects alternate between depressive-like and manic states characterized by locomotor hyperactivity, euphoria, lack of sleep, and addictive episodes [Belmaker and Agam, 2008; Wong et al., 2013]. Schizophrenic patient symptoms are classified clinically as positive and negative. The former includes delusions, hallucinations (including auditory and/or visual), confused and illogical speech and thought processes. Negative symptoms, on the other hand, encompass lack of motivation or social behaviors [Picchioni and Murray, 2007].

Structural changes in the brain that are associated with these disorders include synaptic pruning defects as well as spine and dendrite atrophy. Impaired pruning (during childhood and adolescence) and spinogenesis defects at the level of the cortex lead to altered brain plasticity that is associated with susceptibility and onset of schizophrenia [Glausier and Lewis, 2013]. The onset of depression is thought to require in addition, an earlier "hit" such as maternal/perinatal stress event or exposure to triggering environmental factors [Schmitt et al., 2014]. In bipolar disorder, several studies suggest that a persistent inflammatory state underlies synaptic pruning defects, leading to compromised mood and impaired cognitive function [Rosenblat et al., 2015]. Immune dysfunction can also disturb the hypothalamic-pituitary axis leading to elevated cortisol, which in turn exacerbates neuronal dysfunction. Under conditions of chronic stress exposure, excessive cortisol leads to dendritic retraction and synaptic density loss, resulting in regional atrophy in the hippocampus, amygdala, and prefrontal cortex, as detected in MRI scans of neuropsychiatric patients [McEwen et al., 2015].

As for microtubule alterations in the pathophysiology of depression, several lines of correlative evidence exist. For example, patient samples grouped according to general distress, anhedonic depression and anxious arousal (the tripartite model of depression) [Clark and Watson, 1991], show an association with genes encoding cytoskeletal regulators. Thus, *MAP4* (a glial enriched MAP), is significantly altered in patients with general distress, while *MAPT* and *MAP2* are altered in the anhedonic dimension of MDD [van Veen et al., 2012]. Also, changes in tubulin PTMs are observed in MDD and schizophrenia samples and are reported to disrupt physiological connections within the brain by imposing abnormal cytoskeletal organization [Wong et al., 2013].

Tubulin Isotypes and Psychiatric Dysfunction

In the brain, tubulin isotypes derive from 19 genes (10 α and 9 β isotypes in humans). α_{1A}, α_{1B}, α_{1C}, α_{3C}, α_{3E}, α_{4A}, α_{8}, and α-$_{like3}$ and β_{I}, β_{II}, β_{III}, β_{IVa}, β_{IVb}, β_{V}, and βVI [Greenberger and Loganzo, 2008]. They display variable structural and interaction properties and show differential PTM within the C-terminal domain, contributing further to heterogeneity. Isoform expression is temporally regulated during brain development [Lee et al., 1990], while α_{1B}-, α_{1C}-, β_{I},- and β_{IVb}-tubulin isotypes are ubiquitously expressed, α_{1A}, β_{II}, and β_{III} are enriched in brain, peripheral nerves and muscles [Ait-Belkacem et al., 2013], where they function in cell differentiation [Guo et al., 2010]. Evidence for global, disease-relevant changes in tubulin isotypes derives from proteomics studies in rodent models of depression (Table I). Thus, in the restraint stress [Bianchi et al., 2003] and isolation rearing rodent models of depression [Bianchi et al., 2009], α-tubulin expression is decreased. Likewise, in rats that are genetically sensitive to depression (the Flinders sensitive line) there is a large (7.6 fold) decrease in expression of β-tubulin isotypes (β_{IIA} and $\beta_{V)}$ in the hippocampus compared to resistant rats [Piubelli et al., 2011]. However, when subjected to the maternal separation stress model of depression, it is only Flinders resistant mice that show a drastic 100 fold decrease in α and β tubulin expression [Piubelli et al., 2011]. Overall, these studies indicate that decreased α/β tubulin expression in the hippocampus is a hallmark of depression in rodent models. However, the data from Flinders sensitive line suggests that it a lower baseline expression of tubulin in the hippocampus that correlates with early life stress susceptibility rather than intrinsic regulation that occurs upon exposure to maternal separation stress. It may be therefore that adaptability in microtubule homeostasis is impaired in the disease state. Interestingly, chronic administration of fluoxetine, a widely used antidepressant drug of the serotonin reuptake inhibitor (SSRI) class, rescues alterations in tubulin isoform expression that occur in mouse models of depression [Bianchi et al., 2009; Yang et al., 2009] suggesting that disturbed microtubule levels may play a causal role in the disease pathology.

In humans, β-tubulin expression is decreased in the prefrontal cortex of postmortem brains from subjects with schizophrenia or bipolar disorder compared to healthy controls [Prabakaran et al., 2004; English et al., 2009]. Consistent with this, gene expression analysis shows that *TUBB4* and *TUBB2C* isotypes are down-regulated in the dorsolateral prefrontal cortex of MDD patients [Kang et al., 2012]. In contrast to the above, in schizophrenic (non-medicated) patients, βI-tubulin expression is increased in the dorsolateral prefrontal cortex (although it is increased in the anterior cingulate cortex) [Moehle et al., 2012]. What is consistent among these data is that tubulin isotype expression is significantly altered in clinical, and in experimental models of psychiatric disease, indicating that perturbed microtubule homeostasis is a common hallmark in these conditions.

