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The Role of Nicotinic Anti-Inflammatory Pathway in Prostaglandin Mediated Inflammatory Response in Sepsis: A Short Review

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ABSTRACT

Sepsis is a severe and multifaceted condition of body in response to an infection, which affects multiple organs systems that makes it difficult to treat and enhances the mortality rates. Release of inflammatory cytokines can initiate an inflammatory response during sepsis. However, the response can be modified by the control mechanism inside the body that are essential for the keeping the balance and survival. The cholinergic anti-inflammatory pathway is defined as a comprehensive neurohumoral pathway that diminishes pro-inflammatory cytokine release through the vagus nerve and cholinergic receptors, predominantly α7 nicotinic acetylcholine receptors (α7nAChR) that expressed on inflammatory mononuclear cells. Thus, cholinergic agonists might be a part of prospective treatment approach in inflammatory diseases such as sepsis. This review covers the role of cholinergic system in prostaglandin mediated inflammatory response.
Keywords: Cholinergic anti-Inflammatory pathway, α7nAChR, inflammation, sepsis, prostaglandin

INTRODUCTION

Sepsis is a rigorous and multifaceted condition of body in response to an infective state, which affects multiple organs systems that makes it difficult to treat. Replacement therapies, antimicrobial agents, vasopressors, immunoglobulins, anticoagulant drugs and corticosteroids are involved in current treatment of sepsis however it is still one of the most common causes of death in hospitalized patients. On the subject of the pathophysiology of sepsis, many experimental studies have been conducted in last few decades. A good part of these researches focused on the nicotinic anti-inflammatory pathway that plays a crucial role in the control of inflammatory response. This review summarizes the role of cholinergic agonists and their impact on sepsis pathophysiology.

Sepsis is defined as the systemic inflammatory response to infection, and microbial pathogens and inflammatory response are involved in its physiopathology. Primary cause of sepsis is initiation of inflammation by microbial agent and progression of inflammatory state leads a condition called severe sepsis, which is a common cause of mortality in intensive care units. This condition is commenced with the overproduction of inflammatory cytokines that leads systemic inflammation, extensive hypotension and consequently multiple organ damage (1).

Macrophages, dendritic cells, B lymphocytes are antigen presenting cells (APCs) that modifies antigenic structures into small peptide molecules that can be recognized by T-cell surface receptors like antigen-specific CD8+ in case of inflammation and initiate the primary inflammatory response (2,3).

Regarding that lipopolysaccharide (LPS) is an endotoxin of gram-negative bacteria; exposure of LPS can initiate a compelling inflammatory response. Lipid A compartment of lipopolysaccharide can interact with toll like receptors on phagocytic mononuclear cells. These cells releases tumor necrosis factor (TNF), interleukins, platelet activating factor (PAF) as a response to the inflammatory state (4). IL-1 and IL-6 mediates the activation of T cells and release of cytokines such as a-interferon, IL-2, IL-4, granulocyte-macrophage colony-stimulating factor (GM-CSF). These cytokines are useful in the renewal of the local inflammation and tissue regeneration however greater release of them into blood circulation results in widespread endothelial cell damage. Among the released cytokines, TNF can activate adhesion molecules on the surface of leukocytes and cause the neutrophil adhesion onto endothelial cells. Proteases and reactive oxygen species freed from stimulated neutrophils ease the endothelial cell damage. Endothelial impairment is the beginning of hemodynamic changes in sepsis that eventually leads hypotension, organ failure and mortality. Arachidonic acid metabolites; prostaglandins and

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leukotrienes can cause an increase in capillary permeability, which can be produced with the direct effect of endotoxins or cytokines which also contribute the inflammatory response (5,6). Since the release of numerous kinds of cytokines occur in case of sepsis, treatment strategies may involve the diminution of different kinds of cytokines rather than single one in order to be successful. With respect to this aspect, agents that modulate the cholinergic anti-inflammatory pathway come into prominence in the last decade.

