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Cholinergic anti-inflammatory pathway and COVID-19

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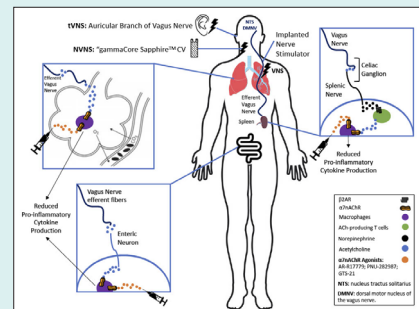
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Abstract

The cholinergic anti-inflammatory pathway (CAP) first described by Wang et al, 2003 has contemporary interest arising from the COVID-19 pandemic. While tobacco smoking has been considered an aggravating factor in the severity of COVID-19 infections, it has been suggested by some that the nicotine derived from tobacco could lessen the severity of COVID-19 infections. This spotlight briefly describes the CAP and its potential role as a therapeutic target for the treatment of COVID-19 infections using vagus nerve stimulation or selective alpha7 nicotinic acetylcholine receptor agonists.

Keywords: Cholinergic anti-inflammatory pathway, Vagus nerve stimulation, Alpha 7 nicotinic acetylcholine receptor, COVID-19



Cholinergic system

The cholinergic system (CS) is composed primarily of organized nerve cells that use or respond to the neurotransmitter acetylcholine (ACh) to communicate with other neurons and cells,^{1,2} most notably, the activation of skeletal muscle contraction by the voluntary cholinergic neuronal stimulation of nicotinic ACh receptors. The CS can be subdivided into neuronal, in which ACh acts as a neurotransmitter, and non-neuronal in which ACh, in a paracrine manner, acts as a local cellular signaling molecule, involved in the regulation of the cellular functions.³

Cholinergic anti-inflammatory pathway

The vagus nerve which is the major parasympathetic nerve, is the body's longest nerve which innervates several major organs including the lungs, the heart, and the gastrointestinal tract.⁴ The parasympathetic nervous system via the vagus nerve, plays an important role in mediating inflammatory responses.⁵⁻⁷ The afferent vagus nerve can detect inflammation in peripheral tissues, sending this information to the brain. The dorsal motor nucleus of the vagus in the brainstem, through the efferent vagus nerve, can exert anti-inflammatory effects. This is known as the cholinergic anti-inflammatory pathway

(CAP) in which ACh, is the key anti-inflammatory mediator.^{7,8}

Alpha 7 nicotinic acetylcholine receptor

As shown in Fig. 1, ACh exerts its anti-inflammatory effects via the alpha 7 nicotinic acetylcholine receptor ($\alpha 7nAChR$) subtype on macrophages via a circuitous pathway from the ganglia of the celiac-superior mesenteric plexus, traveling along the splenic nerve⁹⁻¹¹ resulting in noradrenergic stimulation of ACh secreting T-cells.¹²

In animal models, activation of $\alpha 7nAChRs$ on macrophages downregulates the production of proinflammatory cytokines primarily via the JAK2-STAT3 signaling pathway, and through prevention of activation of the NF- κ B pathway.¹³⁻¹⁶

The lability of ACh and the non-specificity of nicotine and ACh for the $\alpha 7nAChR$ limits their use as therapeutic agents. However, there are $\alpha 7nAChR$ selective agonists, such as AR-R17779,¹⁷ PNU-282987,¹⁸ and GTS-21,¹⁹ that are potential therapeutic agents.

Vagus nerve stimulation

The CAP can be activated through external vagus nerve stimulation in two ways: Invasive vagus nerve stimulation, applied to the cervical branch of the vagus nerve, via



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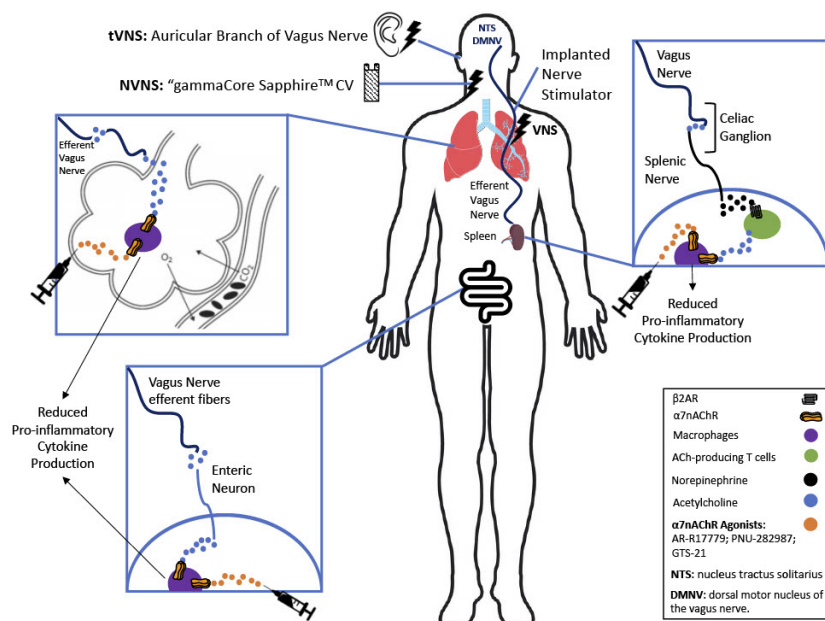