Tubulin PTMs and Neuropsychiatric Disorders

PTMs of tubulin further increase its functional heterogeneity. These modifications give rise to what is known as the "tubulin code" [Verhey and Gaertig, 2007]. This code is decoded by MAPs, which physically interact with

Table I. Microtubule and Microtubule Regulatory Protein and Gene Anomalies Associated with Psychiatric Disorders

Disorder	Genes/ proteins	Effect	References
Mood disorders (depression, bipolar)	α-Tubulin β-Tubulin CRMP1 CRMP2	Altered (protein) expression in cortex of patients with depression and bipolar disorder suggesting cytoskeletal dysfunction	[Beasley et al., 2006]
	β-tubulin	Decreased (protein) expression along with other cytoskeletal proteins (NF-L, NF-M, NF-H) in postmortem brains of bipolar patients	[English et al., 2009]
	βIII-tubulin	Altered cytoskeletal organization in patients with bipolar disorder	[Solís-Chagoyán et al., 2013]
	TPPP	Methylation changes in saliva samples from maltreated children associated with susceptibility to depression	[Weder et al., 2014)
		Upregulation of protein expression in rodent maternal stress model of depression	[Glombik et al., 2015]
	DISC-1	Susceptibility to major depression conferred by S704C mutation	[Hashimoto et al., 2006)
	Hdac6	Hyper-acetylation of α-tubulin in brains of *Hdac6-/-* mice, resulting in a low depressive like phenotype	[Fukada et al., 2012)
	Tyr-tubulin Acet-tubulin	Altered protein expression following restraint stress and unpredictable chronic mild stress models of depression in rats. Reversible with fluoxetine treatment	[Bianchi et al. 2003, 2009; Yang et al., 2009]
	TTLL11	Balanced translocation (9:17) (q33.2;q25.3) is linked to bipolar disorder	[Rajkumar et al., 2014]
	Map2	Flattened glucocorticoid rhythm associated with reduced *Map2* levels in rats	[Gartside et al., 2003)
		MAPREG (MAP4343) binding to MAP2 stimulates tubulin assembly and recovers depression-like behaviour in rats	[Bianchi and Baulieu, 2012]
Schizophrenia	TUBA1 TUBA2 TUBA6 TUBB5 CRMP2	Altered (protein) expression detected in post-mortem brains of patients with schizophrenia suggesting cytoskeletal dysfunction	[Prabakaran et al., 2004]
	β-tubulin	Decreased protein expression along with other cytoskeletal proteins (NF-L, NF-M, NF-H) in post-mortem brains from patients	[English et al., 2009]
	βI-tubulin	Region specific alterations in protein expression post mortem brains	[Moehle et al., 2012]
	βIII-tubulin	Altered cytoskeletal organization in post-mortem brains from schizophrenic patients	[Solís-Chagoyán et al., 2013]
	DISC-1	Mutation S704C confers susceptibility to schizophrenia in humans	[Hashimoto et al., 2006]
	ULK4	Low levels of acetylated α-tubulin in *Ulk4–/–* mice. Recurrent deletions in *ULK4* are found in patients	[Lang et al., 2014]
	TTLL11	Balanced translocation (9:17) (q33.2;q25.3) combined with micro-duplication 16p13.1 is associated with increased disease susceptibility	[Fullston et al., 2011]

TABLE I. *Continued*

Disorder	Genes/ proteins	Effect	References
	MAP1B	Decreased immunoreactivity in schizophrenic brain hippocampal subiculum suggesting altered cyto-architecture and neurotransmission deficits	[Arnold et al., 1991)
	MAP2	Decreased immunoreactivity is a hallmark in post mortem brains of individuals with schizophrenia	[Broadbelt et al., 2002; Somenarain and Jones, 2002; Rioux et al., 2003; Shelton et al., 2015]
	MAP6	Up-regulation of mRNA isoform2 Neuronal transport defects Deletion of gene triggers altered mood and cognitive performance in mice	[Shimizu et al., 2006; Fournet et al., 2012; Daoust et al., 2014]

Genes and proteins that are found to be disrupted in clinical cohorts or in rodent models of mood disorders and schizophrenia are shown.

microtubules to regulate their stability. PTMs are carried out in the cytoplasm by enzymes that induce chemical modifications to specific amino acid residues [Yu et al., 2015]. Both mono- (addition of a single group or modification of a single residue), and poly-modifications (addition of chains of variable length) of microtubules are common [Garnham and Roll-Mecak, 2012]. Most modifications take place at the C-terminal tail of tubulin subunits. Significantly, these are the interaction sites for molecular motors and MAPs [Magiera and Janke, 2014]. Mono-modifications include:

- **Acetylation/deacetylation** of α-tubulin K40 occurs within the microtubule lumen; catalyzed by acetyl transferases αTAT and Atat-2, whereas β-tubulin can be acetylated on K252 by the Sun acetyltransferase leading to a block of free tubulin assembly [Magiera and Janke, 2014]. Deacetylation, on the other hand, is executed by the histone deacetylase 6 (HDAC6) and nicotine adenine dinucleotide-dependent deacetylase sirtuin-2 (SIRT2) [Hubbert et al., 2002]. The anti-depressant action of HDAC inhibitors in a variety of rodent tests for depression has been recently reviewed [Fuchikami et al., 2015]. Although most HDACs act on histones in the nuclear compartment, HDAC6 is cytosolic and acts on tubulin. Interestingly, it is highly expressed in brain where studies in mice have associated its deacetylase activity with the regulation of emotional behavior. HDAC6 deficient mice display hyperactivity, low anxiety, and a low depressive like phenotype indicating that reversible acetylation maintains neuronal activity associated with emotional responses [Fukada et al., 2012]. Moreover, expression of the SIRT2 deacetylase is decreased in rodent models of depression and this is proposed to play a causative role in depressive behavior [Liu et al., 2015]. The specific regulation of tubulin deacetylases in these animal models points towards tubulin acetylation as a possible contributing factor in the pathophysiology of depression.

Neuronal plasticity is essential for adaptive responses to adverse situations, such as chronic stress exposure in both humans and rodents. Decreased levels of acetylated tubulin are found in the hippocampus of rats following social isolation [Bianchi et al., 2009]. In contrast to this, tubulin acetylation is increased in the hippocampus of rats exposed to unpredictable chronic mild stress [Yang et al., 2009] and following restraint stress [Bianchi et al., 2003]. Interestingly, acetylated α-tubulin levels are diminished (suggesting destabilized microtubules) upon knockdown of *Ulk4* (Unc-51 like kinase-4), a gene that is disrupted in schizophrenia and bipolar disorder [Lang et al., 2014]. ULK4 is a Ser/Thr kinase, expressed in neurons. Knockdown of *Ulk4* leads to reduced dendrite length, decreased branching, and agenesis of the corpus callosum. Interestingly also, JNK activity is decreased in ULK4 depleted mice. As JNK is a major regulator of microtubule homeostasis and dendrite complexity (as discussed later in this chapter) [Coffey, 2014], it represents one possible pathway whereby ULK4 could modify microtubule integrity. Taken together, these findings indicate that tubulin acetylation is altered in rodent models of depression and schizophrenia. This causes anomalies in axonal tract formation in developing brain and may alter synaptic plasticity. Moreover, kinase genes that are associated with schizophrenia converge on a pathway that regulates microtubule stability, suggesting that loss of cytoskeletal homeostasis may contribute to the pathological outcome.

