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Altered microtubule dynamics in neurodegenerative disease: Therapeutic potential of microtubule-stabilizing drugs

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ABSTRACT

Many neurodegenerative diseases are characterized by deficiencies in neuronal axonal transport, a process in which cellular cargo is shuttled with the aid of molecular motors from the cell body to axonal termini and back along microtubules (MTs). Proper axonal transport is critical to the normal functioning of neurons, and impairments in this process could contribute to the neuronal damage and death that is characteristic of neurodegenerative disease. Although the causes of axonal transport abnormalities may vary among the various neurodegenerative conditions, in many cases it appears that the transport deficiencies result from a diminution of axonal MT stability. Here we review the evidence of MT abnormalities in a number of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and traumatic brain injury, and highlight the potential benefit of MT-stabilizing agents in improving axonal transport and nerve function in these diseases. Moreover, we discuss the challenges associated with the utilization of MT-stabilizing drugs as therapeutic candidates for neurodegenerative conditions.

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1. Introduction

As discussed throughout this special issue, a common feature of many neurodegenerative disorders is an apparent disruption of normal axonal transport that likely contributes to the neuronal dysfunction observed in these diseases. Axonal transport is critical to the health and viability of neurons, as maintenance and functioning of axonal projections, which can reach many feet in length in certain motor neurons, requires the delivery of a variety of cellular cargo to and from the axon terminus (Roy et al., 2005). The process of axonal transport depends on the integrity of the microtubule (MT) architecture within the neuron, as MTs serve as the conduits upon which cellular constituents are shuttled in both the anterograde (towards the axonal terminus) and retrograde (towards the neuronal soma) directions. The movement of materials along the MTs is facilitated by molecular motors, with kinesins responsible for anterograde transport (Hirokawa and Noda, 2008) and dyneins (Ishikawa, 2012) for retrograde transport. Thus, the faulty axonal transport observed in neurodegenerative disease could result from alterations in MT structure and/or the molecular motors required for axonal transport (Ballatore et al., 2012; Brunden et al., 2014).

As there are reviews in this issue dedicated to the molecular motors involved in axonal transport, this topic will not be further discussed in detail herein. Instead, we focus on the potential contribution of MT deficits in neurodegenerative disease. In this regard, it is important to recognize the unusual features of MTs that allow them to play a critical role in fundamental cell biological processes, such as mitosis and the distribution of intracellular organelles, as well as the more specialized function they serve in axonal transport. MTs are polymeric structures comprised of repeated assemblies of α- and β-tubulin heterodimers that form linear protofilaments which align to form MTs, with 13 protofilaments found within typical MTs (Desai and Mitchison, 1997; Wade, 2007). There are a large number of α- and β-tubulin isoforms and the composition within MTs can vary depending on cell type and developmental stage, although the differences in structure and/or function conferred by these various isoforms is not fully understood (Wade, 2007). MTs have directionality that results from the orientation of the assembled α- and β-tubulin heterodimers, such that the (−) end of a MT has an exposed α-tubulin subunit whereas the (+) end has an

Abbreviations: BBB, blood-brain barrier; CBD, cortical basal degeneration; CTE, chronic traumatic encephalopathy; EpoD, epothilone D; FTLD, frontotemporal lobar degeneration; MAP, microtubule-associated protein; MT, microtubules; MTOC, microtubule organizing center; PSP, progressive supranuclear palsy; SOD1, superoxide dismutase 1; TBI, traumatic brain injury.

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exposed β-tubulin (Fig. 1a). In many cells, the (−) end of a MT is associated with a MT organizing center (MTOC), although neurons appear not to have a classical MTOC and MTs are discontinuous in neuronal processes (Ori-McKenney et al., 2012; Stiess et al., 2010). A key property of MTs is their dynamic behavior, in which elongation can occur at the (+) end through the addition of α/β heterodimers in which each of the subunits contain a bound GTP molecule (Desai and Mitchison, 1997). This GTP is hydrolyzed to GDP after addition to a MT, and prolonged exposure of a terminal GDP-α/β heterodimer at the (+) end can lead to MT depolymerization. Such MT dissociation appears to be less common at the (−) end due to the association of the MT with a MTOC, although as noted, it appears that a classical MTOC may not exist in neurons. Thus, periods of MT growth can be followed by bouts of MT shortening and this "dynamic instability" is critical to certain cellular processes, such as the eventual collapse of MTs after the segregation of chromosomes along MTs during cell division. MTs within neurons appear to have a lower degree of dynamic instability than in most other cell types, presumably because of the specialized role that MTs play in axonal transport. MT dynamics in neurons appear to be governed, at least in part, through interactions with MT-associated proteins (MAPs) (Wade, 2007).

