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Sympathetic nervous system and neurotransmitters: their possible role in neuroimmunomodulation of multiple sclerosis and some other autoimmune diseases

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Abstract: Multiple sclerosis is still a disease without a cure. Although intensive research efforts have led to the development of drugs that modify the activity of the disease, most of them have various side effects and are expensive. At the same time it is becoming apparent that some remedies usually used to treat somatic and psychic disorders also have immunomodulating properties, and may help manage multiple sclerosis and other autoimmune diseases. We describe here the role of the sympathetic nervous system in the neuro-immune interaction in multiple sclerosis and other immune diseases with increased cellular immunity as well as neurochemical disturbances that take place in these disorders.

Keywords: Multiple sclerosis, neuroimmunomodulation, sympathetic nervous system, adrenoreceptor, neurotransmitter, autoimmune disease

1 Introduction

The sympathetic nervous system (SNS) together with the hypothalamic-pituitary-adrenal (HPA) axis has a strong interaction with the immune system, thereby regulating all phys-

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iological functions and maintaining physiological equilibrium. Lymphoid organs have enormous sympathetic innervation, and neurotransmitters released into these organs from sympathetic terminals are able to modify the migration of lymphocytes, their circulation and proliferation, as well as change the functional activity of various lymphoid cells and modulate their cytokine profile. The ability of some neurotransmitters to influence the production of inflammatory or anti-inflammatory cytokines by altering adrenoreceptor activity is of great interest because it allows us to modulate the immune response. This is of special importance when therapeutic approaches dissatisfy to requirements of efficiency and safety. In this connection, attempts at immunomodulation using agonists and antagonists of various receptors are worth careful consideration. The aim of the present manuscript is to elucidate some aspects of interaction between the nervous and immune systems in MS and other autoimmune disorders, and thereby to encourage neurologists and other health care professionals to find alternative strategies for treatment.

2 Sympathetic innervation of lymphoid organs and control of the immune system

The SNS innervates various organs within the human body; some organs also receive parasympathetic innervation (e.g., the gastrointestinal tract). As a rule, one type of innervation predominates in an organ. The thymus, spleen, lymph nodes and amygdala, bone marrow, blood vessels, and gut-associated lymphoid tissues receive sympathetic innervation [1, 2]. The presence of sympathetic nervous fibers to the lymphoid organs was confirmed in the 1960s-70s using histofluorescence and immunohistochemical techniques [3–6]. Immature and mature thymocytes, epithelial cells of the thymus, T-lymphocytes, macrophages and mast cells as well as plasmatic and enterochromaffin cells are the main targets of SNS (noradrenergic) innervation [7]. SNS activity begins early in embryogenesis and show its activity before the formation of the cellular immunity thereby confirming the important role of neurotramsmitters (in particular, noradrenaline) in the maturation of the immune system. The influence of noradrenaline and adrenaline on target cells is mediated by α- (subtypes α_1- and α_2-) and β- (subtypes $\beta_{1,2,3}$) adrenergic receptors. The various types of lymphoid cells have different numbers of receptors; for example, the density of β_2-adrenoreceptors is maximal on the natural killer (NK) cells, minimal on the T-helpers, and intermediate on the cytotoxic lymphocytes, B-lymphocytes and monocytes [8, 9]. Noradrenaline and adrenaline act via adrenoreceptors that activate G-proteins and thereby alter the activity of adenylate cyclase and phospholipase C. This leads to production of secondary messengers like cyclic adenosine monophosphate (cAMP), diacylglycerol, and some others. An amount of cAMP is controlled by adenylate cyclase and phosphodiesterase. Activation of β_2-adrenoreceptors results in increased cAMP within immune cells [10] thereby favoring the inhibition of tumor necrosis factor alpha (TNF-α) and interleukin 12 (IL-12) as well as increase of IL-10 [11–16]. Although many cells have β_2-adrenoreceptors, natural killers are the most sensitive to catecholamines. Agonists of β_2-adrenoreceptors are able to inhibit T cell proliferation (degree of inhibition depends on

level of cAMP) [17]. Selective (β_2-) and non-selective agonists of β-adrenoreceptors may show this action [18, 19]. Inasmuch as IL-12 is an active factor that increases interferon-gamma (IFN-γ) production, inhibition of IL-12 seems a real mechanism to vary the synthesis of other pro- and anti-inflammatory cytokines. Thus, enhancing sympathetic activity may modulate the entire immune response.