- **Phosphorylation**—the addition of phosphate to a serine, threonine, or tyrosine residue results in a gain of three negative charges that affect the chemical and conformational properties of proteins. Neuron-enriched βIII tubulin is phosphorylated on serine [Alexander

et al., 1991] and is constitutively phosphorylated in brain. α-tubulin on the other hand is phosphorylated on tyrosine [Matten et al., 1990]. Surprisingly perhaps, the mechanism of tubulin phosphorylation is not clear, but it increases during neuronal differentiation and may facilitate tubulin assembly into microtubules [Greenberger and Loganzo, 2008]. The phosphorylation state of tubulin isoforms change upon exposure to the mood stabilizing drugs lithium, valproate, and paliperidone indicating that this modification may be disease relevant [Corena-McLeod et al., 2013]. These drugs also alter mitochondrial transport to synapses a process that may be directly linked to microtubule track modifications.

- **Tyrosination/detyrosination** of α-tubulin occurs in cycles. Detyrosination confers stability whereas tyrosination increases microtubule dynamics. Catalyzed by tubulin tyrosine ligase (TTL), tyrosination is important in neurons during axonal growth and transport [Magiera and Janke, 2014]. Detyrosination refers to the removal of Tyr from the C-terminal of α-tubulin to expose a Glu residue. **Glutamylation** takes place when the side chains of glutamates are added to the carboxy terminal tails of α– and β-tubulin by enzymes belonging to the tubulin tyrosine ligase-like (TTLL) family. This occurs at high levels in the nervous system. Deglutamylation is catalyzed by cytosolic carboxypeptidase enzymes, which are capable of removing glutamate side chains. Polyglutamylation changes the surface charge of tubulin, and influences the binding of MAPs and motor proteins [Janke, 2014]. Indeed impaired protein transport and disrupted binding of MAPs is proposed to contribute to the underlying pathology in schizophrenia [Ikegami et al., 2007]. The TTLL11 polyglutamylase is linked to schizophrenia where a combined disruption in *TTLL11* (a balanced t(9;17) (q33.2;q25.3) translocation, and a microduplication at 16p13.1) is associated with an additive predisposing effect [Fullston et al., 2011]. Interestingly, this same chromosomal aberration is also linked to bipolar disorder [Rajkumar et al., 2014].
- **Polyglycylation** of α- and β-tubulin is analogous to polyglutamylation except that of glycines are added instead of glutamates. This modification is limited to cilia and flagella. The responsible enzymes are again members of the TTLL family [Fukushima et al., 2009]. Tubulin glycylases and glutamylases are important for stabilization and motility of ependymal cilia, which line the ventricles of the brain [Grau et al., 2013], while interestingly, neuropsychiatric risk genes have been shown to converge on regions encoding proteins found in cilia [Marley and von Zastrow, 2012].

Clinically relevant evidence for altered α-tubulin modifications in postmortem brain from patients with Alzheimer's [Zhang et al., 2015] Huntington's and Parkinson's disease [Perdiz et al., 2011] have also been reported, however the involvement of the microtubule cytoskeleton in the molecular mechanisms of neurodegenerative diseases has been extensively reviewed elsewhere [McMurray, 2000; Lingor et al., 2012; Baird and Bennett, 2013].

Microtubule Associated Proteins and Psychiatric Disorders

Microtubule associated proteins (MAPs) represent a group of proteins that bind to microtubules and regulate stability. Interaction of MAPs with microtubules is primarily controlled by PTMs, which are fine-tuned in developing and mature brain. MAP2 is exceptionally abundant in the brain [Matus, 1988] and its function has been long studied in the context of neuronal plasticity [Friedrich and Aszodi, 1991], while MAP1B and MAP1A are associated with axonal elongation and somatodendritic structure [Schoenfeld et al. 1989; Villarroel-Campos and Gonzalez-Billault 2014]. Since these proteins are core regulators of the microtubule network in neurons, it is not surprising that a range of developmental, neurodegenerative and psychiatric disorders have been associated with them.

- **MAP2—**Multiple MAP2 isoforms are generated by alternative splicing from 19 exons [Kalcheva et al., 1995]. MAP2 isoforms can be divided into high molecular weight MAP2 (HMW-MAP2) isoforms, MAP2A and MAP2B and low molecular weight MAP2 (LMW-MAP2) isoforms, MAP2C and MAP2D. LMW-MAP2 lacks the 1362 amino acid central domain of HMW-MAP2 but is otherwise homologous. HMW-MAP2 is exclusively expressed in neurons, whereas LMW-MAP2 can be found also in glial cells [Matsunaga et al., 1999]. MAP2 binds longitudinally along the outer rim of microtubule protofilaments and crosslinks neighbouring microtubules via its projection domain, leading to formation of long, stable bundles with characteristic spacing [Chen et al., 1992; Ludin et al., 1996; Teng et al., 2001; Al-Bassam et al., 2002]. Lowering of MAP2 expression using antisense oligonucleotides leads to impaired neurite initiation [Caceres et al., 1992], while cytoplasmic protrusions are formed when MAP2 is over-expressed in non-neuronal cells, such as COS-7 [Kalcheva et al., 1998; Bjorkblom et al., 2005]. MAP2 binding induces characteristic changes in microtubule organisation. For example, it increases the probability of MTOC-independent microtubule polymerisation [Weisshaar et al., 1992], suggesting that MAP2 can behave as a nucleation factor for tubulin polymerisation [Hugdahl et al., 1993]. Additionally, MAP2 is reported to cross-link actin filaments [Pedrotti and Islam 1997; Dehmelt and Halpain, 2004]. A study of mice lacking *map2* has shown that it is dispensable for brain development [Teng et al., 2001], though dendrite elongation is reduced in its absence [Harada et al., 2002]. MAP1b compensates for many MAP2 functions, as genetic

Table II. What Is Known About MAP2 Phosphorylation and Microtubule Stability?

