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Any beneficial effects of mycobacteria on multiple sclerosis and experimental autoimmune encephalitis may include stimulation of the sympathetic nervous system

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Summary The inhibitory effects of mycobacterial infection and mycobacterium components on multiple sclerosis (MS) and experimental autoimmune encephalitis (EAE; an animal model for MS) have been known for years. However, this effect seems like a paradox that both mycobacterial infection and MS induce type I immune responses. Some mechanisms have been proposed or even proven for this effect in different studies, but among them there is no hint of a possible role for the nervous system (NS). Regarding the close relations between sympathetic nervous system (SNS) and MS disease course, it can be hypothesized that SNS may have a role in the effects of mycobacterium on MS.
Hypothesis: SNS can be stimulated by pro-inflammatory cytokines such as TNF-α and IL1-β, production of which are induced by mycobacterial infection or mycobacterium components. Although these cytokines can inhibit SNS in the site of inflammation caused by mycobacterium, they increase sympathetic tone in other places. The beneficial role of SNS in inhibiting or attenuating the course of MS and EAE has been suggested. Inhibitory effects of stimulated SNS on MS may occur via different ways such as inhibiting the production of pro-inflammatory cytokines and inducing the synthesis of anti-inflammatory cytokines, in other words, shifting the immune responses from type 1 toward type 2, as well as, induction of suppressor/regulator T lymphocytes, induction of heat shock proteins in brain and increasing the expression of Fas and Fas-ligand. Therefore, it seems that stimulation of SNS by mycobacterial infection or mycobacterium components is a key step in the mechanism of beneficial effects of mycobacterium on MS.

Introduction

It has been demonstrated that infectious agents contribute to the development of autoimmune diseases [1] including multiple sclerosis (MS) [2]. However, there is evidence indicating that infection

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diseases could have a protective effect on autoimmunity. In particular, it has been shown that mycobacterial infection and mycobacterium components can modulate MS and experimental autoimmune encephalomyelitis (EAE; an animal model for multiple sclerosis) in mice [3—8] through some mechanisms such as deletion of auto reactive T cells, induction of suppressor (regulator) T cells and redirected trafficking of activated auto antigen-specific T cells to the local inflammatory sites, induced by mycobacterial infection [3,6—11].

To support the beneficial effects of Bacillus Calmet-Guerin (BCG) on human autoimmunity,an inverse relationship between incidence of MS and spontaneous positive tuberculin skin tests was reported by Andersen et al. [12]. They suggested that early mycobacterial infection may be protective against MS. BCG vaccine has been used in recent clinical trials against MS and resulted in a 51% reduction in lesions, demonstrated by gadolinium-enhanced magnetic resonance imaging [13].

The beneficial effects of mycobacterium on MS are an apparent paradox that a Th1-promoting immune stimulus can have a useful effect on a purported Th1-mediated autoimmune disease [7].

As mentioned, some mechanisms have been proposed or proven for the effects of mycobacterium on MS, but there is no hint to the possible role of nervous system. Regarding the close relations between sympathetic nervous system and MS course [14], it can be hypothesized that SNS may have a role in the effects of mycobacterium on MS.

Therefore, in the present paper we will discuss this hypothesis that sympathetic nervous system (SNS) may have a crucial role in the beneficial effects of mycobacterium and its components on MS. Mycobacterial infection or mycobacterium components can increase systemic sympathetic tone including sympathetic tone of central nervous system, leading to the attenuation of the MS disease course via the ways that will be mentioned in coming paragraphs.

Mycobacterium components can stimulate the sympathetic nervous system

Mycobacterium components can induce local immune system cells to produce pro-inflammatory cytokines including TNF-α, IFN-γ, IL-12, IL-1β and IL-6 [15—20]. These cytokines can inhibit local sympathetic tone, whereas they increase systemic sympathetic tone [21]. Therefore, what appears during the infection by mycobacterium is the reduction of sympathetic tone in the infection loci and its increase in other places including CNS.

