



The Depression/Schizophrenia Continuum: Does Cytoskeletal Tensegrity Play a Role?

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ABSTRACT

There is mounting evidence that schizophrenia and depression are polar extremes of the same processes. The neuronal microtubule cytoskeleton is regulated through the actions of microtubule-associated proteins, the centrosome, tubulin posttranslational modifications and differential expression of tubulin isoforms. It is beginning to be thought that they may be important in the development of consciousness itself. It is proposed here that cytoskeletal tensegrity architecture plays a pivotal role in the etiology of psychiatric conditions. If the subcellular architecture is too tense, schizophrenia, if too loose, depression. This review focuses on the role of the microtubule cytoskeleton in schizophrenia, bipolar disorder and depression. Schizophrenia appears to be a disorder of microtubule architecture, depression one of intracellular transport along microtubules and bipolar disorder shares aspects of both schizophrenia and depression. Both current and potential treatments for these disorders target the microtubule cytoskeleton.

Key Words: Antidepressants, Autism, Cytoskeleton, Microtubules, Schizophrenia, Tensegrity

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Introduction

“And tell me, Sona, when the strings of your lute were too taut, was your lute tuneful and easily playable?”

“Certainly not, Oh Lord.”

“And when the strings of your lute were too loose, was your lute tuneful and easily playable?”

“Certainly not, Oh Lord.”

(From “Parable of the Lute” in “Teachings of the Buddha”, Kornfield and Fronsdal 2007)

Evidence for a Depression/Schizophrenia Continuum

Several lines of evidence are beginning to suggest that depression and schizophrenia may be polar ends of a continuum. It has generally been thought that depression is a condition concerning the serotonergic system and schizophrenia the dopaminergic. However, some work posits a role

for the dopaminergic in depression and (Dailly *et al.*, 2004) serotonergic in schizophrenia (Eggers 2013) so maybe the two are not as separate as was once thought. Indeed antidepressants are now thought to cause autism in infants when taken by pregnant mothers. Although there have been some contrary studies, the most rigorous to date found they nearly double the risk (Boukhris *et al.*, 2016). Anecdotal evidence is also accruing that antidepressants cause psychosis (Goldberg and Truman 2003). Thus drugs used to treat depression can cause schizophrenia-spectrum disorders.

Other studies suggest a depression/schizophrenia continuum. Psychotomimetics, which recapitulate psychosis-like symptoms such as ketamine, sometimes display powerful antidepressant effects (George *et al.*, 2017). While research is underway to try to develop treatments for depression without the

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side-effects it certainly seems possible that the two are inextricably linked. Another piece of evidence suggesting the depression/schizophrenia continuum comes from population studies. African-Americans have higher rates of schizophrenia (Schwartz and Blankenship 2014) than the general population yet have decreased rates of depression (Dunlop *et al.*, 2003). Thus their mental health is “frame-shifted” with respect to the Western component of the population. Interestingly it appears that there may be a societal component to mental health as well (Boydell *et al.*, 2001).

Microtubules

Structure and function

Microtubules are ubiquitous cytoskeletal components made up of protofilaments of $\alpha\beta$ -tubulin heterodimers. Typically there are 13 protofilaments forming a tube around an inner lumen. Microtubules are dynamic structures. When it polymerises, β -tubulin is bound to GTP and this GTP can then be hydrolysed to GDP (Weisenberg, 1972). GDP-bound tubulin is more prone to depolymerisation than GTP-bound tubulin (Weisenberg *et al.*, 1976). Thus as long as there is a cap of GTP-tubulin at the plus end of a microtubule it will continue to grow. However, if the hydrolysed GDP-tubulin reaches the plus end of the microtubule it will undergo rapid shrinkage, or “catastrophe”. If GTP-tubulin begins to be added to the plus end once more this is called “rescue” and the microtubule will begin to grow again. The coexistence of growth and shrinkage at the plus end of a microtubule is known as “dynamic instability” (Mitchison and Kirschner, 1984). The rate of microtubule polymerisation, depolymerisation and catastrophe varies depending upon which microtubule-associated proteins (MAPs) are also present.