3 Alterations in immune system function and neurotransmitter profile in multiple sclerosis and related disorders

The primary pathogenesis of MS remains undiscovered. Various microorganisms (human herpesvirus 1 and 6 (HHV-1 and 6) and Epstein-Barr virus (EBV), papovavirus, Semliki Forest virus, Visna virus, varicella zoster virus, *Chlamydia pneumoniae*, some mycoplasmas) have been suggested with the development of MS and its animal analogs [20–27]. Unfortunately, a similar situation is observed in MS genetics: at least 32 alleles of the major histocompatibility complex (MHC) have been associated with the development of MS [28, 29]. Moreover, it is extremely important to note that some researchers have pointed out that infections may have a protective role, by preventing migration of autoagressive cells to the site of autoimmune destruction [30, 31].

In this situation, interruption of normal interactions between the nervous and immune systems (in particular, cancellation of sympathetic activity and imbalance of neurotransmitters) seems worth of further consideration.

The immune response is mediated by antigen-presenting cells (monocytes/macrophages, dendritic cells and other phagocytes) as well as by T helper lymphocytes. T helpers of the first class (Th-1) secrete cytokines of cellular immunity while T helpers of the second class (Th-2) produce cytokines of humoral immunity. T helpers of the "zero" class (Th-0) are able to differentiate into Th1 or Th2 depending on the IFN-γ to IL-10 ratio [32]. Activity of proinflammatory cytokines triggers the synthesis of nitric oxide and other inflammatory mediators. Increased levels of IFN-γ, IL-12 and TNF-α have been demonstrated by many authors in MS patients [33–35].

The SNS and the HPA axis are involved in the regulation of autoimmune conditions. Hypoactivity of either system may provoke a shift to production of inflammatory cytokines in MS and other autoimmune disorders (rheumatic arthritis, Crohn's disease, autoimmune thyroiditis and others). Studies performed with a rat line [F344] showed that SNS hyperactivity prevented the induction of experimental allergic encephalomyelitis (EAE), arthritis, and uveitis [36]. The quantity of β-adrenoreceptors on lymphocytes was shown to be correlated with the severity of MS [37]. Chemical sympathectomy with 6-hydroxydopamine aggravates EAE [38] while application of isoproterinol and terbutaline (non-selective and selective agonist of β-adrenoreceptors, respectively) alleviated EAE in rats [39]. A similar positive action on the course of EAE was detected using rolipram (a selective inhibitor of phosphodiesterase type IV) [40, 41]. Additionally, we would like to discuss here the role of some other neurochemical regulators (in particular, serotonin and β-endorphins).

Serotonin is a widely studied neurotransmitter present in brain tissue and other cells including thrombocytes, lymphocytes, monocytes, mast cells, enterochromaffin cells of the gut, and pulmonary neurpendocrine cells – thereby regulating many physiological functions [42]. Many cells have serotonin receptors, in particular of 1A-subtype [43].

Para-chlorophenylalanine, an inhibitor of tryptophan hydroxylase, results in decrease of serotonin synthesis and favors diminution of the functional activity of NK by inhibiting IFN-γ [44–46] and other inflammatory cytokines [47]. Moreover, serotonin entering immune cells through 1A-receptors decreases intracellular cAMP and thereby increases the proliferative and cytotoxic activities of T cells [43].

It is important to note that correlations exist between plasma serotonin concentrations and the severity of MS: levels of 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) were significantly lower in the cerebrospinal fluid of MS patients compared to healthy people [48, 49]. In secondary progressive MS patients, levels of 5-HIAA were lower than in relapsing-remitting MS patients [49, 50]. Also, a strong correlation exists between activation of inflammatory events and major depression in MS patients. It is also known that depletion of serotonin may be mediated by activation of indoleamine-2,3-dioxygenase (IDO) by inflammatory cytokines [51–53]. Some reseachers showed that tryptophan derivatives (3-hydroxy-kynurenine (3OH-KYN) and quinolinic acid (QUIN) arising in the kynurenine cycle have neurotoxic effects [54, 55]. Increased levels of these derivatives is observed in various neurodegenerative disorders as well as MS-associated and non-associated major depression [54, 56]. In turn, 3OH-KYN is able to induce the formation of reactive oxygen species whose cytopathogenic effect is well documented [57]. We must note here that glucocorticoids frequently used to treat MS are able to induce IDO (an enzyme participating in tryptophan catabolism); this fact has been known since the 1980s [58]. Similarly, β-interferon drugs may provoke analogous alterations in serotonin biosynthesis and transmission abnormalities in the CNS [59–62].