Kinase	Effect of MAP2 phosphorylation on MT stability/binding	Domain of MAP2 and phosphorylated domain
JNK1	↑	PRD, T*PGT*PGT*PSYPR (MS/MS and site directed mutagenesis validation) [Komulainen et al., 2014]
GSK3	↓	PRD, T*PGT*PGT*PSYPR (antibody 305) [Sanchez et al., 2000] and TBD, KXGS* motifs by homology to Tau [Song and Yang, 1995]
CAMKII	↓	TBD, [Yamauchi and Fujisawa, 1982; Yamamoto, 1985; Hernandez, 1987]
PKA	↓	TBD, S350 KXGS* (MS/MS and site directed mutagenesis validation) [Ozer and Halpain, 2000]
MAPK	↓	TBD [Hoshi et al., 1992; Sanchez et al., 1995]
PKC	↓	TBD [Ainsztein and Purich, 1994]
MARK	↓	TBD on KXGS* motif [Drewes et al., 1997]

MAP2 phosphorylation has been studied extensively. This table summarizes findings from the literature where MAP2 phosphorylation and microtubule (MT) polymerisation are linked. Domains in MAP2 are abbreviated as PRD and tubulin-binding domain (TBD). Mass spectrometry- or site directed mutagenesis-based site validation, when utilized, is stated. Site assignment was otherwise done using antibodies generated against phosphorylated peptides, or by homology. The kinase list presented is not exhaustive. For example, MAP2 phosphorylation on T1650 is significantly reduced in *cdk5*–/– mice [Contreras-Vallejos et al., 2014], however the effect on microtubule stability in this case is not defined. There is a strong consensus from these studies that phosphorylation of the TBD of MAP2 leads to its dissociation from MTs. The role of PRD phosphorylation is less clear. Studies of PRD phosphorylation by JNK1 (which does not phosphorylate the TBD), indicate that PRD phosphorylation enhances MAP2 binding to MTs.

deletion of both *map2* and *map1b* leads to perinatal lethality, indicating that they serve crucial, overlapping functions [Teng et al., 2001]. These MAPs also cooperate to control the microtubule spacing and the organisation of microtubules in growth cones.

Shaping the Neuronal Cytoskeleton through PTMs of MAP2

MAP2 is one of the most highly phosphorylated proteins in the nervous system. The stoichiometry of HMW-MAP2 phosphorylation can reach as high as 46 moles of phosphate/mole protein in brain, while that of the LMW-MAP2 is ∼10–16 moles/mole [Tsuyama et al., 1987]. Although antibodies recognising phosphorylated motifs on MAP2 have been generated and have facilitated site specific study of MAP2 phosphorylation [Berling et al., 1994; Sanchez et al., 1996], much remains unknown regarding the function of specific phosphorylation sites.

Several kinases phosphorylate MAPs. These include extracellular signal regulated kinase (ERK), protein kinase A (PKA; on Thr220) [Alexa et al., 2002], protein kinase C (PKC; on Ser1703/Ser1711/Ser1728) [Ainsztein and Purich 1994] and c-Jun N-terminal kinase-1 (JNK1; on Thr1619/The1622/Thr1623) in the proline rich domain (PRD) [Komulainen et al., 2014] (Table II). MAP2 is dephosphorylated by protein phosphatase-1 (Sim 1991), –2A [Wera and Hemmings, 1995], –2B [Guerini, 1997] and –2C [Goldberg, 1999]. Importantly in the context of psychiatric disorders, which result from impaired synaptic function [Penzes et al., 2011; Gao et al., 2015], MAP2 phosphorylation is regulated by synaptic activity. Specifically, glutamate acting through N-methyl-D-aspartate (NMDA) receptors induces rapid dephosphorylation of MAP2 on Ser-136 [Halpain and Greengard, 1990; Quinlan and Halpain, 1996; Kapitein and Hoogenraad, 2011]. It is proposed that this dephosphorylation leads to sequestration of EB3 dendritic shaft microtubules, preventing it from entering the spinehead where it promotes microtubule plus end growth and spine head maintenance [Kapitein et al., 2011]. Additionally Arc, a synaptic activity regulated gene, binds to MAP2 and may contribute to activity-dependent dendrite remodelling [Fujimoto et al., 2004].

HMW-MAP2 encodes 43 Ser/Thr-Pro motifs, which are putative targets of MAP-kinases and other proline-directed protein kinases [Davis, 1993]. The X-Pro peptide bond can induce a kink in the polypeptide, altering its 3D structure, protein:protein interactions and further PTMs [Reimer et al., 1998]. The PRD, which is located in the C-terminal region, is conserved among MAP2 isoforms. JNK1 phosphorylates this domain *in vivo* in brain and in the cortex and hippocampus of *Jnk1*–/– mice, phosphorylation on Thr1619/Thr1622/Thr1623 is reduced, indicating that JNK1 serves a nonredundant role in the phosphorylation of these sites at least in early postnatal brain [Komulainen et al., 2014] (Fig. 1).

Implications for MAP Function in Psychiatric Disorders

MAPs contribute to normal cytoskeletal organization and dendritic arborisation, both of which are essential for healthy neuronal function and network formation [Li and Gundersen, 2008; Witte and Bradke, 2008; Hoogenraad and Bradke, 2009]. Decreased dendritic spine density and reduced

