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Medicinal nicotine in COVID-19 Acute Respiratory Distress Syndrome, the New Corticosteroid

Nicotine in COVID ARDS

Abstract

The Cholinergic Anti-Inflammatory Pathway (CAP) refers to the anti-inflammatory effects mediated by the parasympathetic nervous system. Existence of this pathway was first demonstrated when acetylcholinesterase inhibitors showed benefits in animal models of sepsis. CAP functions *via* the Vagus Nerve. The systemic anti-inflammatory effects of CAP converges on the α7 nicotinic AcetylCholine receptor on splenic macrophages, leading to suppression of pro-inflammatory cytokines and simultaneous stimulation of anti-inflammatory cytokines, including Interleukin 10. CAP offers a novel mechanism to mitigate inflammation. Electrical Vagal Nerve Stimulation has shown benefits in patients suffering from rheumatoid arthritis. Direct agonists like nicotine and GTS- 1 have also demonstrated anti-inflammatory properties in models of sepsis and ARDS,, as have acetylcholinesterase inhibitors like Galantamine and Physostigmine. Experience with COVID-19 induced acute respiratory distress syndrome indicates that immunomodulators have a protective role in patient outcomes. Dexamethasone is the only medication currently in use that has shown to improve clinical outcomes. This is likely due to the suppression of what is referred to as a cytokine storm, which is implicated in the lethality of viral pneumonia. Nicotine transdermal patch activates CAP and harvests its anti-inflammatory potential by means of an easily administered depot delivery mechanism. It could prove to be a promising, safe and inexpensive

additional tool in the currently limited armamentarium at our disposal for management of COVID-19 induced acute hypoxic respiratory failure.

Key Words: COVID19; Acute respiratory distress syndrome; Medicinal Nicotine; Cholinergic anti-inflammatory pathway

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Core Tip: Cholinergic anti-inflammatory pathway is novel pathway of the inflammatory reflex. Activation of this pathway can suppress maladaptive inflammatory response seen in Covid 19 ARDS. Nicotine is a potent activator of this pathway and may offer benefits in the management of Covid 19 ARDS , *via* immune suppressive effects similar to Dexamethasone.

INTRODUCTION

Introduction

A dramatic inflammatory response is a common manifestation of severe COVID-19 infection.[1] The purpose of such an inflammatory surge, under normal conditions, is to allow the body to attack, constrain, and kill invading organisms. However, that same inflammatory cascade has negative downstream consequences which can cause direct damage to the host.

Sepsis is the consequence of this hyperactive immune state, most commonly due to a poorly controlled infection or significant tissue injury[2]. The unbalanced immune reaction perpetuates further injury. Neutrophils are recruited and infiltrate the lungs where they undergo apoptosis, further causing tissue damage leading to the development of shock and Acute Respiratory Distress Syndrome[3]. These cells and the molecules they release are a potent force designed to neutralise pathogens, but cause

significant collateral damage in the process. Another casualty of this inflammatory dysregulation is vasodilatation and microvascular thrombi that lead to poor tissue perfusion, further perpetuating the cycle of destruction. This self-perpetuating cycle of tissue damage and release of pro-inflammatory cytokines[4,5] causes further dysregulation of the immune system.

Cytokine is a term given to molecules that carry out inflammatory responses of the immune system, each having their respective receptors distributed across the body. They orchestrate most, if not all, of the consequences of sepsis. This phenomenon is now dubbed a 'cytokine storm' [6] and has been particularly devastating in the current pandemic of COVID-19 infection[7,8].