$\beta-$endorphins are endogenous opioid peptides with important regulating functions in the CNS [63]. Receptors for these neurotransmitters have been detected in immune system cells [64]. Interestingly, β-endorphins are able to decrease cAMP in immunocytes when its initial level is high, and vice versa, increase cAMP when it is low. Thus these neurotransmitters modulate levels of cAMP [65]. At present, it is known that β-endorphins may be synthesized both in the CNS and in immune cells [66, 67].

Patients with MS have decreased level of β-endorphins. MS sufferers with a progressive disease course show lower values of that neurotransmitter. Similar findings were observed in patients with rheumatic arthritis and Crohn's disease [68, 69]. The possible benefit of β-endorphins may include stimulation of anti-inflammatory cytokines [70, 71].

Thus, neuroimmunomodulation by balancing neurotransmitters seems a rational approach to these diseases.

4 Neuroimmunomodulation in ms and other autoimmune diseases

Unfortunately, modern immunomodulating drugs have not significantly influenced the progression of these diseases, have low safety profiles, and sometimes provoke somatic [72–75] and psychiatric [76] diseases. The accumulated clinical data indicate there is limited correlation between brain lesions and clinical presentation. For example, researchers have known since the 1960s that recovery of vision after an attack of optic neuritis cannot be explained by remyelination [77]. Moreover, people with extensive demyelination sometimes show no neurological deficits [78] while brain and spinal cord lesions may appear long before the first clinical sign of MS [79–82]. Although magnetic resonance imaging (MRI) may be useful to exclude some causes of neurological deficit (e.g., tumors), the lesions observed by MRI remain pathologically nonspecific [83]. Moreover, demyelination may be detected in other neurological and rheumatic pathologies [84] as well as in inflammatory diseases of the gastrointestinal tract [85]. As a result, some authors have stated that MRI "is of limited utility for both ruling in and ruling out multiple sclerosis" [86].

Consequently, the search for new diagnostic criteria and therapeutic approaches remains ongoing, and efforts to modulate SNS activity and neurotransmitter profiles seems a rational approach. In the 1970s it was shown that administration of L-tryptophan (precursor of serotonin) to MS patients resulted in improvement of autonomic, motor, and sensory functions [87]. Currently, the rationale for administration of selective serotonin reuptake inhibitors (SSRI, sympathomimetic antidepressant) is under discussion [88]. SSRI are able to cause the Th2 shift [89], reduce fatigue [90], and improve quality of life [91]. Moreover, SSRI were shown to be efficient in controlling pain [92–94] – a real problem for MS patients.

Since the 1960s, intensive investigations of neurotransmitters and their metabolites have been carried out by the Institute of Experimental Medicine in Caracas, Venezuela. Over 30,000 healthy and diseased individuals have been analyzed and some general conclusions made. In particular, the investigators showed that patients with Th1 immune profile [increased cellular immunity] display neurochemical features similar to those observed in major depression [95]. Namely, in patients with MS, Grave's ophthalmopathy, Crohn's disease, rheumatic arthritis, psoriasis and many others, similar neurochemical disturbances are observed: increased norepinephrine-to-epinephrine ratio, and decreased levels of tryptophan in blood plasma. Alternatively, in Th2 (humoral immunity) diseases – myasthenia, thrombocytopenic purpura, hemolytic anemia and others – the opposite neurochemical defects are detected (a profile of maladaptation to stress) [95]. Numerous works by these authors have demonstrated that rectifying the observed neurotransmitter imbalance may result in improvement. Moreover, one therapeutic scheme may work efficiently in patients with different disorders but belonging to one group (Th1 or Th2 diseases) [96–100]. The opinion of these authors is that therapy should be aimed at modulating noradrenergic and serotonergic neurotransmission by administering serotonin precursors, SSRI and norepinephrine reuptake inhibitors, as well as antagonists of

α_2-adrenoreceptors and serotonin 1A-receptors (5-HT_{1A}-receptors).

The serotonin precursors L-tryptophan and 5- hydroxytryptophan (5-HTP) were found to be useful in neuroimmunomodulation and arrest of various somatic and psychic symptoms including fibromyalgia, insomnia, and chronic headaches [101, 102]. 5-HTP crosses the blood-brain barrier without difficulty, and significantly increases serotonin synthesis in the CNS [103]. Administering SSRI may decrease IL-1, IL-2, IL-6, TNF-α and IFN-γ synthesis and thereby decrease production of reactive oxygen species (ROS) [104–107]. The precise anti-inflammatory mechanisms of SSRI and 5-HTP actions may be revealed in the future; however, at present it is known that the ratio of IFN-γ to IL-10 is not caused by changes in the activity of adenylate cyclase [108]. It is interesting to note that administration of salicylates favors the increase of serotonin synthesis in the CNS [109–111]. It seems very likely that the analgesic and anti-inflammatory properties of these drugs are related to their ability to modulate neurotransmitters in the CNS [112, 113].

