Medical Hypotheses 144 (2020) 110000

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

How does stellate ganglion block alleviate immunologically-linked disorders?

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A B S T R A C T

Background: The stellate ganglion is an autonomic nervous ganglion, formed by the fusion of the inferior cervical sympathetic ganglion and the first thoracic sympathetic ganglion, which is present in about 80% of people. It is anterior to the neck of the first rib and contains neurons that supply sympathetic innervation to the head and neck. Injection of local anesthetics near the stellate ganglion (stellate ganglion block; SGB) has been used for multiple clinical indications including sympathetic-mediated pain and vascular insufficiency syndromes of the upper extremity. In addition, reports on SGB having significant impact on conditions linked to immune dysfunction have been published for a century, but the mechanisms of SGB action have been poorly understood.

Hypothesis: SGB hinders the sympathetic innervation of the immune organs, thus modulating the immune system activity and leading to the alleviation of the disease.

Evidence: All primary (thymus and bone marrow) and secondary immune organs (spleen, lymph nodes, mucosa-associated lymphoid tissue) receive a substantial sympathetic innervation, with norepinephrine (NE), as the main neurotransmitter. Complementarily, T and B lymphocytes express β2-adrenergic receptors, while innate immune cells express both α- and β-adrenergic receptors. The consequences of adrenergic receptor signaling can be summarized as immuno-modulatory. Activation of adrenergic receptors leads to decreased levels of pro-inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α) and increased levels of anti-inflammatory cytokines, like IL-10 or TGF-β. Cellular changes include increase in the number of regulatory T cells and shift of the Th1/Th2 balance towards the Th2 response. Since the changes in immune response are global, the explanation has to include generalization of the SGB effect. A likely explanation includes centripetal neuronal pathways between the stellate ganglion and deep brain regions such as insula, amygdala, and hippocampus. Those, in turn, have reciprocal innervation with locus ceruleus, a brain-stem structure involved in the control of the autonomous nervous system.

Conclusion: Various pathologic conditions have been shown to be SGB responsive, where the symptoms have been reduced or eliminated. Many of those clinical improvements have been mirrored by measurable immunologic changes. A plausible explanation, consistent with the evidence available so far, is that SGB exerts its effects by regulating the immune system, through a central, reflex-like pathway. Our hypothesis provides a theoretical framework for understanding the effects of SGB and could, thus lead to wider usage of the technique in immune-linked disorders such as ulcerative colitis.

Overview of stellate ganglion block

Stellate ganglion is a sympathetic ganglion, formed by a fusion of the inferior cervical and first thoracic sympathetic ganglia, which can be found in about 80% of people. It is located at the level of the seventh cervical vertebra (C7), anterior to the transverse process of and the neck of the first rib. Its branches join the seventh and the eight cervical spinal nerve, as well as the first thoracic spinal nerve (somatic branches), contribute to the inferior cardiac nerve (visceral branches), and join the nervous fibers along the vertebral and brachiocephalic arteries (vascular branches). The ganglion also communicates with the vertebral nerve and its branches, thus forming the cervical sympathetic "plexus" [1].

The stellate ganglion block (SGB) involves injecting a local anesthetic (e.g., ropivacaine or bupivacaine) next to the sympathetic ganglion and the procedure has been in clinical practice for just under a century [2]. It is a well-established pain management technique in wide use with a low complication rate of 1.7 per 1,000 procedures [3]. The procedure is regularly used to treat various painful syndromes and conditions (e.g. chronic regional pain syndrome types I and II, post-herpetic neuralgia, neck-shoulder-arm syndrome, neuropathic pain) or conditions related to the organs innervated directly by the stellate ganglion branches, such as ventricular arrhythmias [4]. However, the indications have over the years been extended well beyond head, neck, and upper extremity (an extensive, but not exhaustive list can be found in Uchida, 2002 [5]). As Uchida pointed out, the clinical indications for SGB are much wider in Japan than in Europe or the United States [5].