In recent years many immune modulators have been administered to mitigate sepsis and shock but with limited success in changing the disease course, morbidity, and mortality outcomes. Tocilizumab was used widely during the initial phase of the COVID-19 pandemic in ICUs across the world. But it failed to demonstrate mortality benefits.[9] The reason could partly be explained by the fact that it has a narrow scope of action, only blocking the IL-6 receptor. Upregulation of alternate pathways of inflammation likely are at play. A mechanism to reduce the global immune response is required to suppress collectively the molecules perpetuating inflammation. Corticosteroids are touted as one of the strongest tools in our arsenal to achieve such a goal. Dexamethasone is the only drug we have at our disposal that has shown mortality benefits during the COVID-19 pandemic[10]. Although corticosteroids are considered to globally suppress inflammation, patients are still succumbing to this coronavirus infection despite high doses administered over several days. Other medications for global suppression of inflammation are needed.

One potential pathway that may hold promise in achieving global suppression of the immune system is the Cholinergic Anti-Inflammatory Pathway (CAP). CAP is a

component of the inflammatory reflex, mediated by the cholinergic nervous system and augmenting its tone has been shown to decrease inflammation in both human and animal models. The first evidence of the cholinergic system having immunomodulatory properties dates back to 1987. Prof. P.F Zabrodski showed that Armin, an irreversible acetylcholinesterase inhibitor reduces mortality in animal models of sepsis.[11] It was first recognized in humans when patients with Rheumatoid Arthritis and drug-resistant epilepsy underwent Vagal Nerve stimulation to ameliorate their recurrent seizures. After initiation of Vagal Nerve stimulation, patients incidentally reported improvement in joint pains.[12]

INFLAMMATORY REFLEX

The inflammatory reflex[13] is a central nervous system mediated reflex arc that modulates the immune system. Like other prototypical reflexes, it has an incoming and outgoing arm. Instead of a sensory input that begets a motor response, this circuit senses inflammation and responds with appropriate inflammatory inhibition to reestablish homeostasis. The afferent arm is activated by the products of sterile or infectious inflammation.

The efferent arm is termed the cholinergic anti-inflammatory pathway (CAP) which, through diverse mechanisms, suppresses inflammation[14]. Both the afferent and efferent limbs of the reflex are transmitted predominantly by the Vagus Nerves. Dr. Kevin Tracey has conducted extensive research in the potential therapeutic application of vagal stimulation in modulating the immune system, thereby providing initial major contributions to mapping this pathway.[15,16]

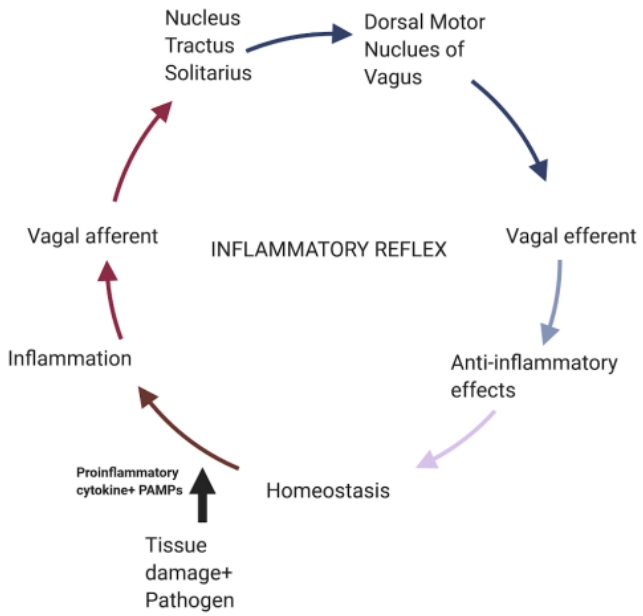

Fig 1. THE INFLAMMATORY REFLEX: The above graphic demonstrates the inflammatory reflex. The afferent limb is activated by pro-inflammatory cytokines like TNF and IL-1β or by PAMPs *via* TLRs. The afferent limb connects to the NTS, the primary vagal afferent nuclei. The Mammalian febrile response is initiated at the NTS. Interneurons connect NTS to DMV incoming signals. The DMV is the primary efferent nuclei of the Vagus Nerve. This efferent signal initiates an anti-inflammatory effect, reestablishing homeostasis.