Cholinergic System and Inflammatory Response

Release of inflammatory cytokines can trigger an inflammatory response. However, the response can be controlled by the control mechanism inside the body that are essential for the keeping the balance and survival. This control mechanism on inflammation can be achieved by two mechanisms; activation of neuronal and non-neuronal cholinergic system (4,7). Neuronal cholinergic system involves triggering the vagus nerve whereas non-neuronal cholinergic system activation comprises nicotinic receptor activation expressed on cells that contribute inflammation such as lymphocytes, macrophages, mast cells, dendritic cells, basophils, microglia (8–10).

The cholinergic anti-inflammatory pathway is defined as a comprehensive neural mechanism that attenuates pro-inflammatory cytokine release through the vagus nerve and cholinergic receptors, predominantly α7 nicotinic acetylcholine receptors (α7nAChR). These are homopentameric receptors of cholinergic nicotinic acetylcholine receptor family that composes of five α7 subunits and acetylcholine binding sites. Nicotinic acetylcholine receptors are ligand gated ion channels that characterized as their permeability to sodium ion upon the receptor activation, however α7nAChR are highly permeable for calcium influx. Increments of intracellular calcium ion may trigger many signaling cascades that are required for communication between cholinergic nerves and the immune system. It has been shown that α7 nicotinic acetylcholine receptors are expressed on mononuclear cells of immune system and especially macrophages takes a part in the anti-inflammatory action of cholinergic system. For that reason, this pathway is also called a nicotinic anti-inflammatory pathway. (4,11,12).

Liberation of inflammatory cytokines during an inflammatory response can stimulate brain in order to activate cholinergic anti-inflammatory pathway. The activation of pathway occurs in two ways. One of them is afferent vagus nerve stimulation by the inflammatory cytokines released by activated inflammatory cells via inflammatory stimulus (13). Another way is the passage of cytokines to brain via the transporters on blood brain barrier or through circumventricular organs (14). Cytokines can interact with the capillary endothelium of brain and induce the production of prostaglandins, which in turn may cause fever, pain and the production of glucocorticoids via hypothalamus-pituitary-adrenal (HPA) axis activation (15,16). In response of stimulation via the inflammatory cytokines, brain activates the hypothalamus-pituitary-adrenal (HPA) axis to generate glucocorticoids, sympathetic nervous system to generate catecholamine and efferent vagus nerve for the release of acetylcholine. Acetylcholine that released from the vagal nerve terminals is induced the splenic nerve that results in the discharge of norepinephrine (NE). T lymphocytes are abundant in spleen and beta-adrenergic receptors expressed on the cell surface can be triggered via the NE released from splenic nerve in order to release acetylcholine. Consecutively α7nAChR receptors on macrophage surface is activated by acetylcholine. As a result an effective immunomodulatory action is produced (7,17).

Pertaining to the role of cholinergic system in inflammation, many experimental studies have been conducted in last decades. The role of cholinergic agonists such as nicotine, choline, phosphatidylcholine, CDP-choline in inflammatory conditions like inflammatory bowel diseases, pancreatitis, sepsis, arthritis have been investigated with animal models and clinical researches (18–23). Supporting data has been observed that stimulation of the vagus nerve moderates the inflammatory response by triggering of cholinergic anti-inflammatory pathway in endotoxemic animals (10,24,25). In another study, electrical stimulation of the vagus nerve has been shown to increase acetylcholine release and decrease TNF-α levels through α7nAChRs in experimental sepsis model in mice (24,26). However, electrical stimulation of vagus nerve has been unsuccessful to reduce inflammatory mediators in case of splenic nerve injury or splenectomized mice supports the role of spleen in anti-inflammatory effect of cholinergic system (27).

These findings bear the idea out that vagus nerve has a control over inflammation via the α7nAChR. As well as the physiological approaches, pharmacologic interventions especially drugs act on α7nAChRs have been investigated in quite a lot of studies to activate the cholinergic system.

