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Review

Promoting sympathovagal balance in multiple sclerosis; pharmacological, non-pharmacological, and surgical strategies

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ABSTRACT

Accumulated evidence suggests that cardiovascular autonomic nervous system (ANS) dysfunction may be the underlying cause of many MS clinical presentations, including neurodegeneration and reduced response to immunomodulatory therapies, depression, fatigue and sleep disorders, migraine, osteoporosis, and chronic cerebrospinal venous insufficiency, the newer MS vascular etiology. We have recently described the genetic, epigenetic, and environmental factors with the potential influencing ANS activity, and the interactions among these factors.

This review expands upon previous ones, describing the pharmacological, non-pharmacological, and surgical strategies that could be adopted to prevent and minimize the deterioration in ANS function, promoting a state of sympathovagal balance. However, these strategies should not be applied as "one size fits all", but should take into account the nature and the degree of ANS dysfunction. These strategies would be effective in improving ANS function not only in MS, but also in other autoimmune and neurodegenerative diseases, where the dysfunction of this system plays a role.

Contents

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1. Introduction

Multiple sclerosis (MS) is a progressive, autoimmune, demyelinating disease of the CNS [1]. MS is a heterogeneous disease, involving multiple clinical and neuroimaging pathologies [2]. Among common MS clinical presentations is the cardiovascular autonomic nervous system (ANS) dysfunction. The ANS system consists of the sympathetic branch, which functions through the neurotransmitter norepinephrine, activating the α- and β-adrenergic receptors, and the parasympathetic branch, which functions through the neurotransmitter acetylcholine (Ach), activating the muscarinic and nicotinic receptors. The sympathetic ANS regulates the short- and the long-term blood pressure (BP) whereas parasympathetic ANS regulates the heart rate (HR). The dysfunction of both sympathetic and parasympathetic ANS responses has been reported in MS patients [3,4], correlating with disease activity and the progression to disability [5].

We have recently described the involvement of ANS dysfunction, particularly, that of low sympathetic function, in MS clinical presentations, such as inflammation and neurodegeneration [6], and in the occurrence of chronic cerebrospinal venous insufficiency (CCSVI) [7]. Accumulated evidence suggest that ANS dysfunction plays a role in many other MS-related morbidities, including depression, fatigue and sleep disorders, migraine, and osteoporosis (under peer review). These clinical symptoms have a significant negative impact on MS patients' quality of life.

Among mechanisms contributing to MS inflammatory and neurodegenerative processes, is the dysregulation in both cellular and humoral immunity. MS patients show higher th1 to th2 ratio [8] and increased levels of autoantibodies to myelin, and many CNS cells types, including neurons, oligodendrocytes and astrocytes [9]. Since ANS regulates the immune system [10], the improvement in ANS function would translate to a reduction in th1 derived inflammatory cytokines and in levels of autoantibodies. These changes in turn will reduce inflammation and improve myelination, promoting neuroprotection. Improvement in ANS function would also lead to neuroprotection by inhibiting astrocytes [11] and microglial [12] activation, and enhancing the production of brain-derived neurotrophic factor (BDNF) [13].

This review will describe pharmacological, non-pharmacological, and surgical strategies with the potential for improving ANS function, and promoting a state of sympathovagal balance. This improved balance will likely reduce inflammatory and neurodegenerative processes, and minimize the clinical presentation of the aforementioned MS-related morbidities.

2. Pharmacological strategies

2.1. Sympathomimetic agents

MS patients demonstrate sympathetic dysfunction more often than parasympathetic dysfunction [14], suggesting that these patients have low sympathetic to parasympathetic ratio, an index of sympathovagal balance. This index is often measured by analyzing the ratio of the low-frequency (LF) (indicator for the sympathetic activity) to high frequency (HF) (indicator for the parasympathetic activity) domain of heart rate variability (HRV). The low LF/HF ratio in female MS patients is mainly attributed to low sympathetic activity [15]. Therefore, sympathomimetic agents, especially the ones with the ability to cross the blood brain barrier (BBB), would be useful in augmenting LF/HF ratio in this group which constitute the majority of MS patients. The sympathomimetic agents work either directly, stimulating α- and or β-adrenergic receptors, or indirectly, by stimulating the release of norepinephrine, and or inhibiting its reuptake.

2.1.1. β-Adrenergic agonists

The β-adrenergic agonist could be either non-selective, biding to both B_1- and B_2-adrenergic receptors, or be selective, binding only to β_2-adrenergic receptors, when administered in low to moderate doses. However, B_1-adrenergic receptors have mainly cardiac effects, and therefore, a selective β_2-agonist, such as albuterol, a noncatecholamine with the ability to cross the BBB may be a more optimal choice for improving sympathetic ANS activity. This assumption is supported by the results of a clinical study, where the addition of albuterol to Glatiramer acetate improved the clinical efficacy of the latter in MS patients [16].

2.1.2. α_1-Adrenergic agonists

Among α_1-adrenergic agonists with a positive impact on ANS function, is the centrally acting Modafinil [17,18]. Two weeks of daily administration of 200 mg Modafinil has been shown to reduce fatigue in MS patients [19]. Modafinil's beneficial effects are thought to involve the activation of the wakefulness-promoting center, the noradrenergic locus coeruleus [19], which was thought to be damaged in MS patients [18]. Similarly, the results of a double-blind, placebo-controlled cross-over study shows that Modafinil improves delayed verbal recall in MS patients [20]. However, similar to antidepressants, Modafinil may reduce the parasympathetic ANS function, indicated by a decrease in the HF spectral domain of the HRV [17].

Other pharmacological drugs with α1-adrenergic agonistic actions are ephedrine, Metaraminol, and desglymidodrine, the active metabolite of the prodrug, Midodrine. These drugs are used to treat hypotension due to dysautonomia and/or due to other medications. However, the clinical efficacy of these drugs in MS is questionable, because their effect is mainly peripheral, increasing vascular tone and BP, and a poor ability to cross the BBB.

2.1.3. α_2-Adrenergic antagonists

The selective α_2-adrenergic receptor antagonists are a class of sympathomimetic agents that could significantly increase, not only the adrenergic, but also the dopaminergic and serotonergic neurotransmission. Example of this class of drugs is Atipamezole, administration of which to Clonidine-treated rats leads to improvement in locus coeruleus activity [21]. An additional α-$_2$ receptor antagonist is Fipamezole, which has shown efficacy in reducing levodopa-induced dyskinesia in the primate model of Parkinson's disease [22]. The product is currently under investigation as a treatment modality in primary progressive MS patients. Assuming that the drug has the potential for activating the sympathetic ANS function, it would likely show clinical efficacy for other forms of MS, especially the secondary progressive MS with severe ANS dysfunction [5].

2.1.4. Antidepressants

Antidepressants, which are known to increase CNS norepinephrine, have shown neuroprotective effects in MS [23], although some