NTS: Nucleus Tractus Solitarius; DMV: Dorsal Motor Nucleus of Vagus; TNF: tumor necrosis factor; IL-1β: Interleukin 1β; PAMPS: pathogen-associated molecular patterns; TLR: Toll-like receptors

THE AFFERENT LIMB

The Afferent Limb

We are more familiar with the afferent limb of this pathway [19], which plays a role in triggering the mammalian febrile response. Disrupting the afferent arm, for example with a subdiaphragmatic vagotomy, prevented IL-1β induced fever in mice.[20] The afferent limb is activated by pro-inflammatory cytokines like Tumor Necrosis Factor-α (TNF) and interleukin-1β (IL-1β), Neuropeptide Y and prostaglandins. Vagal fibers innervating visceral organs like the lungs and gastrointestinal tract demonstrate sensitivity to IL-1β. Furthermore, the Nodose Ganglion expresses Toll-like receptors[18] which are directly stimulated by pathogen associated molecular patterns (PAMPS) such as those found on bacterial cell walls[21]. Area Postrema directly expresses proinflammatory cytokine receptors.[22] The afferent limb converges on the Nucleus Tractus Solitarius (NTS), the primary central vagal afferent nucleus. Interneurons connect the NTS to the Dorsal Motor Nucleus of Vagus (DMV), which are the primary efferent nuclei of the Vagus Nerve.

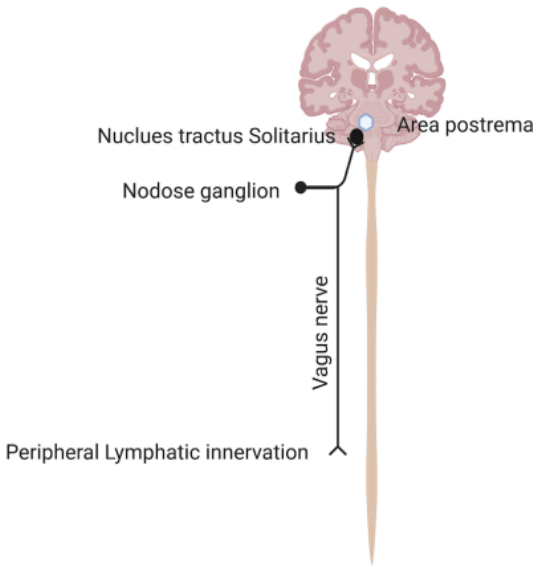

Fig 2. AFFERENT LIMB OF THE INFLAMMATORY REFLEX: This figure demonstrates the mechanisms by which the Vagus Nerve senses inflammation. Vagal sensory neurons directly express receptors for various pro-inflammatory cytokines such as, Tumor Necrosis Factor, Interleukin 1β, Neuropeptide Y and prostaglandins. Vagal fibers innervating the lymphatic system demonstrate sensitivity to Interleukin-1β. In addition, the Nodose Ganglion has been shown to express Toll-like receptors. Area Postrema directly expresses proinflammatory cytokine receptors.[22] The signal is transmitted *via* the vagal afferents to the bilateral Nucleus Tractus Solitarius (NTS), the primary vagal afferent nucleus.[19]

THE EFFERENT LIMB/ CHOLINERGIC ANTI-INFLAMMATORY PATHWAY

The systemic anti-inflammatory effects of CAP are thought to exert its effects *via* the spleen.[23,24] The efferent limb originates at the Dorsal Motor Nucleus of Vagus, the motor nuclei of the Vagus Nerve. Motor signals are transmitted *via* cholinergic fibers down the Vagus Nerve to mount an anti-inflammatory response, reestablishing homeostasis. The Vagus Nerve does not directly innervate the spleen like it does with other visceral organs such as the heart, intestines and liver. So to realize a response from splenic lymphocytes and macrophages, the splenic nerve functions as an intermediary. The efferent pathway is as follows:

Cholinergic fibers from the Vagus Nerve innervate the Celiac Ganglion.