Cholinergic Agonist and Sepsis

As a cholinergic agonist choline was first synthesized in 1966 and since 1998, it has been considered as an essential substance for life. Choline is a precursor in the synthesis of neurotransmitter acetylcholine in the body and at high doses it can directly interacts with acetylcholine receptors. As a result, cholinergic neurotransmission is enhanced by administration of choline. Furthermore, choline also contributes the synthesis of some basic phospholipids such as phosphatidylcholine and sphingomyelin, which are the basic building blocks of cell membrane (28).

Citicoline (CDP-choline, Cytidine 5'-diphosphate choline) is a complex organic molecule that is produced endogenously as an intermediate molecule in the de novo synthesis of cell membrane phospholipids. Collected evidence supports the cholinergic and neuroprotective effects of administration of citicoline. Citicoline is quickly hydrolyzed into choline

and cytidine by the membrane phosphodiesterases when exogenously administered (29). Accordingly, choline levels in the brain and blood circulation increases (30–32). Choline enhances acetylcholine synthesis (32,33) and its release into synaptic cleft (34,35). Citicoline-mediated improved sympathetic and cholinergic system activity leads many pharmacological and physiological effects (31,32,36). Moreover, the beneficial effect of citicoline given as a nutritional supplement has been observed to the structural integrity and functionality of the neuronal membrane (37). Therefore, in clinical cases citicoline supplements are recommended in cerebral ischemia, hypoxia, head trauma, learning and memory development, Alzheimer's disease, cognitive disorders and Parkinson's disease (34,38–42).

Since their impact on the increment in cholinergic signaling and interaction with the α7nAChR; the role of choline and citicoline in inflammation are investigated in several studies (43–46). GTS-21, a α7nAChR agonist, has been shown to decrease cytokine levels in inflammatory conditions and improve survival rates in sepsis induced by cecal ligation and puncture (47–49). Many studies have shown that citicoline and choline increase survival rates (50–53) and exert positive effects on tissue damage and multiple organ failure in endotoxemic animals (51,53,54).

Many studies have shown that citicoline and choline increase survival rates and exert positive effects on tissue damage and multiple organ failure in endotoxemic animals (50–54). Since the cardiovascular system dysfunctions during sepsis is one of the most affected organ systems in sepsis and the main cause of multiple organ failure; there are plenty of studies investigates the effect of citicoline on cardiovascular changes (32,36,55,56). It has been shown that citicoline and choline have a positive effect on disrupted secondary hemostatic and fibrinolytic systems, disseminated intravascular coagulation and the consumption of increased coagulation factors in the LPS-induced septic shock model (45). Citicoline has been shown to regulate microvascular permeability, hemodynamic and inflammatory parameters while improving the hypotension in septic shock (57,58).

In addition to their cardiovascular effects, cholinergic agonists, choline and citicoline, display a protective effect on vital organs in case of sepsis. Choline reduces endotoxin-induced increase of serum proteins, lipids and inflammatory mediators via the vagal anti-inflammatory pathway activation and endotoxin-induced mononuclear cell activation (46,58). In another study, intraperitoneal administration of choline have been reduced TNF-α level in macrophage cell culture and endotoxemic mice. However, modulating TNF-α level was unsuccessful in α7nAChR knock-out mice and the requirement of α7nAChR in the anti-inflammatory action of choline have been supported (7,50,59).

Proposed Mechanisms of Cholinergic Agonists in Sepsis

The effects of choline and other α7nAChR agonists on inflammatory response have been investigated by in-vitro studies using RAW264.7 macrophage cell line. Choline and α7nAChR agonist GTS-21 produced a significant reduction in TNF-α and HMGB-1 levels in endotoxin-activated RAW264.7 macrophages (47,50,60). However, the effects of cholinergic agonists GTS-21 and NS6740, weak agonist of α7nAChR, have been vanished when selective antagonist methyllycaconitine is applied to LPS-activated microglial culture (61). Administration of cholinergic neurotransmitter acetylcholine caused a significant reduction in the level of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-18 and HMGB1 in lipopolysaccharide-activated human macrophage cells emphasizing that nicotinic receptor activation may be a potential pharmacological target in the treatment of sepsis (10,11,48,62).