Some proteins, notably Tau and MAP2 in neurons, have a stabilising effect on microtubules (Mandelkow and Mandelkow, 1995). Motor proteins, including kinesin, dynein and dynamin “walk” along microtubules carrying cargo proteins (Wang *et al.*, 2015). Microtubule function is also modulated through differential expression of α - and β -tubulin isoforms. The different isoforms have different characteristics and this can alter the binding of MAPs or drugs to microtubules (Ganguly *et al.*, 2011). In mammalian cells, microtubules are nucleated from the centrosome which is surrounded by a mass of pericentriolar

proteins. The protein composition of centrosomes and pericentriolar material as now been largely elucidated through proteomic techniques and many of these proteins have been shown to be important in microtubule function (Woodruff *et al.*, 2014). Centrosomes consist of two centrioles at right angles, each with a γ -tubulin ring complex from which the microtubule grows (Kollman *et al.*, 2010).

Microtubules in neurons

Brain-derived neurotrophic factor (BDNF) is one of four principal mammalian neurotrophins, the others being nerve growth factor (NGF), neurotrophin-3 (NT3) and neurotrophin-4 (NT4). Terminals of axons bear receptor tyrosine kinases (TrkA, TrkB, TrkC and the p75 neurotrophin receptor (p75NTR)) that bind the neurotrophins. Following this, the neurotrophins are endocytosed and trafficked to the cell nucleus via the microtubule cytoskeleton and having done this, induce gene expression. Enhancement of Glycogen Synthase Kinase (GSK3 β) activity blocks BDNF-dependent TrkB endocytosis through a dynamin1: a microtubule associated protein involved in retrograde transport (Pareyson *et al.*, 2015), again demonstrating the key role of the microtubule cytoskeleton in neurotrophic support (Liu *et al.*, 2015). These synaptogenic pathways are crucial for associative learning. BDNF enhances synaptic transmission, facilitates synaptic plasticity, and promotes synaptic growth in both developing and adult brains (Sun *et al.*, 2015). It also maintains the mature dendritic spine phenotype (Kellner *et al.*, 2014) and mediates exercise-induced spatial learning and memory (Alomari *et al.*, 2013).

Posttranslational modifications of microtubule are being shown to be very important in microtubule function, in neurons and elsewhere (Janke and Bulinski, 2011). α -tubulin is acetylated at Lys40. This is the only known modification of tubulin in the microtubule lumen, acting as a slow clock for microtubule lifetimes (Szyk *et al.*, 2014). Thus older and more stable microtubules have an increase in acetylated tubulin. One protein (α -tubulin acetyltransferase (ATAT1)) (Vasudevan *et al.*, 2015) and one protein complex (Elongator) which consists of subunits Elongator complex proteins 1-6 (ELP1-6) (Creppe *et al.*, 2009) are known to catalyse microtubule acetylation. Two proteins deacetylate α -tubulin, Histone Deacetylase (HDAC6) (Hubbert *et al.*, 2002) and Sirtuin 2 (North *et al.*, 2003).



ATAT1 and Sirtuin 2, and Elongator and HDAC6 appear to act in tandem. Microtubule acetylation has functional consequences, promoting kinesin-1 binding and thus transport of cargo proteins (Reed *et al.*, 2006). Thus tubulin acetylation plays a key role in neurotropic support in neurons, facilitating the transport of neurotropic factors along microtubules. Other microtubule posttranslational modifications, including tyrosination by tubulin tyrosine ligase (Prota *et al.*, 2013), also have functional consequences (Syzk *et al.*, 2011).

It is beginning to be thought that the neuronal microtubule cytoskeleton is important in the development of consciousness. The Penrose-Hameroff “Orchestrated Objective Reduction” (Orch Or) theory suggests that when a sufficient mass of tubulin subunits are quantum-mechanically linked, the quantum waveform will spontaneously collapse, resulting in a conscious moment (Hameroff and Penrose, 2003). While this is still highly controversial (Reimers *et al.*, 2014), there is certainly evidence linking the microtubule cytoskeleton to conscious thought. Anaesthesia acts via a destabilisation of microtubules in brain neurons (Emerson *et al.*, 2013) and hallucinogens may also indirectly disrupt neuronal microtubules (Van Woerkom, 1990). Electric pulses travel quickly along microtubules, allowing ultrafast signalling (Sahu *et al.*, 2013) and memory may be stored in microtubule lattices through kinase activity of Calcium/calmodulin-dependent Kinase CaMKII, with the potential for storage of vast amounts of information (Craddock *et al.*, 2012).

