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Anti-Inflammatory Reflex - Interaction of The Nervous System and The Immune System

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ABSTRACT

The coordination of body systems is important for overcoming various conditions. The nervous system, as a fast coordinator of the body, reflexively manages many functions. At the same time, the immune system is involved in endogenous and exogenous factors that disturb homeostasis at any time to protect the body. Research has shown negative feedback between the two systems. Inflammatory factors such as pro-inflammatory cytokines stimulate the vagus nerve, which increases afferent signals to the central nervous system. The central autonomic network increases efferent vagus nerve impulses. Amplification of efferent vagus nerve activity promotes the release of acetylcholine. Increased acetylcholine suppresses inflammation through its receptors on immune cells. The aforementioned feedback process, which is the two-way communication of the nervous and immune systems, is called the "anti-inflammatory reflex". In the present article, the role of each component and the therapeutic potential of using the anti-inflammatory reflex will be discussed. Moreover, heart rate variability as an index for measuring the state of the anti-inflammatory reflex is considered.

Keywords: anti-inflammatory reflex; inflammation; autonomic nervous system; vagus nerve; immune system

INTRODUCTION

In biology, various nervous reflexes unconsciously manage many body functions using afferent and efferent neurons [1]. The receptors of the afferent neurons are activated by stimuli. Activation of these receptors increases the impulses of afferent neurons in the central nervous system. The central nervous system processes input neural information and sends back responses through efferent neurons. Upon each reflex, a specific stimulus can affect receptors in the afferent neurons, which triggers circuits [2, 3]. Simultaneously, the body faces certain conditions that can affect all systems, including inflammatory processes.

Inflammation is the body's protective response to injury or infection and is accompanied by swelling, pain, redness, and warmth [4, 5]. Inflammatory diseases are diverse, and there is no specific treatment for them under chronic conditions [6, 7]. During the process of inflammation, the immune cells secrete cytokines, which are divided into two types, pro-inflammatory and anti-inflammatory [8, 9]. The goal is to secrete cytokines that limit inflammation [10]. However, the intense or continuous activity of macrophages leads to excessive production of cytokines, causing them to escape local control and enter the blood circulation system, which widely activates the inflammatory component, systemic inflammatory response syndrome (SIRS) [11-14].

Previous studies have indicated an interaction between the nervous system and inflammation [15, 16]. Among the various parts of the nervous system, the vagus nerve plays the most important role in anti-inflammatory reflexes owing to its extensiveness. Borovikova et al. were the first to

formally describe the role of vagal stimulation in reducing the inflammatory response caused by endotoxins [17]. Subsequently, Kevin J. Tracey proposed a reflex that is activated by inflammation and controls it [15]. Various studies over the last two decades have confirmed the Tracey hypothesis. Inflammation activates the afferent vagus nerve, which triggers the central autonomic network (CAN). Evoked CAN increased efferent autonomic nerve activity, which elevated acetylcholine content. High acetylcholine content modulates inflammation through interactions with immune cells. This entire process is called the "cholinergic inflammatory reflex." Many studies have shown that different inflammatory conditions activate the anti-inflammatory reflex [18-20]. To better define the anti-inflammatory reflex pattern, the available evidence for each stage will be reviewed separately.

Stimulation of the afferent vagus nerve under inflammation

The vagus nerve, which is widely distributed in visceral areas, consists of more afferent fibers than efferent fibers [21]. Previous investigations indicated that stimulation of the vagus nerve is the first step of the anti-inflammatory reflex [22, 23]. Toll-like receptors (TLRs) are critical for triggering the innate immune response to defend against infections [24]. The components of Gram-negative and Gram-positive bacteria interact with TLR4 and TLR2, respectively, in monocytes and macrophages, which release different chemokines and cytokines. These cytokines recruit and activate neutrophils to eliminate pathogens [25, 26]. Pathogen-associated molecular patterns (PAMPs) and pro-inflammatory cytokines such as TNF-α, IL-6, high mobility group box 1 (HMGB1), and IL-1β, which are released under various inflammatory conditions, can stimulate the vagus nerve [27, 28]. It seems that pro-inflammatory cytokines interact with their receptors in the afferent vagus nerve [29]. Moreover, direct stimulation of the vagus nerve triggers an anti-inflammatory reflex [30]. Altogether, the elevation of afferent vagus nerve activity alters CAN.