Since the cells that contribute the inflammatory response have been found to express cholinergic receptors; their contributions to cholinergic inflammatory response have been widely examined. It has been established expression of α7nAChRs on T lymphocytes, B lymphocytes, dendritic cells, monocytes, macrophages and microglial cells (61,63–67). T lymphocytes and microglial cells also show choline acetyltransferase and acetylcholinesterase activity as well (64,68). In other words these cells can be affected by cholinergic transmission. It has been showed that acetylcholine may have an impact on T cells. Studies have been emphasized that stimulation of nicotinic receptors on T cells with nicotine or acetylcholine can affect intracellular calcium concentration and eventually intracellular signaling cascades have been activated (64,69,70).

Since α7nAChRs are ion gated calcium channels that receptor activation may cause an inward of calcium into cells and rapid desensitization via the change in electrochemical gradient. At the molecular level increase in intracellular calcium concentration activates inositol-triphosphate and phospholipase C that cause calcium release from cellular storages and triggers calcium dependent signaling pathways such as ERK/MAPK in neurons and astrocytes (71,72). However quite a few studies has also been shown that of cholinergic anti-inflammatory pathways may be independent from calcium ion passing through the α7nAChR (47,50,73,74). Studies employing whole patch-clamp technique reveals that leukocytes, as one of the mononuclear cells, have failed to establish α7nAChR-mediated changes in electrical current (75,76). Apart from that recent studies have been found the dual action of α7nAChR underlining that G proteins might also have a role in inositol-triphosphate induced calcium release and metabotropic action of this receptor (Figure 1) (77,78).

