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Review

Microtubule-stabilizing agents as potential therapeutics for neurodegenerative disease

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ABSTRACT

Microtubules (MTs), cytoskeletal elements found in all mammalian cells, play a significant role in cell structure and in cell division. They are especially critical in the proper functioning of post-mitotic central nervous system neurons, where MTs serve as the structures on which key cellular constituents are trafficked in axonal projections. MTs are stabilized in axons by the MT-associated protein tau, and in several neurodegenerative diseases, including Alzheimer's disease, frontotemporal lobar degeneration, and Parkinson's disease, tau function appears to be compromised due to the protein dissociating from MTs and depositing into insoluble inclusions referred to as neurofibrillary tangles. This loss of tau function is believed to result in alterations of MT structure and function, resulting in aberrant axonal transport that likely contributes to the neurodegenerative process. There is also evidence of axonal transport deficiencies in other neurodegenerative diseases, including amyotrophic lateral sclerosis and Huntington's disease, which may result, at least in part, from MT alterations. Accordingly, a possible therapeutic strategy for such neurodegenerative conditions is to treat with MT-stabilizing agents, such as those that have been used in the treatment of cancer. Here, we review evidence of axonal transport and MT deficiencies in a number of neurodegenerative diseases, and summarize the various classes of known MT-stabilizing agents. Finally, we highlight the growing evidence that small molecule MT-stabilizing agents provide benefit in animal models of neurodegenerative disease and discuss the desired features of such molecules for the treatment of these central nervous system disorders.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; FTDP-17, frontotemporal degeneration with Parkinsonism linked to chromosome 17; HD, Huntington's disease; MAP, microtubule-associated protein; MT, microtubules; MTOC, microtubule organizing center; NFT, neurofibrillary tangles; PD, Parkinson's disease; Tg, transgenic; 3R, 3-microtubule binding repeat tau; 4R, 4-microtubule binding repeat tau.

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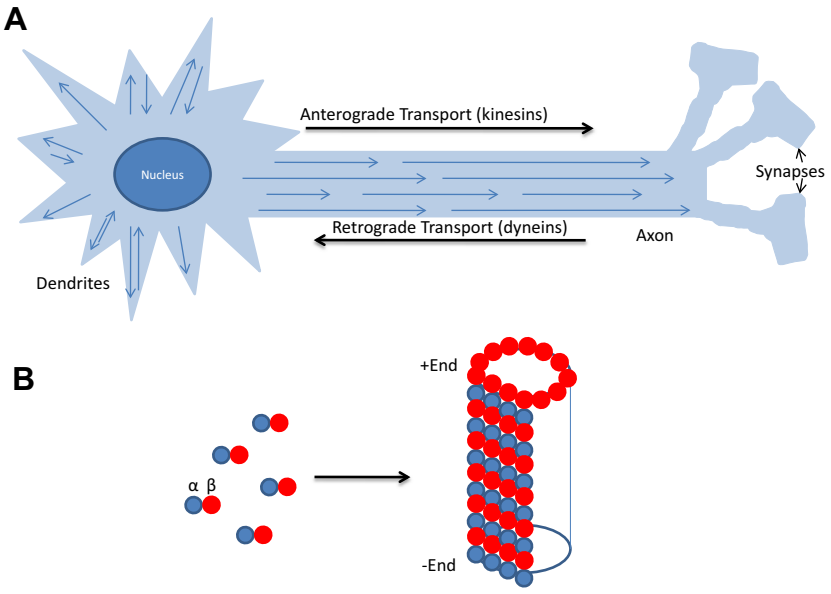

Figure 1. (A) Schematic of a neuron with microtubules (MTs) within axonal and dendritic processes. Arrowheads represent the (+) end of MTs, with dendrites containing both (+)-end distal and (−)-end distal MTs. Distinct molecular motors transport cellular cargo in the anterograde (kinesins) and retrograde (dyneins) directions along MTs. (B) MTs are comprised of aligned protofilaments comprised of α- and β-tubulin heterodimers, with exposed β-tubulin at the (+) end and α-tubulin at the (−) end.