Fig. 1. The cholinergic anti-inflammatory pathway (CAP) exerts its anti-inflammatory effect via efferent vagus nerve stimulation. The CAP then branches off in 3 directions: some vagal fibers innervate the celiac ganglion where they synapse with sympathetic neurons which project to the spleen where they innervate ACh producing T cells. The T cells then release ACh that binds to $\alpha 7nAChR$ on macrophages. Activation of the $\alpha 7nAChR$ on macrophages inhibits the synthesis and release of proinflammatory cytokines from the macrophages, altering them to the M_2 anti-inflammatory phenotype. The second branch of the CAP involves vagal efferents that innervate lung tissue, releasing ACh that directly activates $\alpha 7nAChR$ on alveolar macrophages, again converting them to the M_2 anti-inflammatory phenotype. The third branch of the CAP involves vagal efferents that activate post-ganglionic parasympathetic enteric neurons in the gut, which release ACh that activates $\alpha 7nAChR$ on resident macrophages in the gut again converting them to the M_2 anti-inflammatory phenotype. The effect of the CAP can be mimicked with pharmacological administration of selective $\alpha 7nAChR$ agonists (depicted by the hypodermic needle). Figure derived in part from Koopman et al, Wu et al, and Bonaz et al.²⁷⁻²⁹

neurosurgical intervention which is approved by the FDA for the treatment of depression and epilepsy in patients >12 years of age²⁰; while transcutaneous vagus nerve stimulation (tVNS) of the auricular branch of the vagus nerve is suggested to be a non-invasive alternative means of vagal stimulation.²¹ There are several ongoing clinical trials to assess the tVNS impact on different conditions such as stress response in major depression (NCT04448327), and pediatric inflammatory bowel disease (NCT03863704). Of note, there is an ongoing clinical trial to investigate whether transcutaneous electrical stimulation of the auricular branch of the vagus nerve will decrease the proinflammatory cytokine response in healthy individuals (NCT02910973).

Another type of non-invasive vagus nerve stimulation (NVNS) device, “gammaCore Sapphire™ CV” developed by electroCore, Inc., which fits onto the neck and sends pulses to the vagus nerve, has been granted emergency use authorization (EUA) for the treatment of COVID-19 associated dyspnea (<https://www.fda.gov/media/139968/download>; accessed July 19, 2021).

Role of the spleen in CAP

Acetylcholine is primarily produced by neurons for use as a neurotransmitter, but non-neuronal cells, including T cells in the spleen, can also synthesize ACh. After splenectomy, vagus nerve stimulation is no longer able

to reduce inflammation, therefore the spleen is vital for the CAP response.²²⁻²⁵ As shown in Fig. 1, following vagal stimulation, the anti-inflammatory reflex travels through the sympathetic splenic nerve to the spleen. The splenic nerve, which uses norepinephrine as its neurotransmitter, activates beta-2 adrenergic receptors ($\beta 2AR$) on acetylcholine-producing T cells (choline acetyltransferase positive T-cells (CHAT+)). This stimulates them to secrete ACh in the spleen, establishing an anti-inflammatory response through activation of the $\alpha 7nAChR$ on macrophages,¹³ inhibiting their secretion of proinflammatory cytokines.^{9,26,27}

Of note, this anti-inflammatory effect is not limited to macrophages in the spleen. As shown in Fig. 1, the innervation of vagus nerve into the other organs such as lungs and the gastrointestinal tract can exert a local anti-inflammatory effect.^{28,29} Nonetheless, the spleen is the efferent vagus nerve main targeted organ for the anti-inflammatory effect.^{24,25}

Concluding remarks: CAP and COVID-19

Autopsies of COVID-19 patients show a high infiltration of macrophages within the bronchopneumonia area.³⁰ Furthermore, ACE2 expressing macrophages containing SARS-CoV-2 nucleoprotein antigen densely infiltrate the lymph nodes and spleen of COVID-19 patients, causing significant interleukin-6 (IL-6) production.³¹ In severe

COVID-19 cases, substantial serum IL-6 elevation has been observed.³² The high production of IL-6, together with the macrophage activation syndrome,³³ may explain the high serum level of C-reactive protein,³⁴ which is normally undetectable in viral infections. Therefore, macrophage activation may be an exacerbating factor for severe COVID-19 infection, producing proinflammatory cytokines and contributing to the cytokine storm.^{31,35} Anti-IL-6 or anti-IL-1 treatment of COVID-19 patients significantly improved patient symptoms.^{33,36-39} Of note, a recent study has shown that vagus nerve stimulation inhibits the acute respiratory distress syndrome inflammatory response through activation of the $\alpha 7$ nAChR, via the CAP.¹⁴ Therefore, activation of the CAP through vagus nerve stimulation or pharmacological activation through selective $\alpha 7$ nAChR agonists, may be a possible adjunctive therapy to ameliorate severe inflammation in COVID-19 patients by inhibiting production and release of proinflammatory cytokines by macrophages, thereby reducing the cytokine storm that is a major contributor to COVID-19 morbidity, without causing systemic effects of nicotinic cholinergic receptor stimulation.

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Ethical statement

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Competing interests

None declared.

Authors' contribution

DM and RCS drafted the article, designed the figure, and approved the version to be published.

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