Noradrenergic neurons from the Celiac Ganglion, *via* the splenic nerve, innervate the spleen,and by releasing norepinephrine stimulate β-2 adrenergic receptors on Choline Acetyltransferase(ChAT) positive T cells that reside in the spleen.

Activation of the β-2 adrenergic receptors with norepinephrine induces the release of Acetylcholine (ACh) from these splenic T cells.

ACh then activates α 7nAChr on the splenic macrophages.

Activation of α 7nAChr causes downstream inhibition of the NF-Kappa β pathway and subsequent suppression of pro-inflammatory cytokines. It also induces the release of anti-inflammatory molecules by activating the JAK2-STAT3 pathway[13,14].

Iatrogenic activation of the efferent limb of the inflammatory reflex, irrespective of the modality, has demonstrated anti-inflammatory effects in diverse pathological conditions.[15]

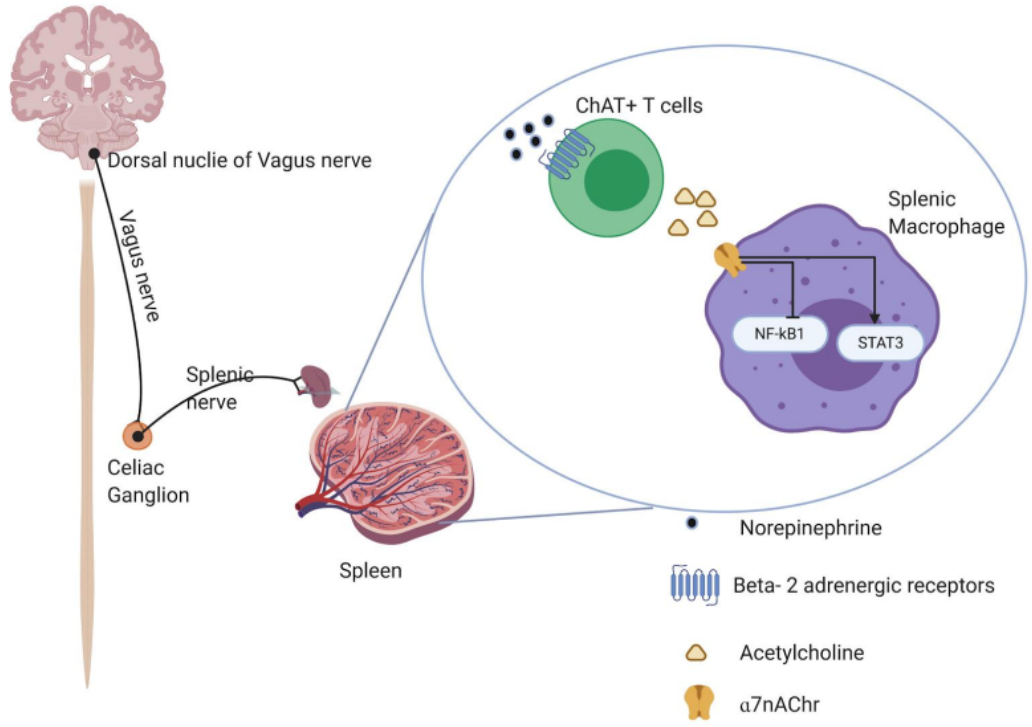

FIG 3. EFFERENT LIMB OF THE INFLAMMATORY REFLEX: Signal from the Dorsal Nuclei of Vagus is transmitted *via* cholinergic fibers of the Vagus Nerve to the Celiac Ganglion. Noradrenergic neurons from the Celiac Ganglion *via* the Splenic Nerve

innervate the spleen. Choline-Acyltransferase (ChAT) positive T cells that reside in the spleen express β-2 adrenergic receptors. Activation of this receptor causes the release of Acetylcholine which binds to the α-7 nicotinic acetylcholinergic receptor(α7nAChr) on splenic macrophages causing the inhibition of NF kappa-β pathway and upregulation of STAT3, ultimately suppressing inflammation[16,23]

