

Endogenous regulator of brain aging and neurodegeneration-One target multiple therapeutic interventions

Shukla M¹ and Govitrapong P^{*1,2}

¹Chulabhorn Graduate Institute, Chulabhorn Royal Academy, Kamphaeng Phet 6 Road, Lak Si, Bangkok, Thailand

²Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Nakornpathom, Thailand

Abstract

Most of the calamitous brain diseases are neurodegenerative in nature and undergo progressive degeneration with advancing age and eventually death. In spite of the immense human affliction and economic impact the medical need for such diseases is largely unmet and is currently facing many drug-development challenges. The potential of the disease modifying drugs pertaining to its cure, slowing the progression, or prevention of the onset is by itself an expensive and time consuming process. Therefore, therapeutic development in this particular area should emphasize on addressing the underlying cause, drug safety, efficacy, cost effectiveness and since the brain cells are rarely replaced in such disorders, priority should be given to interventions which along with preventing the degeneration of neurons also have the ability to stimulate neurogenesis with least toxic effects. Melatonin the pineal neuro hormone is one such therapeutic agent which not only has proved to halt or reverse the progression of most neurodegenerative diseases but its physiology (synthesis, secretion and endogenous levels) provides information about the development and progression of the disease which aids in identifying successful drug targets thus offering assurance in breakthrough treatment strategies.

Introduction

Neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HT) are age-related and the most challenging of all the central nervous system (CNS) diseases. Characterized by progressive decline in neurological function they pose a great socioeconomic burden also. Aging by itself is one of the major risk factor for these neurodegenerative diseases causing changes in brain size, vasculature and cognition with progressive memory loss along with disturbed neurotransmitter and hormonal homeostasis. There are many challenges confronted when it comes to treatment strategies for these diseases and require a deep exploration of specialized mechanisms like safe and efficient delivery of the drugs across the blood brain barrier (BBB), drug toxicity and tolerance, from pharmacokinetics to pharmacodynamics along with drug side effects. In this line of therapeutic intervention melatonin the pineal neurohormone qualifies to be one of the most potent endogenous regulators of brain aging and neurodegenerative diseases as mentioned above.

Therapeutic potential of melatonin in neurodegenerative and neuropsychiatric disorders

Melatonin is a functionally versatile indoleamine which modulates the physiological and molecular homeostasis. In humans melatonin levels decrease with advancing age and interestingly its levels are reduced in AD [1,2] and HT [3]. Whereas in PD; reduced concentration of circulating melatonin has been reported in PD patients [4] with different variations [5]. Changes in melatonin levels have also been observed in multiple sclerosis and cerebral ischemia [6] along with altered secretion and levels in cancer patients (for review; [7]. CSF melatonin levels are significantly decreased in bipolar disorder

whereas decreased serum melatonin levels have been reported in major depressive disorder [8]. Decreased nocturnal synthesis of melatonin has also been accounted in age-related cardiovascular diseases like acute myocardial infarction and coronary artery diseases [9,10]. So, it could be envisioned how melatonin endogenously regulates aging and a plethora of brain disorders.

Melatonin stimulates the neuroprotective mechanisms and prevents neuronal vulnerability to toxic damage. Aging brain is vulnerable to oxidative damage perhaps due to reduced melatonin secretion. In this context, melatonin due to its antioxidant properties [11] provides neuroprotection [12,13] to the aging brain. It has proven to be efficient in treating AD and MCI patients [14] and our latest research delineated a novel mechanism by which melatonin aids in preventing AD pathology [15,16] and reverses age related changes in aged mouse hippocampus [17]. Hippocampal neurogenesis is associated with cognitive abilities and is decreased in AD [18] and melatonin increases stem cell proliferation in hippocampus [19] in a receptor dependent manner [20] whereas when used as a supplement in culture medium it improves the efficiency of *in vitro* produced mammalian embryos [21]. Several lines of evidence have been accounted regarding neuroprotective role of melatonin in PD [22-24] along with its possible therapeutic use in Multiple sclerosis and cerebral ischemia [6]. Not only that melatonin delays disease onset and mortality in a transgenic mouse model of HT [25] and its administration in cancer patients

Correspondence to: Piyyarat Govitrapong, Chulabhorn Graduate Institute, Research Center for Neuroscience, Thailand, E-mail: piyyarat.gov@mahidol.ac.th

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has been associated with improved outcomes and survival along with better tolerance of chemotherapy in such patients [26]. Interestingly, melatonin can exert both direct and indirect anticancer effects [27].

The complex etiology of mental diseases also complicates the development of antipsychotic drugs. Although, role of melatonin in psychiatric treatment has been discussed before (for review; [28]), recent advances in melatonin research have focused on mental diseases like anxiety, depression, schizophrenia, autism, attention deficit hyperactivity disorder etc.; emphasizing on alterations in melatonin secretion with associated changes in biological rhythms of such disorders [29]. Melatonin and its agonists (ramelteon and tasimelteon) are recommended for patients with Bipolar disorder [30] and agomelatine, which is an analogue of melatonin shows similar antidepressant effects like venlafaxine, fluoxetine, and sertraline [31] but with negligible adverse reactions.

Therapeutic effects ascribed to melatonin are not only restricted to above mentioned disorders. This magical neurohormone also regulates and modulates the cardiovascular [32], immune [33] systems and hormone secretion and metabolism [34]. With antitumor [35,36], anti-inflammatory [37], and pain modulating properties [38] it qualifies to be a broad-spectrum therapeutic agent. Although substantial research based studies have well documented the beneficial and therapeutic effects of melatonin; advancement in identifying and developing melatonin and its analogues should be targeted to analyze its potential and mechanisms involved in onset and progression of various diseases for more effective and standardized treatments and drug development.

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