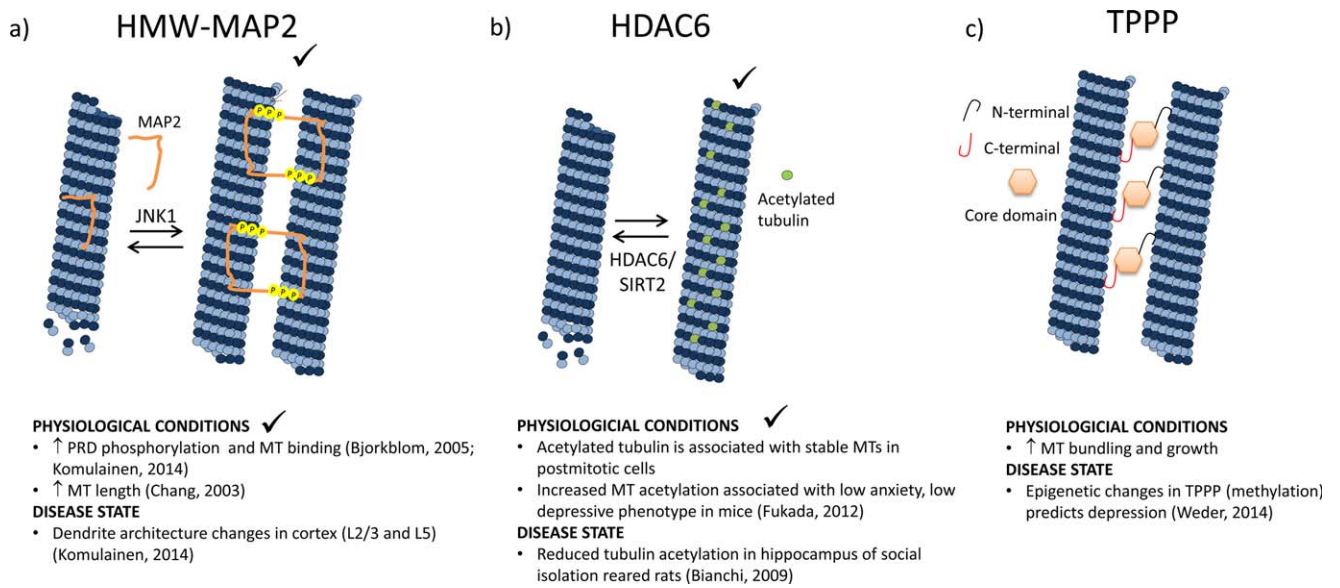


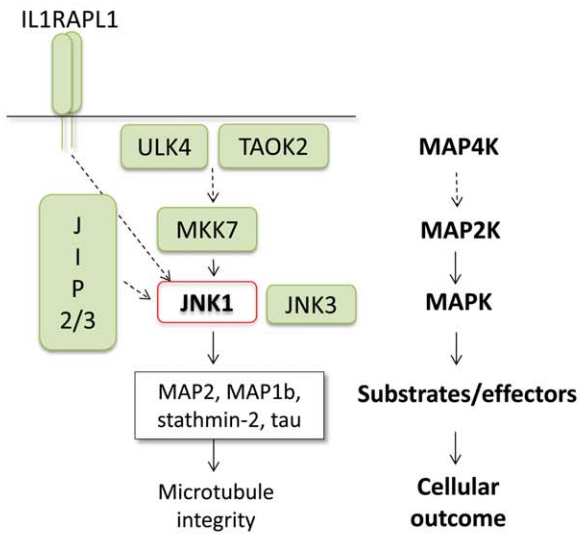
Fig. 1. Microtubule stability is regulated in diseases Examples of physiological and disease states of microtubules. (a) JNK1 phosphorylates the PRD of HMW-MAP2 leading to increased microtubule (MT) binding and stability [Bjorkblom et al., 2005; Komulainen et al., 2014]. JNK1 activity maintains MT polymer length under physiological conditions [Chang et al., 2003]. Antiparallel dimerization of HMW-MAP2 is understood to promote microtubule bundling and generates a defined 65 nm spacing characteristic of dendritic microtubules [Wille et al., 1992; Teng et al., 2001]. **(b)** MT acetylation is high in post-mitotic cells such as neurons and is associated with stable MTs. Mice lacking the tubulin deacetylase *hdac6* show a reduced anxiety phenotype [Fukada et al., 2012] whereas reduced tubulin acetylation is found in rats following isolation rearing [Bianchi et al., 2009]. **(c)** The tubulin polymerization promoting protein (TPPP) facilitates MT bundling under physiological conditions. Epigenetic modification of TPPP has been identified as a predictor of depression [Weder et al., 2014].

dendritic arborisation are extensively associated with neurological diseases [Blanpied and Ehlers, 2004; Penzes et al., 2011], including intellectual disability [Kaufmann et al., 2000], depression [Duman and Canli, 2015; Varidaki et al., 2016] and schizophrenia [Penzes et al., 2011; Glausier and Lewis, 2013]. Typically, atrophy occurs in response to chronic stress in regions such as the hippocampus and prefrontal cortex that play important roles in mood homeostasis. Synapse loss as a consequence of reduced dendritic field size and as an independent event is believed to underlie impaired information processing that is characteristic of schizophrenia. In the case of depression, loss of synapses leads to disturbed feedback loops and reduced adaptive responses to stress [Gold, 2015]. Dendritic spine loss in schizophrenia is associated with overpruning or reduced stability. Notably, spine loss is associated with reduced MAP2 [Shelton et al., 2015], suggesting a role for microtubule homeostasis in regulating spine head stability. Importantly in the context of synaptic disorders, MAP2 influences CREB activity by acting as an anchor for PKA in dendrites [Harada et al., 2002]. CREB regulates expression of BDNF (among other targets), which plays a central role in maintaining synapse health.

Loss of MAP2 Immunoreactivity in Post Mortem Tissues; a Hallmark of Schizophrenia

Several studies over two decades have noted using immunohistochemical analysis that MAP2 immunoreactivity is reduced in brains from schizophrenia patients. For example MAP2 immunostaining is substantially reduced throughout the hippocampus and prefrontal cortex in post mortem tissues [Arnold et al., 1991; Somenarain and Jones, 2010; Shelton et al., 2015], where it is accompanied by decreased numbers of primary and secondary basal dendrites (as little as 11% of controls in the pyramidal neurons of the prefrontal cortex) [Broadbelt et al., 2002]. MAP2 immunoreactivity is also decreased in the auditory cortex of schizophrenia patients and this correlates with decreased synapse number. Notably however, this loss of immunoreactivity does not signify reduced MAP2 protein levels, as proteomic analysis of brains from schizophrenic, bipolar or depressed patients show no significant difference in MAP2 expression [Prabakaran et al., 2004; English et al., 2009]. Similarly, dot-blot analysis of the anterior cingulate cortex from schizophrenic or MDD patients shows no change in MAP2 expression levels, while a 28% reduction is observed in samples from bipolar patients [Bouras et al., 2001]. Consistent with these findings, *MAP2* mRNA is not altered in the hippocampus of individuals with schizophrenia [Law et al., 2004]. It therefore seems most likely that this hallmark, disease-associated reduction in MAP2 immunoreactivity, is due to a PTM of MAP2 (e.g., phosphorylation) that alters epitope recognition. Such a modification may also be functionally relevant and contribute to dendrite atrophy resulting in reduced synaptic area. Ultimately, altered MAP2 function

a)



b)