Administering antagonists of 5-HT_{1A}-receptors may enhance the effect of SSRI [114, 115], significantly attenuate the progression of EAE [116–118] and decrease the functional activity of macrophages [46].

Although it was stated above that lowered serotonergic activity is associated with MS and other Th1 autoimmune disease, and that low plasma tryptophan levels reflect decreased serotonergic neurotransmission in CNS, it remains totally unclear which serotonergic nuclei are hypoactive. Recent work by Venezuelan researchers gave a significant boost to understanding the physiology of serotonergic nuclei [119]. Analyzing large amounts of physiological and clinical data, the authors concluded that the neurochemical profile of major depression corresponded to a predominance of the median raphe (B8, centralis superioris) nucleus over the dorsal raphe (B7) nucleus. Some rationales for use of 5-HT_{1A}-receptor antagonists were discussed above. However, it should be noted that these agents may increase the firing activity of dorsal raphe nucleus and may slightly decrease noradrenergic activity [119]. Moreover, agonists of 5-HT_{1A}-receptors may decrease activity of the HPA axis [120–122]. Impaired activity of the HPA axis is well-documented in MS [123].

We stated at the beginning of this review that enhancement of SNS activity may ameliorate Th1 autoimmune diseases. Antagonists of α_2-adrenoreceptors may, moreover, improve many physiological functions impaired in MS (e.g., erectile dysfunction [124, 125]) and potentiate the therapeutic effects of SSRI [119]. Agonists of α_1-adrenoreceptors may also enhance activity of the dorsal raphe and may stimulate release of serotonin at cortical areas innervated by B7-serotonin axons [126, 127]. It is interesting to note that not only SSRI but also selective serotonin reuptake enhancers (SSRE) may improve the neurochemical profile of major depression: SSRE may reduce the firing activity of the median raphe, and thereby restore the physiological balance between the dorsal raphe and the median raphe nuclei [119, 128, 129]. Agonists of β_2-adrenoreceptors also have analgesic properties, perhaps due to activation of opioid receptors [130] while phosphodiesterase inhibitors may consolidate memory and improve cognitive functions [131].

It is known, for example, that administration of SSRI and tricyclic antidepressants

also increases β-endorphin values [132–134]: this probably explains the observed analgesic effects of the remedies [92–94]. Serotonergic depletion with 5,7-dihydroxytryptamine decreases β-endorphin levels [135]: which is why depressed patients with MS and other autoimmune disorders have an increased algesthesia [136, 137]. The simplest way to increase β-endorphin levels is to administer low-dose naltrexone [LDN]. In general, naltrexone is an antagonist of opioid receptors at standard doses [50-150 mg]. However, at low doses [3-4.5 mg] taken at bedtime naltrexone stimulates opiate production. Anecdotal evidence presented at www.ldninfo.org and www.lowdosenaltrexone.org suggest its beneficial effect in MS; private research on 267 MS patients directed by Dr. Bihari postulated a very low relapse rate [0.226 per year] and stabilization of the course of MS. Some possible mechanisms of LDN and opiate action are under discussion [138, 139]. However, it should be noted that LDN also shows positive effects in cancers [140–143]. Therefore, it is possible that LDN acts as a neuroimmunomodulator rather than an immunoactivator or immunosuppressant.

In conclusion the evidence presented suggests the possibility of modifying the course of multiple sclerosis and other diseases by correcting neurotransmitter profiles and SNS activity. Many examples exist of SNS stimulation yielding positive results in animal models and in humans. For example, administration of the inexpensive β_2-agonist salbutamol resulted in a whole spectrum of anti-inflammatory events (increase in IL-10, IL-4, IL-5, decrease in IL-12, IFN-γ production) in patients with secondary progressive MS [144, 145]. Similarly, application of SNS-enhancing Bacillus Calmet-Guerin vaccine was found to be protective in MS patients and resulted in a 51% reduction of brain lesions [146]. Amelioration of MS during pregnancy is well-established fact [147, 148]. The sympathetic nerve activation during pregnancy [149] may contribute to a reduced clinical activity of MS. Thus, these therapeutic strategies are, in our opinion, worth further investigation.

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