It thus seems timely to look at how dysfunction of the neuronal microtubule cytoskeleton may contribute to the pathogenesis of psychiatric disorders, which display perturbations to the flow of consciousness (Venkatasubramanian, 2015). Here I focus on schizophrenia, bipolar disorder and depression. These are probably the psychiatric disorders that have received the greatest amount of attention in the scientific literature. Schizophrenia is a disorder with principally psychotic symptoms (Lally and MacCabe, 2015), depression is an affective (mood) disorder (Breland *et al.*, 2015) and bipolar disorder sufferers can display both psychotic and affective symptoms (Altamura *et al.*, 2015). A “tensegrity” model of the cytoskeleton has been suggested, whereby microtubules and actin act as compression-resistant and tensional

components within cells respectively (Figure 1; Ingber *et al.*, 2014).

I have previously suggested that the development of the brain may depend upon both cytoskeletal thermal ratchets and cytoskeletal tensegrity (Gardiner *et al.*, 2008). There is burgeoning interest in mechanotransduction in the nervous system and if the tensegrity model is correct then function of the mature brain may depend upon these processes as well. Indeed the microtubule-severing protein katanin preferentially severs microtubules at points of stress and this severing is important in differentiation of neurons, through breaking dendrites (Lee *et al.*, 2009). It is not such an extrapolation to suggest that the reduced complexity of the cerebral cortex seen in schizophrenia sufferers (Ha *et al.*, 2005) might be due to overactive microtubule severing. Thus perhaps mental illness can be seen as a disorder of cellular architecture. If the cytoskeletal network is too tense, schizophrenia results. If it is too loose, depression results.

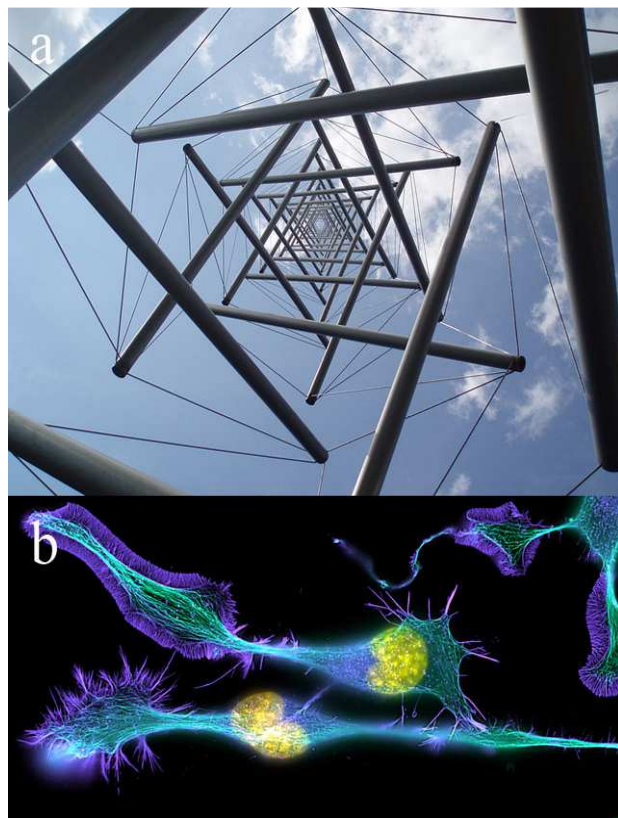


Figure 1. (a) “Needle Tower” by Kenneth Snelson demonstrating tensegrity architecture of tensional and compression-resistant elements. (b) Microtubules (green), actin (purple) and DNA (yellow) in differentiating neurons. Photo by Dr Torsten Wittmann, The University of California, San Francisco, USA. Photo used with permission

Schizophrenia and the microtubule cytoskeleton

Microtubule-associated proteins

It has been suggested that the microtubule cytoskeleton, and in particular its microtubule-associated proteins may play an important role in the pathogenesis of schizophrenia (Benítez-King *et al.*, 2007). Dendrites are beginning to be seen as playing a key role in the pathogenesis of schizophrenia. MAP2 and spinophilin are dendritic marker proteins. Both typical and atypical antipsychotics induce an increase microtubule-stabilising protein MAP2 mRNA in the hippocampus, occipitoparietal and retrosplenial cortices, which are principal sites of pathology in schizophrenia (Law *et al.*, 2004). No change was detected in spinophilin mRNA, suggesting that dendritic spines are not affected selectively by these drugs (Law *et al.*, 2004). A previous study (Arnold *et al.*, 1991) also found abnormal expression of MAP2 and MAP5 in subfields of the hippocampus in schizophrenia. Loss of MAP2 is closely linked through correlation to dendritic spine pathology of the auditory cortex, which is involved in onset of schizophrenia (Shelton *et al.*, 2014). Presumably this could contribute to auditory hallucinations that develop in schizophrenia. Interestingly, around 70-80% of schizophrenia sufferers smoke. While this has been seen as a possible co-morbidity (Evins *et al.*, 2015) there is also the possibility that it is a form of self-medication (Winterer 2010). Indeed nicotine prevents glutamate-induced proteolysis of MAP2 in cultured cerebellar neurons (Minana *et al.*, 1998). There is similarity in structure and function between MAP2 and another microtubule-associated protein Tau, which is involved in the pathogenesis of Alzheimer's disease. This raises the interesting prospect that treatments for Alzheimer's may be able to be translated into schizophrenia treatments.