Any immune challenge that threatens the stability of the internal milieu can be regarded as a stressor, i.e. under certain conditions; an immune response can activate the stress system. It seems that an inflammatory/immune response to mycobacterium components may actually activate SNS, as other stressors or stimuli do [21]. It has been shown that IFN-α, which can be induced by mycobacterium components [17], TNF-α, IL-1 (especially IL-1β) and IL-6 can signal the brain to trigger the activation of both SNS and Hypothalamus-Pituitary-Adrenal (HPA) axis through a complex Corticotropin-releasing Hormone (CRH)-dependent pathway [21]. Thus, the SNS, similar to HPA axis [21],is involved also in a long feedback loop between lymphoid organs and CNS. The afferent limb of this loop seems to be operated by blood-borne cytokines, which activate the central components of the stress system via circulation or through the vagus nerve afferents. The efferent loop consists of the SNS, its projections to different organs and the release of NE from the sympathetic nerve terminals in these organs [21].

Although the above-mentioned cytokines trigger centrally the sympathetic output, which results in an increase of NE turn over in several organs, it has been shown that TNF-α and IL-1 inhibit SNS activation in the place of administration [21], so the local effect of these cytokines might be absolutely different. Therefore, it seems that mycobacterium infection and mycobacterial components can decrease sympathetic tone via inducing the above-mentioned cytokines production in the inflammation loci.

Effect of increased sympathetic tone on the pathogenesis of MS

Suppression of inflammatory molecules production and shifting the immune system from type 1 toward type 2

There are many indications showing that NE and epinephrine, inhibit the production of type 1/pro-inflammatory cytokines, such as interleukin 12 (IL-12), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) by antigen-presenting cells and T helper1 (Th1) cells through stimulation of the β_2-adrenoreceptor-cAMP-protein kinase A pathway, whereas they stimulate the production of anti-inflammatory/Th2 and Th3 cytokines such as interleukin 10 (IL-10) and transforming growth factor-β

(TGF-β). Through this mechanism, endogenous catecholamines may act systemically to cause a selective suppression of Th1 responses and cellular immunity,and result in a Th2 shift toward the dominance of humoral immunity [21]. Stimulation of SNS seems to pose similar effects on CNS.

Now, it has been clearly demonstrated that Nor-Adrenalin (NA) can suppress the expression of inflammatory molecules, including adhesion molecules, class II MHC molecules and NOS, in both glial and endothelial cells [22]. It has also been shown that the capacity of both astroglial and microglial cells to synthesize the pro-inflammatory (IL-1β and TNF-α) cytokines, is potently reduced by NA. There are many other studies suggesting that activation of β-adrenergic receptors on astrocytes can inhibit inflammatory molecules production and ameliorate EAE [14].

Furthermore, it is known that there is a shift toward type 1 immune responses in MS disease and that the shifting of the immune responses toward type 2 can attenuate the course of the disease [5]. For instance, it has been shown that the protective effect of Schistosomiasis on EAE and MS is due to the shifting of the immune responses toward type 2 in Schistosomiasis [23].

Induction of heat shock proteins

All cells, from bacteria to human, show a common intricate response to stress, which protects them from injury. Heat shock proteins (HSPs), also known as stress proteins and molecular chaperones, play a central role in this response and protect cellular homeostatic processes from environmental and physiological insults [24]. Heat shock proteins (HSPs) act as molecular chaperones and/or have anti-apoptotic activities under physiological conditions. Expression of two heat shock proteins namely HSP70 and HSP27 in the brain is notable as they are highly inducible in glial cells and neurons following a wide range of stressors including ischemia, epileptic seizure and hyperthermia. Both of these HSPs have neuroprotective effects on the brain and spinal cord due to their anti-apoptotic and chaperoning activities [25]. Accumulation of these HSPs, whether induced physiologically, pharmacologically or genetically, or by direct administration of the proteins, is known to protect the brain and spinal cord from neurodegenerative diseases [24—26].

Stimulation of SNS can act as a sublethal stress and induce HSPs in various organs including the brain. Stimulation of adrenoreceptors can induce HSP-70 expression in the brain cells [27—30] and protect these cells from neurodegenerative diseases, including MS. While the mechanism of this protection has largely been thought to be due to chaperoning and anti-apoptotic functions of HSPs, it has been also shown that these proteins may directly interfere with inflammation [31]. According to these findings, some anti-inflammatory effects of SNS on the brain may be explainable via induction of HSPs.

Other effects of increased sympathetic tone on immunopathogenesis of MS disease

It has been shown that stimulation of SNS can induce regulatory (suppressor) T lymphocytes and attenuate immune responses. Different adrenoreceptors are known as molecules responsible for the induction of regulatory T lymphocytes and increasing the T regulatory (suppressor) vs. T helper and T regulatory (suppressor) vs. T cytolytic ratios [32,33].