A predominant MAP that is thought to affect MT structure in neurons is the protein tau (Drechsel et al., 1992; Gustke et al., 1994). In the human CNS, there are six isoforms of tau (Fig. 1b) that result from differential splicing of three exons (Ballatore et al., 2007; Brunden et al., 2014). One of these alternatively spliced exons (exon 10) encodes a MT-binding repeat domain that bears sequence homology to additional MT-binding repeats within the tau molecule, such that human tau contains either 3 or 4 MT-binding repeats (referred to as 3- or 4-R tau). These MT-binding domains, in conjunction with additional tau sequences, promote MT binding. Tau appears to interact predominantly with the more labile distal regions of MTs (Black et al., 1996; Kempf et al., 1996), and there is evidence that fluorescently-tagged tau may have a highly reversible interaction with MTs (Janning et al., 2014), although there is some disagreement about the relative "dwell" time of tau on MTs (Konzack et al., 2007). Tau is believed to be a MT-stabilizing protein (Amos, 2004), as it can facilitate MT assembly in vitro and mutations in tau associated with inherited forms of frontotemporal lobar degeneration can reduce this MT-assembly activity (Hasegawa et al., 1998). However, there is also evidence to suggest tau may prevent spontaneous MT collapse through its binding to more labile regions of MTs (Black et al., 1996; Kempf et al., 1996), as well as reduce MT severing by proteins such as katanin and spastin (Qiang et al., 2006; Sudo and Baas, 2011; Yu et al., 2008) and perhaps fidgetin (Leo et al., 2015). Although a variety of in vitro and neuronal culture studies indicate that tau can affect MT structure, it should also be noted that mice in which tau has been constitutively knocked out do not show dramatic phenotypic changes, although some CNS deficits have been reported (reviewed in (Ke et al., 2012)), and the neurons from these mice may not have compromised axonal transport (Yuan et al., 2008). This might suggest that tau is not required for normal MT structure and function, although the interpretation of results from constitutive knockout mice can be confounded by compensatory changes and there is evidence of other MAPs being increased in tau knockout mice (Dawson et al., 2001; Harada et al., 1994). In addition to its presumed role in regulating MT dynamics, tau may also govern the association of MT motors (Dixit et al., 2008; Vershinin et al., 2007), and thus although there is not universal agreement, tau is believed to play a critical role in proper MT function in neurons.

2. MT dysfunction in Alzheimer's disease and related tauopathies: the potential therapeutic utility of MT-stabilizing agents.

A number of neurodegenerative diseases referred to as tauopathies are characterized by the deposition of insoluble inclusions comprised of fibrils of hyperphosphorylated tau protein (Kidd, 1963; Lee et al., 1991; Lee et al., 2001). These aggregates of tau are typically found in the neuronal soma and dendrites, where they are referred to as neurofibrillary tangles (NFTs) and neuropil threads, respectively. The major disorders among the tauopathies are Alzheimer's disease (AD) and frontotemporal lobar degenerative (FTLD) conditions associated with tau pathology (FTLD-tau), including Pick's disease, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Whereas the non-AD tauopathies have tau inclusions as their primary pathological feature, the AD brain also has extracellular Aβ peptide-containing senile plaques (Ball et al., 1997). In addition, most AD cases also have α-synuclein and TDP-43 inclusions (Irwin et al., 2013; Nelson et al., 2016), so AD is most commonly a mixed proteinopathy,

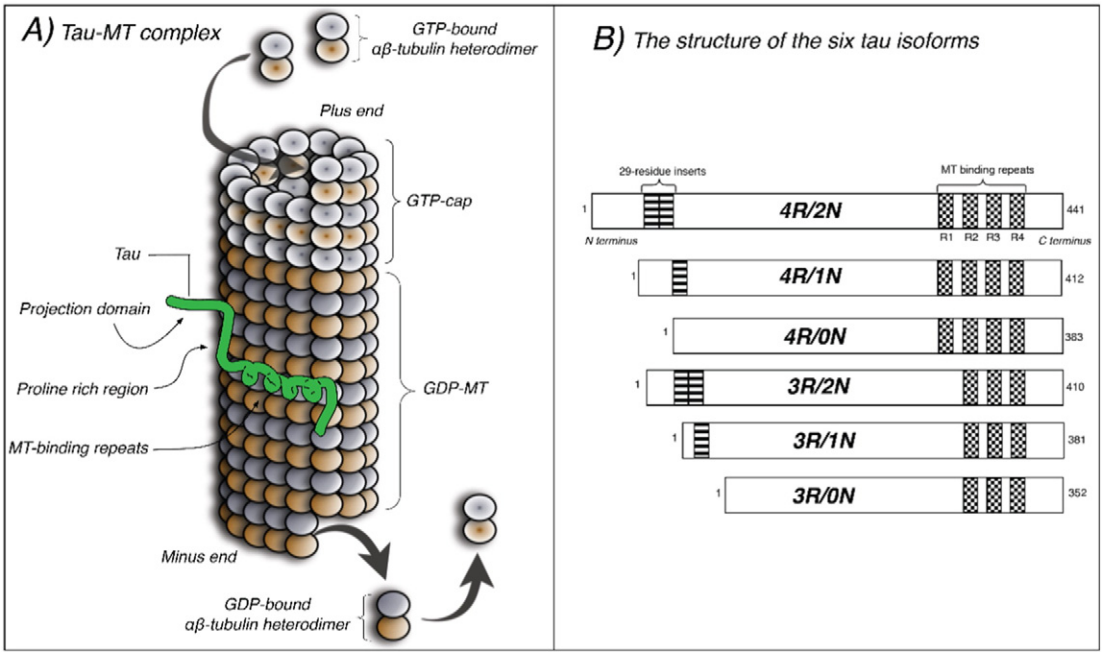

Fig. 1. A. Schematic representation of the complex between tau (drawn in green) and a MT, as well as B. the structure of the six human tau isoforms.

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