Exonic deletions of *unc-51-like kinase* (*ULK4*) were present in schizophrenia patients from the International Schizophrenia Consortium but not in controls. Subsequently, similar deletions were found enriched in Icelandic schizophrenia and bipolar patients. ULK4 regulates signalling pathways including Janus kinase (JNK) and knockdown of ULK4 disrupts microtubule composition, neuritogenesis and cell motility (Lang *et al.*, 2014). Stable tubulin only polypeptide (STOP/MAP6) mice show behavioural abnormalities related to schizophrenia. Since mouse models of psychiatric

schizophrenia are a work in progress (Jones *et al.*, 2011), it has been suggested that STOP Het mice might be useful in evaluating preventative treatments (Volle *et al.*, 2012). Indeed the small peptide NAP, an active fragment of activity-dependent neuroprotective protein (ADNP) reduces hyperactivity and improves visual memory in STOP-deficient mice. This may be through its role in neuronal plasticity (Gozes, 2011). And lastly, the actin-microtubule crosslinking protein Adenomatous Polyposis Coli is involved in the etiology of schizophrenia (Cui *et al.*, 2005). Perhaps this is through its role in regulating neuronal tensegrity?

Neuritogenesis and differentiation

Disrupted in schizophrenia 1 (DISC1) is the protein which influences microtubule dynamics with the clearest link to schizophrenia. Originally identified as having an open reading frame at a breakpoint of a balanced chromosomal translocation inherited in a large Scottish pedigree (Millar *et al.*, 2000), more recent linkage and association studies indicate that DISC1 has a role in schizophrenia in the general population (Ekelund *et al.*, 2001; Hodgkinson, 2004). Indeed there are alterations in DISC1 levels and subcellular distribution in bipolar and schizophrenia patients, suggesting a possible role during early neural development (Munoz-Estrada *et al.*, 2015). In mice a schizophrenia-associated mutation perturbs cerebral cortex development (Kamiya *et al.*, 2005). DISC1 forms a functional complex with nude neurodevelopment protein 1-like 1 (NDEL1), which regulates microtubule organisation during cell division and neuronal migration (Narayanan *et al.*, 2011). However, mutation in DISC linked to schizophrenia causes a change in the oligomerisation of the protein, exhibiting higher order self-oligomerisation but not interfering with its binding to NDEL. β -tubulin expression is decreased in the anterior cingulate cortex and increased in the dorsolateral prefrontal cortex in schizophrenia. β -tubulin isoform have been shown to play distinct roles in neuronal differentiation and cell viability (Moehle *et al.*, 2012).

The centrosome

DISC1 also interacts with kendrin, which provides microtubule nucleation sites through anchoring the γ -tubulin ring complex to the centrosome (Takahashi *et al.*, 2002). Further evidence links centrosomal function and the microtubule



cytoskeleton to schizophrenia. Another protein whose gene is sometimes mutated in schizophrenia, serologically defined colon cancer antigen 8 (SDCCAG8), is involved in centrosome function. It is important in recruiting pericentriolar material 1 to the centrosome and knockdown or disruption of this gene results in impaired centrosomal recruitment of γ -tubulin and pericentrin. Its disruption leads to microtubule disorganisation, decouples the centrosome and the nucleus and disrupts neuronal migration (Insolera *et al.*, 2014). NDE1: which is a protein related to NDEL1 and similarly involved in centrosomal function, microtubule organisation and neuronal migration, has been found to be linked to schizophrenia. Single-nucleotide variants of *NDE1*: which are becoming to be seen as increasingly important in disease through deep sequencing, have been found to be present in bipolar disorder and schizophrenia. Functional assays of the ser214phe variant implicated in schizophrenia found that it interfered with NDE1 and 14-3-3 epsilon, a protein important in neurodevelopment (Kimura *et al.*, 2014).