Gene Name	Effect on JNK1	Disease association	References
IL1RAPL1	IL1RAPL1 activates JNK1	Mutations associated with monogenic cognitive impairment	(Pavlowsky et al. 2010)
TAOK2	TAOK2 activates JNK1	16p11.2 deletion in ASD and schizophrenia	(de Anda et al. 2012; McCarthy et al. 2009)
JIP2/JIP3	JIP2/3 activate JNK1	CNVs associated with ASD	(Cooper et al. 2011; Heo et al. 2004)
MKK7	MKK7 activates JNK1	SNPs associated with schizophrenia	(Winchester et al. 2012)
JNK3	n.a.	Truncation variants found in patients with intellectual disability	(Baptista et al. 2008; Shoichet et al. 2006)

Fig. 2. JNK1 is a dominant regulator of microtubule stability. Genetic anomalies in upstream regulators of JNK1 are associated with a variety of psychiatric disorders. (a) Positioning on the JNK pathway, of JNK1 regulators that are associated with psychiatric disease, are shown. Abbreviations are as follows: mitogen activated protein kinase (MAPK); mitogen activated protein kinase kinase (MAP2K); mitogen activated protein kinase kinase-7 (MKK7); JNK interacting protein-(JIP)–2/3. (**b)** The disease association of JNK1 upstream activators is listed.

could contribute to impaired information processing that occurs in psychiatric disorders, although considerable more work is needed to gain a precise mechanistic understanding. One possible phosphorylation mechanism is described below. Notably, reduced MAP2-immunoreactivity and dendritic spine loss is not restricted to schizophrenia. In the CA3 hippocampal subfield of patients suffering from anxiety, MAP2 staining and spine number is also decreased [Soetanto et al., 2010], consistent with reduced excitatory input from the dentate gyrus, while in animal models of depression induced by chronic stress, dendrite, and spine number is diminished [Varidaki et al., 2016].

Kinase Regulation of MAP2 and Psychiatric Dysfunction

Given that MAP2 is a highly abundant brain protein that is phosphorylated by kinases that are in one way or another implicated in psychiatric disorders, it seems likely that aberrant phosphorylation of MAP2 may contribute towards the disease pathology. Notably MAP2 kinases calcium calmodulin kinase II (CAMKII; Robison) and glycogen synthase kinase-3 (GSK-3) [O'Leary and Nolan, 2015] (Table II) are both implicated in psychiatric dysfunction. These kinases, among others (MARK, PKC, ERK, and PKA) phosphorylate the tubulin binding domain of microtubules leading to decreased association with microtubules and decreased microtubule stability (Table II). Interestingly, JNK, which phosphorylates MAP2 on specific sites in the PRD [Bjorkblom et al., 2005; Komulainen et al., 2014], is implicated in schizophrenia and autism spectrum disorders as well as mental retardation [Coffey, 2014] (Fig. 2). In contrast to TBD phosphorylation, PRD phosphorylation by JNK1 leads to increased microtubule binding [Komulainen et al., 2014] (Table II). Among those kinases mentioned here, JNK1 has emerged as a dominant regulator of microtubule homeostasis in neurons. In perinatal mice lacking *Jnk1*, microtubule stability is already decreased in the neocortex, as inferred from increased levels of tyrosinated tubulin [Westerlund et al., 2011]. This suggests that JNK1 is required to maintain microtubule homeostasis in developing brain. Moreover, in the neocortex of one month old mice lacking *Jnk1*, microtubule length is significantly decreased [Chang et al., 2003], indicating that JNK1 continues to maintain microtubule stability during postnatal life. These findings have identified JNK1 as a dominant regulator of microtubule homeostasis in neurons. The effects of JNK1 on microtubule stability are thought to be mediated by phosphorylation of MAP2 [Chang et al., 2003; Bjorkblom et al., 2005; Komulainen et al., 2014], whereas MAP1b is another target of JNK1 that is likely to contribute [Chang et al., 2003; Wang et al., 2007], but is less well studied than MAP2 in this context.

It is interesting therefore that dysregulation of the JNK pathway is implicated in a range of psychiatric disorders. Specifically, genetic anomalies in upstream regulators of JNK namely; *IL1RAPL1, ULK4, TAOK2, MKK7, JIP2/3*, and in *JNK* itself (Fig. 2), are associated with schizophrenia, autism spectrum disorders and intellectual disability [Shoichet et al., 2006; Baptista et al., 2008; McCarthy et al., 2009; Pavlowsky et al., 2010; de Anda et al., 2012; Winchester et al., 2012; Coffey, 2014; Lang et al., 2014]. *TAOK2* and *ULK4* regulate dendrite growth [Mochizuki

et al., 2011; de Anda et al., 2012] while physiologically active JNK1 has been shown to be a dominant regulator of dendritic architecture *in vivo* [Chang et al., 2003; Bjorkblom et al., 2005; Komulainen et al., 2014]. Thus in *Jnk1–/–* mice, dendritic field size is increased in cortical layer V and decreased in layers II/III and this phenotype is rescued by expression of $MAP2^{T1619D/T1622D/T1623D}$ [Komulainen et al., 2014] (Fig. 1). Similarly in neurons isolated from *Jnk1–/–* mice, or in JNK inhibitor-treated neurons, dendrite complexity is increased. This regulation of dendrite complexity has been shown to be a consequence of JNK activity in the cytoplasm [Bjorkblom et al., 2005]. Additional microtubule regulator targets of JNK1 such as stathmin 2 (SCG10) also contribute to dendrite architecture in neurons [Tararuk et al., 2006]. Based on these studies, one can anticipate that the genetic disruption of *TAOK2*, *ULK4*, and *MKK7* that occurs in patients, will directly disturb the phosphorylation of JNK1 effectors of microtubule homeostasis such as MAP2, MAP1b, and stathmin-2. Depending on the brain region, inhibition of JNK1 activity can increase or decrease dendritic length, that is, alter the synaptic integration space [Komulainen et al., 2014]. This will have a direct impact on synaptic transmission.