HARVESTING THE POTENTIAL OF CHOLINERGIC ANTI-INFLAMMATORY PATHWAY

Augmenting the cholinergic anti-inflammatory pathway offers an effective tool in controlling maladaptive inflammatory responses.[25,26] Modulating the cholinergic tone, irrespective of the modality used, has been shown to suppress inflammation.[27] Direct electrical stimulation of the Vagus Nerve aims to trigger an action potential that consequently activate this pathway downstream. Vagal Nerve stimulation has been shown to suppress inflammation and decrease serum levels of TNF, IL-1β and IL-6[28-32] . Pharmacological modalities to increase the activity of CAP have also yielded similar results. Direct agonists of α7nAChr like the pharmacological agent nicotine have demonstrated anti-inflammatory properties.[33-39]. Ongoing trials using GTS-1, a specific α-7 nicotinic acetylcholinergic receptor agonist, are being conducted in human models of sepsis.[40,41] Another feasible pharmacological strategy is to use inhibitors of acetylcholinesterase to delay degradation of acetylcholine and, thus, enhance the tone of this pathway [42-47]. It must be noted that acetylcholinesterase inhibitors require a functional vagal pathway and fail to demonstrate anti-inflammatory effects in vagotomized animals.[48]

Practical modalities for bedside manipulation of CAP is limited. Vagal Nerve stimulation has limited feasibility for critically ill septic patients. GTS-1, an α7nAChr agonist, is in an experimental phase Acetylcholinesterase inhibitors like Physostigmine increase cholinergic tone systemically and cause undesirable muscarinic side effects. That currently leaves nicotine as the only feasible and medically available potentiator of

CAP as an agonist of α7nAChr. As such, it has demonstrated anti-inflammatory properties in ulcerative colitis and models of human sepsis.[33,34]

NICOTINE

Humans have been using nicotine since prehistoric times[49], mostly in the form of tobacco. Even though it is widely acknowledged that smoking or chewing tobacco is unequivocally injurious to health, nicotine by itself has not been shown to be harmful. Medicinal nicotine has demonstrated potent anti-inflammatory properties while being safe and possessing a low side-effect profile in short term administration. Nicotine administration in animal models of acute respiratory distress syndrome and sepsis have shown improved survival with lower serum inflammatory markers and reduced migration of neutrophils.[36,37,38] Human models of Lipopolysaccharide (LPS) induced sepsis show faster resolution of sepsis.[33] nicotine has also shown anti-inflammatory effects in patients with ulcerative colitis.[34,35]

Nicotine patches are well suited as a modality for increasing nicotinic cholinergic receptor activity, and possess the following advantages:

Nicotine does not have any underlying muscarinic effects and, therefore, lack concerns of increasing airway secretions that occur with acetylcholinesterase inhibitors like Galantamine or Physostigmine.

Using a nicotine patch achieves therapeutic levels of nicotine in the blood within 4-6 hours, offering a rapid drug onset profile.[50]

The active drug nicotine has a short half-life of 2 h. Its metabolite, cotinine, has minimal biological activity.[51] This allows for rapid withdrawal of treatment if necessary. Most acetylcholinesterase inhibitors have a much longer half-life.

The depot mechanism of drug delivery for the nicotine patch allows for a rapid onset, prolonged drug delivery during the duration of application, with a quick withdrawal time.

The 24-hour depot administration avoids repeated administrations and minimized nursing exposure for delivery of the medication.

Ease of administration.

Nicotine transdermal patches are widely used as clinical medication for nicotine replacement therapy in both the hospital and outpatient settings.

