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# RESTORATION OF BALANCE IN THE AUTONOMIC NERVOUS SYSTEM AS AN INNOVATIVE APPROACH TO THE TREATMENT OF RHEUMATOID ARTHRITIS

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**Annotation**

The immunomodulatory effect of the autonomic nervous system has gained significant interest in recent decades. Studying the influence on the immune system and the roles in inflammation of both sympathetic and parasympathetic nervous systems not only expands our understanding of the disease mechanism, but also may lead to the discovery of potential new therapeutic targets in chronic immune-mediated inflammatory diseases, such as rheumatoid arthritis (RA). An imbalanced autonomic nervous system with reduced parasympathetic and increased sympathetic tone is consistently found in patients with RA. Animal studies of arthritis models have shown that influencing the sympathetic (via α- and β-adrenergic receptors) and parasympathetic (via the α7nAChR nicotinic acetylcholine receptor or electrical stimulation of the vagus nerve) nervous systems can have a beneficial impact on inflammation and arthritis markers. The immunosuppressive effect of the parasympathetic nervous system appears to be less unequivocal than the immunomodulatory effect of the sympathetic nervous system, the activation of which can lead to amplification or reduction of inflammation depending on the timing, dose, and type of adrenergic agent used. In this review, we discuss current knowledge about the roles of both sympathetic (SNS) and parasympathetic nervous system (PNS) in inflammation, with a particular focus on their role in RA. Additionally, potential anti-rheumatic strategies that can be developed by targeting these autonomic pathways are discussed.

**Keywords:** Immunomodulatory effect, nervous system, pathology, inflammatory diseases, rheumatoid arthritis, parasympathetic nervous system.

## INTRODUCTION

Rheumatoid arthritis (RA) is a common immune-mediated inflammatory disease that affects approximately 1% of the adult population worldwide. RA is characterized by inflammation of the synovial membrane, leading to progressive destruction of cartilage and bone. Although its exact etiology remains unknown, progress in

understanding the pathogenesis and underlying mechanisms has led to the development of new and more effective anti-rheumatic drugs. Despite these improvements, a significant number of RA patients do not respond to modern treatment methods, and the need to identify new pathways involved in modulating inflammation for the development of novel anti-inflammatory treatment methods still exists.

## MATERIALS AND METHODS

One such approach could be manipulation of the autonomic nervous system. The nervous system is divided into the peripheral nervous system, which includes the sensory, somatic (voluntary), and autonomic (involuntary) divisions, and the central nervous system. The classic autonomic nervous system is divided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), which are in a delicate balance. These systems typically act in opposition to each other but are capable of acting synergistically, making it difficult to predict the effects of autonomic nervous system activation. Overall, SNS stimulation puts the body into a state of increased activity and alertness, commonly referred to as the "fight or flight" response: heart rate and blood pressure increase, liver glycogen is converted to glucose, and gastrointestinal peristalsis is temporarily suppressed. In contrast, PNS stimulation can be characterized as a rest and digest response, as it returns the body's functions to normal: blood pressure decreases, heart rate slows, gastrointestinal peristalsis resumes, and the liver begins to produce new glycogen.

## RESULTS AND DISCUSSION

It has become evident that the nervous system has numerous anatomical and physiological connections with the immune system. Through these pathways, the nervous and immune systems have extensive communication utilizing neurotransmitters, cytokines, and endocrine hormones. Therefore, the nervous system is capable of detecting and regulating inflammation in peripheral tissues and participates in maintaining immune homeostasis. An overview of the role of the autonomic nervous system in inflammation is shown in Figure 1.