The role of regulatory T lymphocytes in the effects of mycobacterium tuberculosis components on EAE has been demonstrated [7,9].

It has been shown that the number of Gamma Delta T lymphocytes and their activity increases due to the activation of SNS [34,35]. There are some evidences that Gamma Delta lymphocytes play an important role in attenuating the course of EAE [36]. In addition, production of TGF-β by Gamma Delta T cells has been suggested as a potential mechanism in mycobacterium-induced protection against EAE [7].

Another effect of increased sympathetic tone is the increase of activated T lymphocytes apoptosis. It has been shown that catecholamines can inhibit T- and B-lymphocytes activities, mediated via induction of Bcl-2/Bax and Fas/FasL involved apoptosis [37]. This finding indicates a mechanism for the regulation of lymphocytes activity in the central nervous system, whereby elevated regional levels of catecholamines might lead to the apoptosis of auto-reactive lymphocytes [36] and immunoprivilege of the brain [37].

It has been also shown that catecholamines can inhibit the function of effector cytotoxic T lymphocytes [21] involved in the pathogenesis of MS [38].

The activity of auto-reactive T lymphocytes can be directly affected by increased sympathetic tone. Bedoui et al. [39] have shown that neuropeptide Y(NPY) significantly inhibits myelin oligodendrocyte glycoprotein (MOG) specific Th1 lymphocytes in EAE. They showed that these auto-reactive T cells, which have a key role in pathogenesis of EAE, are a major target for NPY [39].

Discussion

The present paper suggested stimulation of SNS and sympathetic tone increase may be one of the possible mechanisms for the inhibition or attenuation of EAE and MS disease courses, caused by mycobacterial infection and mycobacterium components.

The beneficial role of SNS in inhibiting or attenuating the course of MS and EAE has been suggested. Chemical sympathectomy with 6-hydroxydopamine (6-OHDA) at birth, led to a more severe course of the disease in an EAE rat model, as well as in an adoptive transferred EAE [40,41]. In a study with secondary progressive course MS (SPMS) patients, Makhlouf et. al. [42] showed that after 14 days of treatment with Salbutamol, the in vitro production of IL-12 by monocytes and dendritic cells significantly decreases compared to baseline, with persisting effects for, at least, 1 week after the treatment. Furthermore, they reported an increase of Th2 cytokines [43]. Based on these findings, a randomized trial of add-on treatment of Salbutamol to glatiramer acetate is under progress [14].

As mentioned above, it is absolutely possible that mycobacterium components can stimulate SNS through production of specific pro-inflammatory cytokines. The finding that IFN-γ or TNF-α has protective effects on EAE models, when administered late during the disease process [3], supports this hypothesis that induction of pro-inflammatory cytokines production by mycobacterium may has a key role in the protective effects of mycobacterium on EAE and MS.

The suggested mechanisms of the beneficial effects of mycobacterium components on EAE models and MS disease can also be related to the stimulation of SNS. These mechanisms include the induction of suppressor T lymphocytes and inhibition of auto-reactive T lymphocytes, induced by mycobacterium [3,6–9]. As mentioned above, both induction of suppressor T lymphocytes and inhibition of auto-reactive T lymphocytes can be caused by increase in sympathetic tone [32,33,39]. It has also been suggested that redirected trafficking of activated auto antigen-specific T cells to local inflammatory sites, induced by mycobacterial infection, is one of the mechanisms, through which BCG infection can ameliorate the EAE course [7]. As SNS can influence lymphocyte trafficking and recirculation [21], it may has an effect on the trafficking of activated auto antigen-specific T cells. As mentioned above, the sympathetic tone may decrease in local inflammatory sites, induced by mycobacterial infection, and increase in other places including CNS. Therefore, stimulation of SNS can be one of the first steps in the mechanism of Mycobacterium effects on MS disease course, and other proven or suggested mechanisms can be due to this increased sympathetic tone.

In summary, it has been hypothesized that stimulation of SNS by mycobacterial infection or Mycobacterium components and other possible effects of increased sympathetic tone on CNS immune and non-immune cells may have an important role in beneficial effects of mycobacterium on MS disease course, whereas interaction of other mechanisms is highly possible.

This hypothesis could be tested via different ways for example according this hypothesis a chemical sympathectomy should inhibit the beneficiary effects of BCG on EAE.

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