Other Microtubule Regulatory Proteins Implicated in Psychiatric Disorders

MAP6/Stable Tubule Only Polypeptide (STOP) and Schizophrenia

MAP6, also known as STOP, is a protein involved in microtubule binding in many cell types, but it is especially enriched in neurons. MAP6 is encoded by a single gene but exists in many splice forms in mammalian cells [Bosc et al., 1996]. It binds to and stabilizes microtubules and induces nocodazole resistance and tubulin detyrosination [Bosc et al., 2003]. Like MAP2, MAP6 stabilizes microtubules by bridging the binding between adjacent microtubules and this is regulated by calmodulin binding [Lefèvre et al., 2013]. Genetic deletion of MAP6 leads to a severe phenotype where mice display a range of features associated with schizophrenia. These include anxiety, impaired cognition, hyperactivity, and social withdrawal [Fournet et al., 2012], altered serotonergic function [Fournet et al., 2010] and hypoglutamatergic activity [Brenner et al., 2007]. Specifically, MAP6 deletion impairs cognitive function by disrupting synaptic connectivity [Fournet et al., 2012; Gozes, 2011]. Single nucleotide polymorphisms (SNPs) in *MAP6* have been identified alongside increased *MAP6* mRNA in the prefrontal cortex of patients with schizophrenia. These findings together with the data from animal models suggest that further study of the processes whereby MAP6 could contribute to the schizophrenia is warranted [Shimizu et al., 2006].

TPPP

Increased risk for developing depression in children with early traumatizing experiences of maltreatment has been correlated to epigenetic changes in *TPPP* genes, which encode the tubulin polymerization promoting protein that is specifically expressed in brain. TPPP modifies microtubule dynamics and stability. It is a brain specific microtubule bundling protein that is enriched in Lewy bodies [Tirián et al., 2003; Vincze et al., 2006]. A genome-wide methylation study carried out in saliva-derived DNA samples from maltreated and healthy children revealed methylation changes in TPPP establishing it as a predictor of depression [Weder et al., 2014]. In rodents subjected to the prenatal stress model of depression, TPPP protein is upregulated [Głombik et al., 2015]. TPPP is also associated with neurodegenerative disease. It interacts with alpha-synuclein leading to formation of inclusion bodies [Szunyogh et al., 2015]. These studies highlight TPPP as microtubule regulatory protein that is epigenetically regulated in depression.

CRMP-1 (collapsin response mediator protein-1) also known as DRP-1 (dihydropyriminidase-related protein-1) and **CRMP2** (DRP-2 or DPYSL2) are tubulin binding proteins that are enriched in the hippocampus and dentate gyrus of adult brain. They regulate neuronal differentiation and modulate L- and V-type calcium channel activity [Quach et al., 2015]. Binding of CRMP2 to tubulin increases microtubule formation and this binding is decreased upon phosphorylation by Rho kinase [Fukata et al., 2002]. Phosphorylated CRMP1 and CRMP2 are found in dendrites and are important for dendrite patterning. Significantly, *CRMP1* and *CRMP2* are susceptibility genes for psychiatric disorders [Quach et al., 2015]. Thus the *CRMP1* gene locus on chromosome 4p16 is associated through suggestive evidence with bipolar disorder [Baron, 2002], while the *CRMP2* (*DPSYL2*) gene locus on chromosome 8p21 is within a schizophrenia susceptibility region [Hensley et al., 2010], and is linked broadly through genetic and translational studies with psychiatric disease including mood disorders [Quach et al., 2015]. Consistent with this genetic linkage data, proteome-wide analysis has revealed increased expression of CRMP2 in postmortem brains from individuals with schizophrenia and MDD, while CRMP1 is increased in bipolar patients [Prabakaran et al., 2004; Beasley et al., 2006]. Further study will be needed to understand better how these tubulin binding proteins confer susceptibility.

Disrupted in Schizophrenia-1 (DISC1)

DISC-1 is a candidate schizophrenia gene that affects cytoskeletal conformation. It plays several crucial roles during development of the central nervous system where it

regulates axonal transport and microtubule organization through interaction with nuclear distribution element-like protein and pericentriolar material-1 protein [Gurling et al., 2006; Taya et al., 2007]. Genetic association studies have identified a S704C SNP in DISC-1, which increases the risk to develop schizophrenia as well as MDD. Healthy subjects carrying this allele display reduced gray matter volume in the cingulate cortex while diffusion tensor imaging has revealed disrupted white-matter integrity in the prefrontal cortex of S704C-DISC-1 carriers [Hashimoto et al., 2006]. This is consistent with abnormal grey matter volumes and white matter ultra-structures in patients with mood disorders and schizophrenia. Interestingly, the S704C-DISC-1 variant fails to interact with NDEL1, indicating that the microtubule cytoskeleton disruption contributes to the pathologies in these individuals [Hashimoto et al., 2006].

Therapeutic Intervention in Psychiatric Disorders; the Microtubule Cytoskeleton as a Target

Antioxidant Treatment and the Microtubule Cytoskeleton

Oxidative stress is a major factor that causes aberrant cytoskeletal organization. Free radicals can depolymerize microtubules leading to loss of polarization and induction of apoptotic signaling [Sponne et al., 2003]. Thus, an early response to oxidative stress involves modification of β-tubulin and MAP2 microtubule binding leading ultimately to neuronal death [Benítez-King, 2006]. It has been shown in many cases that melatonin acts as a neuronal antioxidant and improves outcome in cases where the cytoskeleton is disrupted, such as in experimental models of Alzheimer's disease [Cardinali et al., 2010], Parkinson's disease associated sleeping disorders [Mayo et al., 2005] and Huntington's disease [Kalliolia et al., 2014]. Moreover, elevated levels of MAP2 are found in melatonin-exposed cells, providing a possible mechanism for the increased microtubule polymerization and dendrite stabilizing action of this hormone [Melendez et al., 1996; Prieto-Gomez et al., 2008]. However, the use of melatonin as a pharmacological agent in the treatment of depression or anxiety remains largely experimental.