CAN processing of increased vagus nerve activity under inflammation

The first part of the CAN that receives afferent messages from the vagus nerve is the nucleus tractus solitaries (NTS) [31]. As a hub, the NTS sends the desired messages received from the vagus nerve to the rest of the CAN and other parts of the central nervous system [32]. Different key components are observed in CAN, including the insular cortex, amygdala, hypothalamus, periaqueductal gray matter, parabrachial complex, NTS, and ventrolateral medulla [33]. Finally, after processing, the efferent output of the vagus nerve originates from the dorsal motor nucleus of the vague (DMNV) [34]. Moreover, the direct stimulation of some neuronal pathways in the CNS can increase afferent vagus nerve signals. For example, activation of the cholinergic brain network through muscarinic agonists augments efferent vagus nerve signals [35]. Furthermore, the areas of CAN are known components of higher brain function [33, 36]. Higher brain functions such as cognition and emotion interact with CAN which alters vagus nerve activity [37]. Therefore, CAN as a processor combines different signals and finally changes the activity level of the vagus nerve.

Increasing the efferent vagus nerve activity

Extensive research has been conducted on the anti-inflammatory effects of increasing the excitatory responses of the vagus nerve. Stimulation of the vagus nerve can directly elevate the amount of acetylcholine secretion [38, 39]. Increasing the secretion of vagal acetylcholine affects various receptors in the areas innervated by it, such as the heart, intestine, stomach, and liver [35, 40]. Research has shown that a type of nicotinic acetylcholine receptor can induce anti-inflammatory processes. Acetylcholine magnification affects alpha$_7$-nicotinic acetylcholine receptors (α_7nAchR) in immune cells, including macrophages, and prevents the release of more pro-inflammatory cytokines, resulting in inflammation control [41-43]. α_7nAchR is present in many tissues of the body and is not limited to the nervous system, but with its effect, it can help limit inflammation through immune cells [44, 45].

Moreover, a branch of the autonomic nerve is sent to the celiac ganglion, the postganglionic splanchnic extension of which releases norepinephrine in the spleen. Norepinephrine release in the spleen interacts with beta2-adrenergic receptors (β2AR) in CD4 + T-lymphocyte cells [46]. This type of cell contains choline acetyltransferase (ChAT), which reacts with norepinephrine by releasing acetylcholine [47, 48]. Acetylcholine produced by splenic T-lymphocyte cells can act on α_7nAchR in the spleen and other tissues, thereby reducing inflammation [49].

Hypothalamus-Pituitary-Adrenal axis on the management of inflammation

In addition to the above-mentioned processes, the hypothalamus-pituitary-adrenal (HPA) axis can reduce inflammation [50]. This pathway aligns with the anti-inflammatory reflex. Therefore, stimulation from the NTS to the hypothalamus increases the production and release of corticotropin-releasing hormone (CRH). The effect of CRH on the anterior pituitary gland is to increase the release of adrenocorticotropic hormone (ACTH) into the blood, which can affect the adrenal gland. The effect of ACTH on the cortex of the adrenal gland is to elevate the release of cortisol, which will reduce inflammation and related processes [51, 52]. It seems that the alignment of the anti-inflammatory reflex and HPA axis can significantly inhibit inflammatory processes.

Therapeutic potential of using anti-inflammatory reflex

According to previous studies, using different methods to increase the stimulation of the vagus nerve or components related to the anti-inflammatory reflex can improve inflammatory disease [53, 30]. Clinical trials that activate the anti-inflammatory reflex include pharmacological and non-pharmacological interventions. Pharmacological treatments include acetylcholinesterase inhibitors, nicotine, and α_7nAchR. Non-pharmacological methods include invasive vagal nerve stimulation (VNS), non-invasive VNS, and pulsed ultrasound of the spleen [54]. Nicotine is a toxic agonist of all types of nicotinic receptors and has various side effects [55]. The inhibition of acetylcholinesterase, an enzyme that is highly distributed in different cells, has many side effects that restrict its use. However, a suitable formulation of the α_7nAchR agonist has not yet been achieved in humans. Therefore, the use of drug therapy to activate inflammatory reflexes has several limitations. However, various studies have shown that VNS can reduce various inflammations [54]. For example, VNS has improved the inflammation of rheumatoid arthritis and lupus erythematosus [56, 57].

Heart rate variability; a natural phenomenon for evaluation of autonomic activity

The role of the autonomic nervous system in the anti-inflammatory reflex is clear. The status of the autonomic system can change depending on the activity of the anti-inflammatory reflex [58, 44]. Thus, when the anti-inflammatory reflex is activated, vagus nerve activity increases. One of the functions strongly affected by vagus nerve activity is heart rate [58]. Beat-to-beat heart rate variability is called HRV [59]. The autonomic nerves, especially the vagus nerve, are one of the main elements in creating heart rate variability [60]. It has been seen that in people with intensified inflammatory processes, the amount of HRV changes decreases [61]. During inflammation, the patient's HRV level fluctuates close to normal and the prognosis is considered positive. In addition, treatments that improve inflammation are associated with an increase in HRV, which indicates an increase in the activity of the vagus nerve [61, 62].