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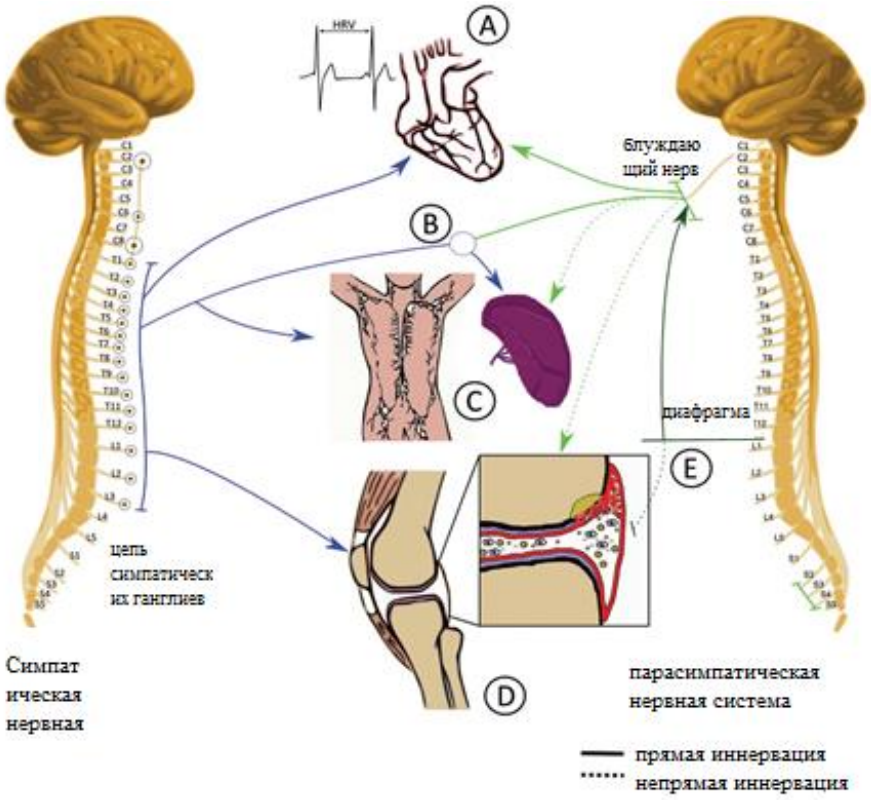


Figure 1. The role of the autonomic nervous system in rheumatoid arthritis.

The autonomic nervous system is divided into the sympathetic (left) and parasympathetic (right) nervous systems. The heart (A) is innervated by both the sympathetic and parasympathetic nervous systems. Both lymphoid organs (spleen and lymph nodes) (C) and joints (G) are innervated directly by the sympathetic nervous system, but innervation by the vagus nerve (parasympathetic nervous system) is not detected. Vagus nerve fibers terminate in the celiac ganglion (B), and further innervation of the spleen via the splenic nerve contains only catecholaminergic fibers from the sympathetic nervous system. Inflammation is detected in the brain through the circulation, as well as through afferent vagus nerve fibers (E). Subdiaphragmatic vagotomy suppresses the transmission of inflammatory signals to the brain. Since the joint is not innervated by the vagus nerve, direct detection of joint inflammation is unlikely.

Several observations have confirmed the notion that there may be an interaction between the nervous system and inflammation in RA. For example, it has been reported that patients with hemiplegia who develop rheumatoid arthritis do not develop arthritis on their hemiplegic (denervated) side (5). Ultimately, this led to the hypothesis that experimental modulation of the body's neural pathways involved in

the regulation of inflammation could potentially lead to the development of new treatments for various inflammatory diseases, including RA.

The autonomic nervous system travels from the central nervous system to peripheral organs through two different neurons: preganglionic and postganglionic neurons. The cell body of the preganglionic neuron is located in the central nervous system between the first thoracic (Th1) and third lumbar (L3) segments of the spinal cord, where its axon connects with the postganglionic neuron. Subsequently, the axon of the postganglionic neuron projects onto the target organ [1]. All regions of the body receive sympathetic innervation. This allows the ANS, together with the hypothalamic-pituitary-adrenal (HPA) axis, to be a key peripheral regulator in maintaining internal homeostasis. Although discussion of the HPA axis is beyond the scope of this review, it should be noted that this axis and the ANS are involved in mutual positive feedback, and activation of one system usually activates the other (7). When homeostasis is disrupted, both the HPA axis and ANS are activated to restore the internal environment.

The role of alpha-adrenergic receptor (α-AR) subtypes in arthritis is less clear. As mentioned above, only cells of the innate immune system express α-ARs (8,12). In normal conditions, α1-ARs are expressed only on natural killer cells, while α2-ARs are present on natural killer cells, monocytes, and macrophages [2]. However, in vitro studies have shown that treatment of normal monocytes with α2-AR agonists can induce the expression of the α1-AR subtype [3].