The expansion of applications of SGB to the whole body has been mirrored by expansion into the conditions pathophysiology of which cannot be explained by direct lack of sympathetic innervation and consequent peripheral vasodilatation [5]. For instance, SGB has been shown to be effective in treating conditions based on dysfunction of the

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https://doi.org/10.1016/j.mehy.2020.110000
Received 23 April 2020; Received in revised form 4 June 2020; Accepted 13 June 2020
Available online 16 June 2020

immune system such as allergic diseases [6], asthma [6–8], atopic dermatitis 1995 [9], and ulcerative colitis [10]. Having those reports in mind, we hypothesise that the effects of SGB may be mediated by the generalized impact of sympathetic innervation on the immune system.

Sympathetic innervation of the immune system

The autonomic nervous system has an essential role as a regulator of and integrator between diverse body systems, including the immune system [11]. Sympathetic nervous fibers have been well documented in both primary (thymus and bone marrow) and secondary lymphoid organs (spleen, lymph nodes, and mucosa-associated lymphoid tissue) [12], while the existence and the role of parasympathetic innervation is still under debate [13,14]. The sympathetic fibers end in the organ parenchyma, in close proximity of the immune cells, and their main neurotransmitters are norepinephrine (NE) and neuropeptide Y (NPY) [15,16]. Complementary to that, β2-adrenergic receptors and NPY receptors are expressed by all the adaptive and innate immune cell types, while the distribution of α2 receptors is more restricted [17,18].

Effects of the sympathetic innervation on the immune system are complex and are best described as immuno-modulating, rather than being simply stimulating or suppressing [19,20]. Activation of β2-adrenoreceptors and, to a lesser degree, α2-adrenoreceptors found on many immune system cells (i.e. neutrophils, T cells, macrophages) which causes an increase in levels of cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) [21,22]. On the other hand, the activation of the same adrenoreceptors can modulate the immune system by inhibiting the transcription factor nuclear factor (NF)-κB (NF-κB) [23]. Those signaling events, in turn, lead to a shift in the spectrum of the humoral mediators of immunity; on one hand, levels of pro-inflammatory factors such as IL-6, IL-1β, tumor necrosis factor-α (TNF-α), C3, and GFAP are decreased [24]. On the other hand, the sympathetic β2-adrenergic signaling promotes secretion of anti-inflammatory cytokines, such as IL-10, which is another contribution to the sympathetic control of inflammation [25]. Considering the cell populations, the sympathetic nervous system increases the number of $CD4^+FoxP3^+$ regulatory T cells via a TGF-β dependent mechanism [26].

The other sympathetic postganglionic transmitter NPY is, upon stimulation, co-released with NE from sympathetic fibers [27] and, in addition to that, is also produced by the immune cells themselves [28]. Just like NE, NPY has many actions on the immune system: modulation of cell trafficking, regulation of macrophage function, modulation of T cell and dendritic cell activation as well as attenuation of inflammation [29].

Effects of stellate ganglion block on the immune system

Several studies have documented that the SGB has an effect on the immune system of healthy people. To start with, a controlled study on T cell activation, performed on 24 healthy individuals found decrease of both helper and cytotoxic T cell activation [30]. Next, Yokoyama et al., used 10 healthy male volunteers in a placebo-controlled crossover study to determine the effects of the SGB on lymphocyte subsets as well as catecholamines and hypothalamic–pituitaryadrenal (HPA) axis hormones. They reported on significant reduction of both NE and epinephrine levels in the SGB group compared to placebo and control. Furthermore, they detected a decrease in natural killer (NK) cell activity and increase in the ratio of $CD4^+/CD8^+$ lymphocytes [31].