Although HRV is strongly influenced by the activity of the autonomic nerves, various factors can affect it, including hormones, drugs, and temperature [63]. At the same time, according to the spontaneous pacing of the heart, changes have been observed even in the isolated heart that has been inflamed, which shows the powerful effect of inflammation on all parts of the body [64, 65]. Therefore, by using HRV as an inexpensive, non-invasive, and accessible method, it is possible to evaluate the status of the autonomic system as the main component controlling the anti-inflammatory reflex.

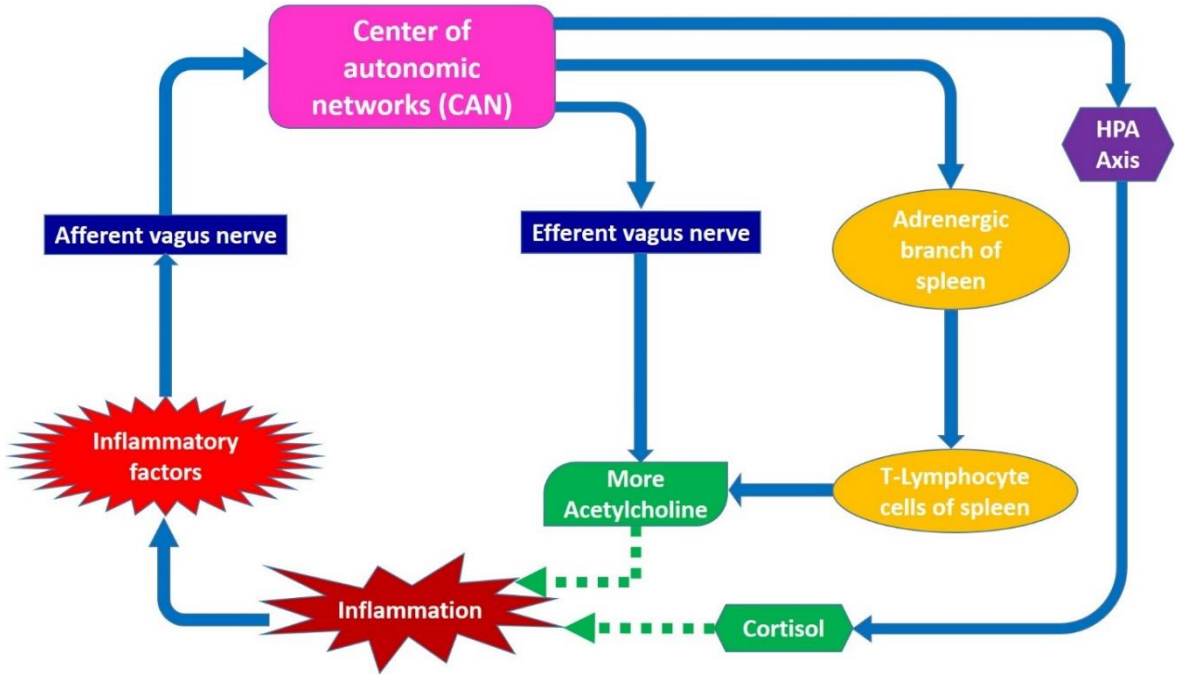

Figure 1. Summary of anti-inflammatory reflex. The solid arrow indicates stimulation, whereas the dashed arrow indicates inhibition. Further details have been provided in the manuscript.

CONCLUSION

The anti-inflammatory reflexes are summarized in Figure 1. Inflammatory factors stimulate the afferent branches of the vagus nerve. The generated messages are processed in the central nervous system and the output is sent to macrophages and other white blood cells through the efferent pathway of the vagus nerve. Moreover, the HPA axis and adrenergic branch of the autonomic nerves in the spleen help control the inflammation (Figure 1). The activation of these responses to inflammation causes a reduction in the release of inflammatory factors, including cytokines. The generated negative feedback shows the interaction between the components of the nervous system and the immune cells, which together control the inflammatory processes. Inflammation is initially helpful for immune system function. However, with the increase in inflammation, positive feedback processes occur in which inflammatory factors enter the blood circulation and create a cascade of inflammatory reactions that are difficult for the body to control. Therefore, proper activity of the anti-inflammatory reflex leads to better management of inflammation along the HPA axis, which increases cortisol secretion. Although the generality of this reflex has been identified, more research can help clarify other branches of its anti-inflammatory effects.

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The author has no conflicts of interest to declare.

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