Tubulin as a Candidate Biomarker or Therapy

A possible use of tubulin as a biomarker for diagnosis of depression in human peripheral cells (i.e., platelets) has been proposed [Cocchi et al., 2010].These authors advocate an underlying role for cytoskeletal rearrangements in psychiatric dysfunction according to the quantum theory of consciousness [Hameroff, 2007]. While this remains controversial, the idea of employing bionic microtubules to rescue impaired function has been proposed [Woolf, 2009]. These would be synthetically produced and introduced to neurons in an attempt to rescue functional deficits that result from disease associated perturbation of the microtubule structure. In support of this proposal, neuronal precursors derived from olfactory biopsies from individuals with schizophrenia and bipolar disorder display perturbations in microtubule organization. Bipolar patient cells exhibit shortened microtubules while those from individuals with schizophrenia are disorganized, indicating that a characteristic cytoskeletal phenotype is associated with each of these disorders [Solis-Chagoyan et al., 2013].

Neurosteroids

A therapeutic approach aiming to ameliorate the defects in dendritic field size that occur in depression uses a MAP2 binding drug, microtubule-associated protein/neurosteroidal pregnenolone (MAPREG), which is a synthetic neurosteroid. In the forced swim test of behavioral despair (a frequently used model of depression), treatment with MAPREG protects rodents from developing a depressed state. It elicits a quicker and stronger anti-depressant action than the SSRI fluoxetine suggesting a different mechanistic action [Bianchi and Baulieu, 2012]. Similarly, MAPREG was shown to abolish stress-triggered avoidance behavior in the tree shrew evoked by psychosocial stress [Parésys et al., 2015]. This study also shows that a 4-week treatment with MAPREG prevents the loss of α-tubulin acetylation and sleep disturbances that occur following psychosocial stress.

Neurosteroids are synthetized de novo from cholesterol in the nervous system [Plassart-Schiess and Baulieu, 2001]. They were first identified as microtubule and MAP2-binding partners upon co-purification with pregnenolone (PREG) [Fellous et al., 1977]. To date, MAP2 proteins are considered to be the only brain-specific receptors for neurosteroid 3-β-hydroxy-delta 5-compounds, such as PREG, pregnenolone-sulfate (PREG-S), dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S) [Tsutsui et al., 2000; Plassart-Schiess and Baulieu, 2001; Fontaine-Lenoir et al., 2006]. In the brain, these molecules are synthetized in multiple cell types, including glia and Purkinje cells [Tsutsui et al., 2000; Fontaine-Lenoir et al., 2006]. They can also derive from steroidal precursors originating in the periphery [Baulieu and Schumacher, 1997]. Binding of PREG and it derivatives enhances the stimulatory effect of MAP2 on microtubule polymerization [Murakami et al., 2000] and promotes neurite growth [Fontaine-Lenoir et al., 2006], while other neurosteroids do not have this effect. Neurosteroids have been shown to have beneficial effects on neurons. They can enhance neuronal survival and improve long-term memory [Roberts et al. 1987; Flood et al., 1992], while they also exert a neuroprotective function [Cardounel et al., 1999; Marx et al., 2000], and

stimulate the birth of new neurons in adult hippocampus [Karishma and Herbert, 2002].

Glutamatergic Receptor Drugs

Antagonists of glutamatergic receptors (especially ketamine and MK-801 acting on NMDA receptors) are known to have rapid and long-lasting antidepressant actions in both treatment-resistant patients and in animal models of depression [reviewed in Browne and Lucki, 2013]. Interestingly, MAP2 interacts with the NMDA-type glutamate receptor subunit NR2B [Kapitein and Hoogenraad, 2011; Kapitein et al., 2011], and the antidepressant action of the NMDA receptor antagonist MK-801 depends on this association. It also depends on the anchoring of PKA by MAP2 at this complex [Corcoran et al., 2015]. This data indicates that MAP2 plays an integral role in the regulation of mood homeostasis via glutamatergic signaling.

Lithium and Microtubule Cytoskeleton Regulation in Depression

Lithium is the gold standard mood stabilizing drug used to treat bipolar disorder. A gene enrichment study involving data from 7000 patients and controls, identified that microtubule-associated pathways may be genetically disrupted in patients with bipolar disorder [Drago et al., 2016]. They further concluded that this dysregulation relates to lithium action. Lithium has a range of known molecular targets, among which GSK-3, which is directly inhibited by lithium, is implicated in depression [Beurel et al., 2011]. Inhibition of GSK-3 by lithium decreases phosphorylation of tau and MAP1B leading to microtubule remodeling [Lucas et al., 1998; Goold et al., 1999; Grimes and Jope, 2001; Bélanger et al., 2002]. This regulation of the cytoskeleton may help restore impaired neuroplasticity in the hippocampus and amygdala, brain areas with major involvement in mood disorders. While more data is needed to ascertain whether microtubule remodeling contributes to the therapeutic effect of lithium, a large number of targets are phosphorylated by GSK-3 itself [Cole, 2013] and thus, the actions of lithium in the brain are likely to be complex [Doble and Woodgett, 2003].

Together, these studies indicate that PTM of MAPs and microtubule regulators is disturbed in animal models of psychiatric disorders and in postmortem tissues and cell biopsies from patients. Some of these modifications have been shown to be rescued by antidepressant drug treatments, while microtubule stabilizing drugs have also shown beneficial behavioral consequences. In clinical studies, genetic associations are found between regulators of the microtubule cytoskeleton and impaired mental health, while diminished MAP2 has become a signature hallmark of psychiatric disease. This is perhaps not surprising given that microtubules play an essential role in forming the polarized neuronal architecture that is required for appropriate synaptic connectivity. The coming years should clarify more molecular details so that repair strategies can be developed.

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