Next, a number of patient studies confirmed that SGB not only has an effect on the immune system, but that the changes in the immune system were also paralleled by the alleviation of the medical disorder. Wajima et al. reported on a patient who was treated with SGB due to a severe adult type atopic dermatitis, refractory to other therapeutic interventions. SGB in that patient led to decrease in serum levels of IgE and decrease of eosinophil counts in the peripheral blood. Those changes were complemented by improvement of the patient's clinical condition [9]. Furthermore, a controlled study on fifty patients enrolled early after traumatic brain injury (within 24 h) reported on a decrease in the level of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, following SGB [24]. The likely mechanism of action was a significant downregulation of the transcription factor NF-κB, which controls the production of the previously mentioned pro-inflammatory cytokines [24]. Similar findings were reported by a randomized controlled trail (RCT) on thirty trauma patients with severe injuries: SGB leads to a decrease in concentration of IL-1β, IL-6, and TNF-α in the SGB. At the same time, no significant difference between the SGB group and the control group was found in the concentrations of anti-inflammatory cytokines IL-4 and IL-10 [32]. Finally, a recent RCT explored the immunomodulatory effects of the SGB in 120 patients suffering from chronic ulcerative colitis. The authors measured serum levels of the pro-inflammatory cytokine IL-8 and demonstrated a significant decrease in the SGB group, lasting for at least a month [10].

We should also add that the study by Yokoyama et al. reported on lower concentration of catecholamines in plasma following SGB but with unaltered concentrations of adrenocorticotropic hormone (ACTH) and cortisol [31]. That decrease of epinephrine levels can be explained by mitigated catecholamine output from the adrenal gland, rather than from the post-ganglionic sympathetic fibers. To rephrase, the changes in the immune system may depend on the hypothalamus–pituitaryadrenal (HPA) axis rather than on the release from the postganglionic sympathetic fibers. If that were the case, however, we would have expected decreased levels of ACTH and cortisol.

Proposed mechanicistic model of stellate ganglion block

Sufficient body of work documents not only the changes in the immune system following SGB, but also alleviation of the symptoms and course of the underlying medical conditions. However, the exact mechanistic explanation remains elusive. An obvious question is why would an anesthetic intervention in a sympathetic ganglion located in the neck have any body-wide consequences? For example, how should one explain clinical relief in patients suffering of chronic ulcerative colitis [10]?

To elucidate the biology, we need to consider two possible routes of SGB action: local and central. Local (or direct) consequences of SGB are related to the effects of sympathetic innervation (or lack thereof) to the lymphatic tissues or organs innervated by the postganglionic fibres of the stellate ganglion. Central (or indirect) consequences are mediated by the central nervous system and are most likely based on a reflex-like response (Fig. 1).

Human data on exact anatomical distribution of stellate ganglion branches are scarce, but animal data show that thymic sympathetic fibers originate from cervical and upper thoracic sympathetic ganglia [13,14,33,34]. Furthermore, animal experiments using sympathectomy or adrenergic antagonists generally found decrease in the thymus weight, reduced thymic cellularity, increased in the rate of apoptotic cell death, and altered proportions of cellular subsets [35]. Thus, SGB effects may be, at least in part, mediated by the diminished thymic innervation. However, it is hard to conceive that this mechanism is responsible for all the immune consequences of SGB, particularly the ones involving components of the immune system which are not related to the thymus, such as the NK cells. For instance, SGB in humans leads to decreased activity of NK cells harvested from the peripheral blood [31], while a study on rats found loss of NK activity in the spleen [36].

Central explanation of the SGB mechanism is more involved. Transneuronal mapping in rats has shown that the sympathetic neurons reaching thymus are controlled by the central neurons located in medulla oblongata, pons, hypothalamus [33,37] and the limbic system [38]. Existence of similar, centripetal pathways in humans is confirmed by functional positron emission tomography, showing a relationship between SGB and decreased brain activity in insula, amygdala and hippocampus [39]. In turn, those areas have been shown to have

