Berberine and Neurological Health

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Restorative Medicine Digest

March 27, 2023

Berberine is an isoquinoline alkaloid found in several plant families that have a long history of medicinal use for a wide variety of health issues.[1] Modern-day research continues to shed light on the multiple cellular targets that berberine modulates, with increasing attention being paid to the potential role this remarkable compound may have in neurological health.

Mechanisms of Action

Berberine's extensive biological reach results from its ability to interface with adenosine monophosphate-activated protein kinase (AMPK).[2] AMPK is the master regulator of several intracellular signaling pathways that govern cellular metabolic processes and the maintenance of energy homeostasis. AMPK also regulates cell growth and survival; stress resistance; cell death; and autophagy, all of which are crucial determinants of healthy aging and lifespan.[3] In addition to interacting with AMPK, berberine has anti-inflammatory and antioxidant properties. It reduces production of reactive oxygen species in the cytoplasm and mitochondria, suggesting it has the potential to regulate oxidative stress and mitochondrial dysfunction, both of which are common pathways in the pathogenesis of neurodegenerative disorders.[4,5]

Overview of Evidence for Neuroprotective Effects

Aging is known to be the primary risk factor for the development of neurodegenerative disorders like Alzheimer's disease and Parkinson's disease. In pre-clinical and in vitro studies, berberine has been shown to ameliorate several of the factors associated with aging that contribute to the pathogenesis of neurodegeneration including neuroinflammation, impaired autophagy, and abnormal protein aggregation.

Substantial evidence from human studies confirms berberine's positive effects on lipid and glycemic dysregulation, both of which are risk factors for Alzheimer's disease. In pre-clinical and in vitro studies, berberine has been shown to reduce the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles,[6,7] as well as lowering endoplasmic reticulum stress and oxidative stress.[8] Berberine downregulates four enzymes (monoamine oxidase A, monoamine oxidase B, acetylcholinesterase, and butyrylcholinesterase) that play key roles in the development of Alzheimer's disease.[9]

In an animal model, berberine was found to facilitate the growth and viability of hippocampal pyramidal neurons through multiple pathways.[10] In another animal study, berberine was shown to improve learning and memory deficits via a number of molecular mechanisms, including hippocampal restoration of sirtuin 1, an NAD-dependent epigenetic regulator important for healthy aging.[11] Berberine improved spatial learning and memory retention in an animal model of Alzheimer's disease, by promoting autophagy and inhibiting production of amyloid beta.[12,13] Amyloid beta can induce astrocytes to produce proinflammatory factors and

free radicals, thereby triggering neuroinflammation and, ultimately, neuronal death. Berberine has been shown to inhibit the overexpression of astrocytes by reducing amyloid beta production and neural cell apoptosis.[14] Berberine has also been shown in an animal model of “chemobrain,” to reduce doxorubicin-induced cognitive impairment by modulating brain growth factors; promoting anti-inflammatory and antioxidant effects; and inhibiting neural cell apoptosis.[15]

Berberine was found to increase brain dopamine levels and improve symptoms in an animal model of Parkinson’s disease by upregulating dopamine synthesis in the gut, possibly through modulation of the gut microbiota.[16] Berberine was also shown to prevent activation of the NLRP3 inflammasome, which is linked to chronic activation of microglia in Parkinson’s disease. In addition, berberine activity led to the protection of dopamine neurons by restoring autophagy.[17]

A study of berberine in an experimental model of multiple sclerosis (MS), found that treated mice had lower levels of the proinflammatory cytokines IFN-?, TNF-?, and IL-17; and increased levels of the anti-inflammatory cytokines IL-4, IL-10, IL-27, IL-33, IL-35, and TGF-? compared to control animals. In addition, treated animals had decreased expression of Th1 and Th17 cytokines and their transcription factors, which cause T-cell mediated inflammation and autoimmune reactions, along with increased expression of Th2 and Treg transcription factors and cytokines, which moderate those reactions. Berberine alleviated the severity of MS symptoms, which was attributed to its anti-inflammatory effects, as well as its apparent ability to restore balance and function of Treg and Th2 cells.[18]

Clinical Implications

Berberine has extensive biological reach because of its ability to activate AMPK, the master regulator of multiple processes that govern cellular metabolism and energy homeostasis. Given that AMPK activity declines with age, accumulating evidence from pre-clinical and animal studies suggests berberine has potential to be an important ally in any therapeutic approach to healthy aging.

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DOI: https://doi.org/10.14200/rmd.2022.0002

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