On the other hand, in patients with RA with high disease activity, catecholamines mainly mediate their action through α1-ARs on RVMCs, while demonstrating decreased density of β2-ARs. Functional α1-ARs were also activated on leukocytes from patients with juvenile idiopathic arthritis, but absent on leukocytes from healthy donors, and stimulation of these receptors induced higher levels of IL-6 [4]. In addition, stimulation of α2-ARs can initiate proliferation.

Agonists or antagonists of β2-adrenergic receptors in experimental arthritis. As far as we know, no studies have been conducted on the effect of β1-agonists on experimental arthritis. β2-ARs are believed to play an important role in the time-dependent immunomodulatory effect of the sympathetic nervous system. In studies using a rat model of adjuvant-induced arthritis (AIA), treatment with β2-AR agonists worsened the severity of the disease if started before or during adjuvant provocation, while administration of β2-AR antagonists prior to adjuvant provocation significantly reduced joint damage severity and delayed the onset of the disease.

Regardless of whether it directly innervates immune organs or not, it is widely recognized that the PNS plays an important role in regulating inflammation through

the vagus nerve. Stimulation of peripheral afferent fibers of the vagus nerve by endotoxins or cytokines can activate the HPA axis and central nervous system, leading to peripheral release of anti-inflammatory glucocorticoids and norepinephrine [4]. Furthermore, it has been shown that efferent fibers of the vagus nerve are involved in inflammatory modulation following bilateral cervical vagotomy in a rat model of experimental sepsis. Subsequent electrical stimulation of the peripheral branch of the vagus nerve significantly reduced the level of TNF-α in the serum and prevented the development of shock compared to vagotomized rats that did not receive electrical stimulation.

Recently, we described the role of the cholinergic anti-inflammatory pathway in CIA in mice. Systemic treatment with nicotine or the specific α7nAChR agonist AR-R17779 significantly reduced disease activity, while unilateral cervical vagotomy exacerbated the disease. The effect of AR-R17779 was stronger than that of nicotine, indicating an important role of α7nAChR in mediating the anti-inflammatory effect. Moreover, AR-R17779 penetrates the blood-brain barrier to a very limited extent, suggesting that these effects are achieved through stimulation of peripheral α7nAChR. We also tested the pharmacological and functional profile of two new compounds, CTI-15311 and CTI-15072, with different effects on ion channel activity, and investigated their role in modulating CIA (unpublished data, van Maanen et al.).

As discussed, both the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), as well as the HPA axis, influence immune homeostasis. Inflammatory mediators signal to the brain through circulation or afferent fibers of the vagus nerve, thereby activating the SNS and/or PNS (Figure 1E). Then, the efferent fibers of the SNS and vagus nerve induce local production of catecholamines and ACh by neurons or non-neuronal cells. The final effects are difficult to predict, as a multitude of different signaling molecules and receptors are involved depending on the phase of the disease.

CONCLUSION A new anti-inflammatory strategy could also be developed using optimal VNS generated by a special device. Recently, it has been shown that VNS inhibits the development of CIA in rats using a stimulus of constant voltage (5 V, 2 ms, 1 Hz) starting from the 10th day after the second immunization [5]. Vagus nerve stimulation is already being used in patients with pharmacoresistant epilepsy and depression. The left vagus nerve is stimulated by an implanted electrode. VNS has had a positive effect on both conditions without serious side effects. A recent study that more closely examined the effects of VNS on the immune system in 11 patients with refractory epilepsy showed that VNS restores the balance of the immune system compared to the control group [6]. The effects of VNS on pro- and anti-inflammatory

cytokines in peripheral blood observed in this study, in combination with the results obtained in the rat model of arthritis, suggest that VNS may be a promising strategy in the treatment of patients with RA. Overall, data obtained from a large number of in vitro and in vivo studies show that therapeutic agents that act on the PNS through the cholinergic anti-inflammatory pathway or act on the SNS through AR receptors may be an important treatment option in the future for various conditions. However, further preclinical and clinical studies are needed to further investigate the potential and safety of these approaches in patients with inflammatory diseases.

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