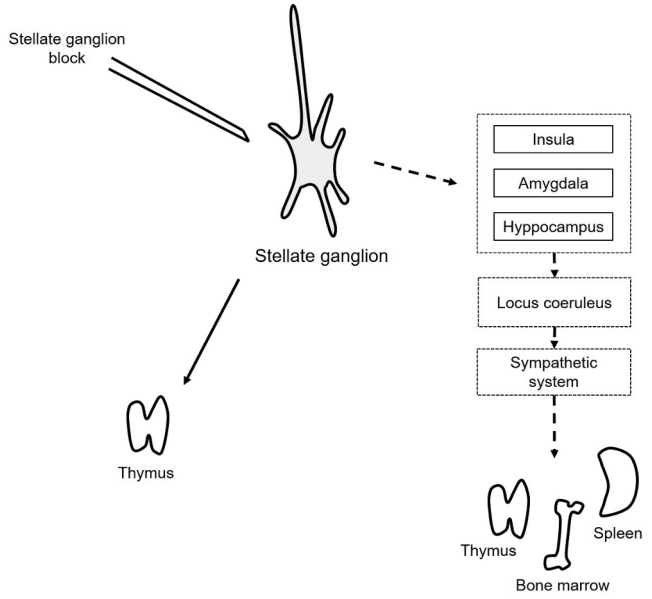

Fig. 1. Proposed mechanism of stellate ganglion block (SGB). Direct mechanism of SGB (unbroken line) is based on the effect of stellate ganglion branches which reach the thymus. Consequently, thymic output may be altered. Indirect mechanism (dashed line) is mediated by centripetal nerve fibers reaching central brain regions such as amygdala, insula, or hippocampus. Those regions have reciprocal innervation with locus coeruleus, which, subsequently, controls the nuclei of the autonomic nervous system. Sympathetic autonomic fibers, in turn, reach primary and secondary lymphoid organs.

reciprocal innervation with locus ceruleus [40], a major noradrenergic nucleus in the brain stem [41]. Axons originating from the locus expand to a number of regions in the central nervous system, including nuclei of the autonomic nervous system [40]. In other words, that means that a stimulatory signal originating from sympathetic ganglia can go "upstream" to the brain, reach the locus ceruleus, and from there go "downstream" (i.e. efferently) to the central sympathetic neurons. From the central neurons onwards, the signal could be "generalised" through the body and propagated down the sympathetic fibres that reach the bone marrow, lymph nodes, spleen, and the thymus [42–44], as well as immune cells attached to the body surfaces (e.g. skin and mucosa) [13]. That signalling pathway can at the end, act on both branches of the immune system: adaptive and innate [45].

When considering impact of the sympathetic innervation on the immune system, some additional aspects should not be forgotten. Sympathetic nerves not only directly innervate cells of the immune system, but also regulate blood and lymph flow [46]. Any changes in the flow have consequence on the immune reaction. Furthermore, it is interesting to note that the regions of the brain that receive centripetal signals originating from stellate ganglion, listed above, are involved in the control of the immune system via pathways that do not directly involve the autonomic nervous system [47]. Available data suggest that a possible mediator could be melatonin: SGB has been shown to correct disorders of melatonin rhytm [5] and melatonin has immunoregulatory properties [48,49].

Conclusions

We are aware of the fact that clinical trials revolving around SGB are still few in number; as the matter of fact, most reports are case studies. On the other hand, there has been considerable progress in the field of neuroimmune interactions, but many questions on the role of sympathetic nervous system in immunity remain open. Nevertheless, the evidence presented here should be taken seriously.

We hypothesise that SGB can modulate the immune response by a complex neuronal pathway starting from the stellate ganglion and ending in the postganglionic sympathetic nerve fibers in the entire body. The proposed pathway can, therefore, be thought of as another neuro-immunomodulatory reflex [23].

Activation of the efferent branch of the hypothesised reflex then leads to the decreased activity of pro-inflammatory transcription factors and, as a direct consequence, lower levels of local or systemic humoral immune mediators. Cellular immune response is also affected, with redistribution of the cell types and increase in proportion of regulatory T cells. In parallel to these changes, and most likely because of them, the disease symptoms are alleviated.

Further elucidation of mechanisms of SGB should provide a solid basis for wider acceptance of the technique in routine clinical practice. To start with, SGB could become more common in treatment of patients suffering of disorders in which central pathogenic role of the immune system is not disputed, such as ulcerative colitis. Popularization of the technique may even encourage the medical professionals to consider it in treatment of conditions such as post-traumatic stress disorder or schizophrenia. Those disorders are traditionally not associated with a primary immune system malfunction, although changes of the immune system in affected individuals have been reported [50,51] and studies have documented beneficial effects of SGB [52,53]. As current treatment options for both conditions have considerable limitations, any new therapeutic strategy should be welcomed.

Conflict of interest

The authors declare no conflict of interest.

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