

Microtubule stabilizing drugs: the potential role in spinal cord injuries and neurodegenerative disorders.

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Abstract

The subject of microtubules and the development of microtubule stabilizing agents have opened up therapeutic avenues in oncology and neurology. In this mini-review, some of the novel therapeutic discoveries utilizing microtubule stabilizing agents used in spinal cord injuries, Alzheimer disease, and Parkinson's disease will be surveyed.

Keywords: Microtubule stabilizing agents, Spinal cord injuries, Alzheimer disease, Parkinson's disease, Etoposide, Docetaxel

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Introduction

Microtubules, which are composed from the polymerization of protein heterodimers α - and β - tubulin, are pivotal to the function of all eukaryotic cells and are an essential component (in orchestration with actin filaments and intermediate filaments) of their cytoskeleton. Microtubule-associated proteins and microtubule motor proteins (known as kinases) provide intricate control over the dynamics of microtubules [1].

The destabilization of the microtubule dynamics precedes the arrest of the cell cycle, which ultimately progresses to cell death. Microtubule stabilizing agents are a class of drugs that inhibit the depolymerization of the microtubules and facilitate the polymerization of tubulin proteins α - and β - into microtubule subunits [2].

Currently, advances in microtubule stabilizing agents and new drug discovery, is being utilized in oncological therapies [3,4]. However, research in microtubule dynamics and drugs that stabilize microtubules may provide a deeper understanding of the underlying pathophysiology, as well as, provide several potential therapeutic options for some neurological disorders. In this review, the role of microtubule stabilizing drugs in spinal cord injury recovery and in neurodegenerative disorders will be briefly examined.

Spinal Cord Injury Recovery

Spinal cord injuries typically disrupt the connectivity of axons in the spinal cord. Recovery is problematic, due in part, because of poor neuron-intrinsic regenerative potential in the central nervous system and these injuries commonly result in the formation of inhibitory lesion scars that further impeded the regeneration of axons after an injury.

Microtubule stabilizing agent, Etoposide, has recently been shown to improve the recovery of spinal cord injury in rodent models. In 2015, Jorg Ruschel and Frank Bradke from the German Center for Neurodegenerative Diseases, Bonn, Germany, demonstrated that Etoposide (intraperitoneal administration) did improve the functional recovery of walking in rats with spinal cord injuries, which was purposed to involve the reactivation of intrinsic axon growth machinery and by

the reduction of the inhibitory lesion scar [5]. Recent research further supports that systemic and post-injury administration of Etoposide did increase the functional recovery of hindlimb control in rodents with mid-thoracic spinal cord contusion injury by promoting axon regeneration, and Etoposide reduced the development of inhibitory fibrotic scar tissue in the lumbar spinal cord [6].

These two sets of data imply that microtubule stabilizing agent Etoposide has great potential to be a novel non-invasive therapeutic candidate for spinal cord injuries.

Neurodegenerative Diseases

The destabilization of microtubule dynamics have been correlated in the involvement of the Alzheimer neurodegenerative triad which consists of: synaptic impairment, dendritic simplification, and neuron cell death [7,8]. In a recent review, the benefits of microtubule-stabilizing agents have been surveyed in Alzheimer disease, as well as other neurodegenerative diseases, e.g., Parkinson's disease, amyotrophic lateral sclerosis, and traumatic brain injury [9].

Microtubule stabilizing agent, Docetaxel, when administered once a week at a dose of 0.1 mg/kg, led to increased microtubule density, reduced axonal dystrophy, reduced deposition of tau pathology in PS19 mice, and demonstrated a strong trend toward the improvement of hippocampal neuron survival [10]. Unfortunately, this study also identified gastrointestinal complications that actually caused death in the test subjects. This demonstrates that Docetaxel does offer potential to address some of the pathological pathways of Alzheimer disease, but more physiological understanding is needed to address the adverse drug reactions.

As with the neurodegenerative disorder Alzheimer disease, Parkinson's disease has also been correlated with microtubule abnormalities, due in part to the extensive axonal arborization of nigrostriatal dopaminergic neurons and the breakdown in the axonal transport that can lead to detrimental effects to these cells [11]. In 2013, Etoposide was shown to increase microtubule stabilization and diminish the nigrostriatal neuron degeneration in MPTP mice models of Parkinson's disease [12]. In addition, it was discovered that, low doses of Etoposide

D have demonstrated an inhibition in striatal dopaminergic neuron loss and that it can preserve dopaminergic markers in the striatum, e.g., dopamine, dopamine transporter, and tyrosine hydroxylase, in rat models of methamphetamine-induced striatal dopaminergic neuron loss [13]. This is significant because it suggests that microtubule stabilizing agents, like Epophione D, may offer a neuroprotective effect against neurotoxic drugs known to induce Parkinsonian-like symptoms, e.g. methamphetamine.

Conclusion

Research into microtubule dynamics has unlocked novel avenues to understanding some of the therapeutic difficulties confronting the treatment of some neurological disorders, e.g., spinal cord injuries and neurodegenerative disorders. There has been clear demonstration in several of the studies mentioned in this mini-review that particular microtubule stabilizing agents have the ability to improve the reactivation of intrinsic axon growth machinery and reduction of the inhibitory lesion scars, which have been shown to improve the outcome in spinal cord injuries.

Some microtubule stabilizing agents have also demonstrated the ability to provide a neuroprotective effect and to preserve microtubule stability in neurodegenerative disorders, e.g., Alzheimer and Parkinson's disease. However, adverse drug reactions have presented a significant hurdle to the progression of an acceptable treatment modality. This highlights the need for further research into the domain of microtubule stabilizing agents, in order to unlock their full potential.

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