There are minimal drug-drug interactions.[52]

IN-HOSPITAL SAFETY DATA ON NICOTINE REPLACEMENT THERAPY

The data on the safety of nicotine on non-smoking patients in an inpatient setting is limited.

Safety data on current or former smokers receiving nicotine replacement therapy in ICU settings and hospital settings fail to demonstrate an increase in adverse events.[53,54,55,56,57,58] Potential side effects of medicinal nicotine administration are few. They may include hypertension and tachyarrhythmias. Rash at the site of the nicotine patch application has been described. Patients with end stage renal disease have a decreased rate of nicotine metabolism so the safety profile for patients on dialysis is uncertain.[59,60]

CONCLUSION

The current ongoing pandemic of SARS-CoV2 proves a new challenge for the medical community. Owing to the tremendous ingenuity and grit demonstrated by teams across the globe, we now have several promising vaccines which demonstrate remarkable efficacy. However, we are yet to develop a similarly promising tool for management of severe infection which is still very prevalent. Consequently, patients continue to succumb in ICUs across the world to the COVID-19 acute hypoxic respiratory failure and septic shock. Several touted treatment modalities during this pandemic have emerged only to quickly fall out of favour due to lack of documented benefit, including Hydroxychloroquine, Tocilizumab, and transfusion of convalescent plasma. Management fo COVID-19 pneumonia, at present, comprises two parallel approaches. Remedesivir or other upcoming potential antivirals, to control viral

replication and immunomodulators like dexamethasone to control the maladaptive immune response. Dexamethasone has shown utility in reducing mortality in patients with COVID-19 induced acute hypoxic respiratory failure. However, despite its use early in the course of the disease, many still deteriorate, requiring increased levels of oxygen support or even mechanical ventilation. Patients continue to die even with dexamethasone as part of their pharmacological regimen. Better modalities are needed to further improve patient outcomes. The hope is bringing to the attention of the medical community a fairly well studied, yet paradoxically unknown pathway of global immune modulation.

Cholinergic anti-inflammatory pathway is a part of a neural reflex termed the inflammatory reflex. It plays a central role in the neural control of inflammation. Inflammatory reflex has an afferent limb that senses systemic inflammation *via* the Vagus Nerve. This signal is relayed to the NTS, the sensory vagal nucleus in the CNS. Interneurons then communicate to the DMV, which is the primary motor nucleus of the Vagus Nerve. The efferent limb of the inflammatory reflex originates from the DMV *via* motor vagal fibers and trigger various anti-inflammatory mechanisms, reestablishing homeostasis. The systemic anti-inflammatory effects of CAP is thought to be due to suppression of pro-inflammatory cytokines from splenic macrophages. Nicotinic acetylcholine receptors on these splenic macrophages are the point of convergence of this pathway's systemic anti-inflammatory effect. This translates to survival benefits with lower levels of serum TNF-α, and IL-6, along with reduced migration of neutrophils in models of sepsis. The potential of augmenting this pathway to mitigate inflammation has been demonstrated in several animal and human studies.

Nicotine is a commonly used molecule that is a potent activator of α7nAChr, with demonstrated anti-inflammatory effects. Animal models of sepsis show improved survival with nicotine administration. Nicotine patch has been studied in the human model of LPS induced sepsis and demonstrated faster resolution of inflammation

compared to controls. Nicotine transdermal patch has been used for decades as a means of nicotine delivery for nicotine replacement therapy in active tobacco users and has demonstrated a favorable safety profile. Thus, nicotine transdermal patch may offer a readily available tool with significant benefit-to-risk ratio in the setting of COVID-19 induced acute hypoxic respiratory failure.

With patients suffering daily across the globe with COVID ARDS, there is little downside to the administration of this relatively inexpensive, widely available medication with a high safety. There is presently a lack of literature regarding the use of nicotine in COVID 19 ARDS patients and it must be further studied first before being applied routinely.

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