Intracellular transport

Other microtubule-dependent functions of DISC1 are beginning to be discovered. For example, it is important in the transport of cargoes along microtubules by kinesin. A schizophrenia-related mutation disrupts the assembly between the kinesin-1 cargo adaptor fasciculation and elongation protein zeta 1 (FEZ1) and the cargo protein synaptogamin-1. Lithium, used in the treatment of bipolar disorder, can normalise this interaction suggesting this maybe an important dimension of the drug's effect (Flores *et al.*, 2011). Kinesin-based transport of GluR2 along microtubules in high activity prefrontal cortex neurons is disrupted by the dopamine D₄ receptor, which has been implicated in schizophrenia. This is through suppression of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor activity and leads to a decrease in microtubule stability (Yuen and Yan, 2011). BDNF, through its roles in neurodevelopment and cognitive function, has been suggested to be involved in schizophrenia (Nieto *et al.*, 2013), although there appears to be little experimental evidence to support this. However, if this is the case, here again microtubules would be important due to their

role in the transport of neurotrophic factors between cell periphery and the nucleus.

Bipolar disorder

There is increasing evidence that disruption of BDNF signalling and its transport along microtubules plays a role in the pathogenesis of bipolar disorder. Various data have converged showing that the val66met allele of *BDNF* is associated with selective minor deficits in subjects with schizophrenia, bipolar disorder, and normal controls. Paradoxically, the better functioning val66val allele is associated with increased risk for bipolar disorder. Mood stabilisers including lithium and valproate increase BDNF (Post 2007). Indeed BDNF levels are decreased in depressive and manic episodes and return to normal levels in euthymia. BDNF levels also decrease as the disorder progresses (Grande *et al.*, 2010). A study of two cohorts of mood-stabilised bipolar patients found that they had an increase in mature BDNF and a decrease in levels of its precursor proBDNF. This may provide an opportunity to develop a clinical test for bipolar disorder, which can be difficult to diagnose in its early stages (Södersten *et al.*, 2014).

There is altered microtubule organization in neural precursors (olfactory neuroepithelial cells in culture) from bipolar patients, with a prevalence of short microtubules. Bipolar neurons also showed a decrease in amounts of tubulin in total homogenates and 40% decrease in the globular fraction. Schizophrenia neurons displayed disorganised microtubules (Solís-Chagoyán *et al.*, 2013). There is genetic evidence for an association of microtubules with bipolar disorder, which is heritable. A study of families with Ashkenazi Jewish descent using single-SNP and haplotype transmission/disequilibrium tests found that α -tubulin 8 was implicated in bipolar disorder, but not in schizophrenia (Fallin *et al.*, 2005). Lithium reduces Tau phosphorylation through inhibition of glycogen synthase kinase 3 (GSK3). This leads to increased binding of Tau to microtubules and thus increased microtubule stability (Hong *et al.*, 1997).

Depression

Microtubules and tubulin post-translational modifications

There is evidence that the pathogenesis of depressive disorders is associated with abnormalities in neuronal brain microtubule



function. Disruption of microtubules and also the actin cytoskeleton in depression may cause dendritic regression and decrease in the number of dendritic spines, which are hallmarks of the disorder (Wong *et al.*, 2013). The long-term delay between the onset of treatment with antidepressants and symptom improvement may be due to the time it takes to rescue these alterations. Changes in the microtubule cytoskeleton under depression and its treatment include alteration of the expression of α -tubulin isoforms and changes in tubulin posttranslational modifications including α -tubulin acetylation. Inhibition of the α -tubulin deacetylase HDAC6 increases α -tubulin acetylation in the mouse brain and stimulates exploratory behaviours in novel environments. Indeed a behaviourally inactive dose of the novel HDAC6 inhibitor ACY-738 potentiates the anti-immobility activity of the selective serotonin reuptake inhibitor citalopram (Jochems *et al.*, 2014). Serotonin slows locomotion in *Caenorhabditis elegans* and this fact has been used to develop a screen for mutants affected in serotonin signalling. One of the genes identified was *ELPC-3* which is an α -tubulin acetylase of the Elongator complex (Gürel *et al.*, 2012). There is electrochemical and behavioural evidence for a direct relationship between serotonin signalling and the microtubule cytoskeleton. Tyrosination of α -tubulin is another posttranslational modification implicated in serotonin signalling in both “physiological” and “pathological” states (Crespi, 2010).