1. Microtubules and their role in neuronal axons

Microtubules (MTs) comprise a key cytoskeletal component of all eukaryotic cells, as they play an integral role in the process of mitosis through their involvement in the segregation of chromosomes along mitotic spindles in dividing cells.[1] In addition to their role in mitosis, MTs also provide structural and functional support in cells; this is particularly evident in the nervous system, where MTs play a fundamental role in the health of neurons.[2] The axons of neurons can extend great distances (up to 3 feet for certain motor neurons in humans), and thus vital cellular components, including nutrients, mitochondria, proteins, mRNA and growth factors, must be shuttled to and from the cell body along these axonal projections. The transport of these species is largely dependent on either fast or slow axonal transport that is mediated by molecular motors that move their associated cargo along the MTs within the axonal processes. In particular, the kinesin family of MT-associated motors are involved in anterograde transport (i.e., away from the cell body),[3] whereas the dynein motors direct retrograde transport[4] toward the cell body (Fig. 1A).

MTs are typically composed of 13 aligned protofilaments, with each protofilament comprised of a polymer of repeating α- and β-tubulin heterodimers[5,6] (Fig. 1A). There are a number of α and β tubulin isoforms in mammals which may confer subtle changes to MT structure or function, although the exact significance of these differing isotypes is largely unknown.[6] The assembly of tubulin heterodimers into MTs is typically initiated at microtubule organizing centers (MTOC), with the addition of α/β heterodimers that contain one GTP each per α and β tubulin subunit to a growing MT in an outward direction, such that β-tubulin is exposed at the 'plus' end, whereas the MTOC-associated 'minus' end has a terminal α-tubulin. Thus, in most cells the minus end is typically near the nucleus. However, in neurons, MTs are discontinuous along the axonal and dendritic processes, such that there are multiple minus and plus ends (Fig. 1A) and a traditional MTOC may not persist as neurons mature.[7,8] The plus end of MTs in neurons thus project outward along the axon towards the terminus.[9] MTs exhibit a feature known as 'dynamic instability', in which a given MT will undergo periods of growth followed by times of disassembly.[5] This results from the hydrolysis of GTP to GDP within β-tubulin subunits, as the conversion of the terminal plus-end β-tubulin GTP to GDP, prior to the addition of another GTP-containing heterodimer, can lead to MT depolymerization. Such disassembly occurs less frequently at the minus-end, presumably because this end is typically stabilized by a MTOC, or perhaps by alternative nucleation sites in neurons.[7,8] MTs can also undergo a process referred to as 'treadmilling', in which growth at the plus-end is accompanied by shortening at the minus-end, and this behavior may be important during mitosis.[5,6] In neurons, MTs appear to have greater stability than in many other cell types, and thus the extent of MT 'dynamicity' is reduced. This MT stability is due, at least in part, to a number of MT-associated proteins (MAPs) that interact with MTs within neurons, with tau protein playing the predominate role in stabilizing MTs in axons.[6,10–12]

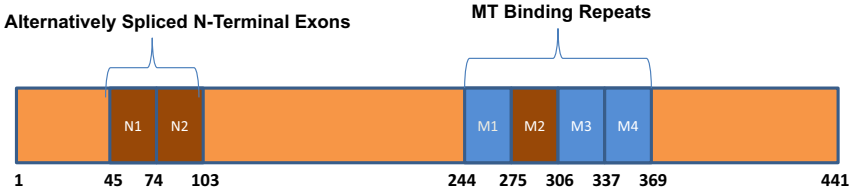

Figure 2. Schematic of human tau. The inclusion or exclusion of the second MT-binding repeat (M2) encoded by exon 10 of the tau gene results in 4R or 3R tau species. Additional isoforms are created by the inclusion or exclusion of two coding exons (N1 and N2) in the amino-terminal region of tau. Amino acid numbers refer to the longest tau isoform.