Neurotrophic support

BDNF and its receptor TrkB are upregulated by both antidepressants and electroconvulsive shock treatment. These treatments increase neurogenesis and synaptic numbers in several brain areas including the hippocampus and prefrontal cortex. This suggests that neurotrophic support is crucial in neuronal plasticity during depression and its treatment (Castrén and Rantamäki 2010). Thus here is a possible link between depression and kinesin-based BDNF transport along microtubules. Kinesins may be important in depression in other roles apart from the trafficking of BDNF. Phosphorylation of kinesin light chain 2 by GSK-3 β causes dissociation of the KLC2/GluR1 complex and pharmacological inhibition of this phosphorylation reduces depression behaviours in mice (Du *et al.*, 2010).

Microtubule-associated proteins

Microtubule-associated proteins may play a role in depression. A study of genes expression under the antidepressant imipramine and St John's wort (also used in the treatment of depression) identified *MAP1A* as one of only six genes upregulated in both treatments (Wong *et al.*, 2004). *MAP1A* may play a role in neuronal differentiation, amongst other things (Bianchi *et al.*, 2005). Imipramine selectively down-regulated *β -tubulin 5* while St John's wort upregulated *Tau* and an *α -tubulin* (Wong *et al.*, 2004). This suggests that while there are similarities in the function of both treatments when it comes to the microtubule cytoskeleton their interactions are complex. The synthetic pregnenolone-derivative MAP4343 binds *MAP2* in vitro and increases its ability to promote microtubule assembly. When administered to rats it improves performance in the forced swimming test, which is used to screen for antidepressant drugs. The drug modifies α -tubulin expression in the hippocampus, amygdala, and prefrontal cortex, suggesting positive feedback between MAPs and tubulin expression (Bianchi and Baulieu, 2012).

And so to the future....

There is a steadily growing body of evidence suggesting that microtubules are important in the development of schizophrenia, bipolar disorder and depression. It appears possible that dysregulation of brain cytoskeletal tensegrity may play a part here since similar cytoskeletal functions are differentially modulated in the three disorders. From the evidence thus far accumulated, it would appear that schizophrenia is primarily linked to the interaction of microtubules with MAPs and the centrosome, thus leading to changes in microtubule dynamics and cell motility. Depression appears to be most closely linked to dysfunction of transport along microtubules in neurons, and reduced neurotrophic support. However, it should be noted that the various regulators and functions of the neuronal microtubule cytoskeleton are interdependent. Indeed the enhancement of *MAP2*-based microtubule stabilisation is a promising treatment for depression as outlined above. In addition, psychiatric conditions form a continuum with, for example, schizoaffective disorder displaying both psychotic and affective symptoms. Indeed drugs used in psychiatry can have more than one benefit, for example, the atypical antipsychotic drug olanzapine also acts as



a mood stabiliser. Bipolar disorder, from the limited number of studies thus far, seems to display both schizophrenic- and depression-like microtubule dysfunctions. Both architectural changes to the neuronal cytoskeleton, and alterations in tubulin post-translational modifications may change the electrical conductivity of microtubules, and thus affect states of consciousness.

There is an increasing convergence between psychiatry and neurology with regard to various disorders. It is to be hoped that treatments developed in one field will be useful in the other. Valproate, which increases α -tubulin acetylation, is already used to treat epilepsy and as a mood stabiliser. Inhibitors of HDAC6 seem promising possible treatments for neurological and psychiatric disorders, although there are some caveats (Didonna and Opal, 2015). Other possible treatments which target the microtubule cytoskeleton in psychiatry are in the pipeline and it is to be hoped, one day, that they will be useful in alleviating the suffering caused by schizophrenia, bipolar disorder, depression and other such conditions.

Abbreviations

α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); α -tubulin acetyltransferase (ATAT1); brain-derived neurotrophic factor (BDNF); calcium/calmodulin-dependent kinase (CaMKII); disrupted in schizophrenia 1 (DISC1); adaptor fasciculation and elongation protein zeta 1 (FEZ1); glycogen synthase kinase (GSK3 β); histone deacetylase (HDAC6); microtubule-associated proteins (MAPs); nudE neurodevelopment protein 1-like 1 (NDEL1); nerve growth factor (NGF); neurotrophin-3 (NT3) and neurotrophin-4 (NT4); p75 neurotrophin receptor (p75NTR); serologically defined colon cancer antigen 8 (SDCCAG8); receptor tyrosine kinases (TrkA, TrkB, TrkC); unc-51-like kinase (ULK4)

Conflict of Interest

JG has no conflict of interest

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