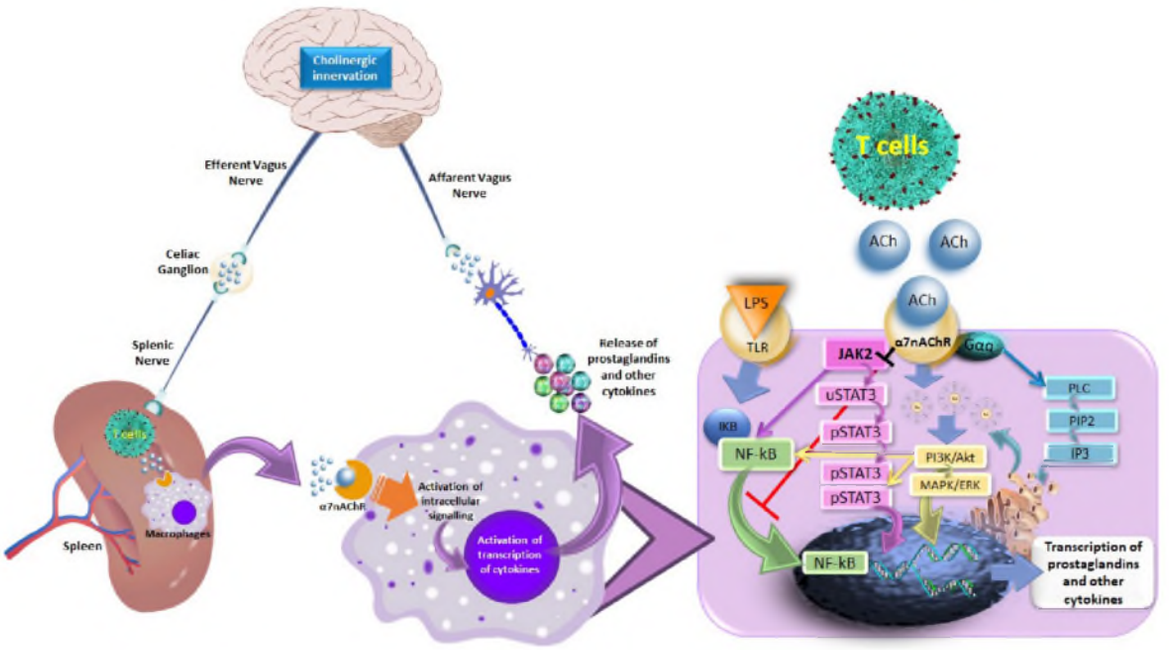

Figure 1: *The neurohumoral mechanism activated during inflammatory challenge and the role of α7nAChR mediated anti-inflammatory response. During LPS induced inflammatory response, ACh released from activated T cells stimulates the α7nAChRs on macrophages which in turn diminishes the proinflammatory cytokine release such as prostaglandins via interfering the intracellular signaling pathways (red arrows indicates the inhibitory action) (details are given in text).*

Regarding the α7nAChR mediated inhibition of pro-inflammatory cytokines in macrophages, two proposed molecular mechanisms is prominent among the others; inhibiting the nuclear translocation of transcription factor NF-KB and JAK2 / STAT3 signaling pathway (67,79,80). α7nAChR agonist nicotine elevates AKT phosphorylation via the activation of JAK2 and PI3K upon the receptor activation and calcium influx. JAK2 and PI3K pathways both have an impact transcription factor NF-kB (81,82). It has been showed that nicotine inhibits the activation of NF-kB cascade and inflammatory cytokine release via the α7nAChR stimulation in macrophages (83). Choline and nicotine, α7nAChR agonists, have been induced the inhibition of NF-KB and consecutive decrease in TNF alpha when administered to LPS-induced RAW 264.7 macrophage cells. Additionally, choline was failed to prevent TNF alpha release in peritoneal macrophage cell culture from α7nAChR knockout mice, supporting the role of α7nAChR for the anti-inflammatory action (50,83). Apart from NF-KB pathway, some studies underline the role of JAK2/STAT3 pathway regarding the anti-inflammatory effect of choline (84). Activation of JAK2 cascade results in production of an anti-inflammatory transcription factor STAT3 that involves the production of anti-inflammatory cytokines IL-6 and IL-10 (85,86). Another study points out the inhibitory effect of choline on increment of LPS-induced TNFα levels but unsuccessful to demonstrate its efficacy in the JAK2-inhibited experimental group (87). Additionally, augmentation of COX-2, NOS expression levels and consequent increase in NO, PGE2, TNFα, IL-6 levels in LPS-induced RAW 264.7 macrophage cells were shown to be mediated by JAK / STAT pathway (88). Taken together, a growing body of data points out that multiple intracellular cascades may be involved in anti-inflammatory action of choline and α7nAChR mediators.

Prostaglandins and Sepsis

As a part of the pro-inflammatory cytokine family, prostaglandins are also contributed to the inflammatory response. Formation of prostaglandins from arachidonic acid involves cyclooxygenase (COX) enzyme that has two isoforms. The COX-1 isoform mostly take a part in the formation of prostaglandins associated with the homeostasis. Oppositely, COX-2 isoform play an important role in production of cytokines induced by tissue damage, tumor promoters, inflammation and cancer. As an inducible enzyme, COX-2 expression level can be increased with cytokines in inflamed tissues that consequently leads the production of prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2). PGG2/H2 are precursors of other prostanoids that contribute inflammation. Prostaglandin I synthase and microsomal prostaglandin E synthase produce PGI2 and PGE2 that plays a major role in the pyretic response which is one of the main symptoms of sepsis (89). PGE2 and PGI2 increase the rate of blood flow by causing vasodilation which further facilitates signs of inflammation such as leukocyte infiltration, pain, and edema (90–94).

Studies have been shown that prostaglandin formation has been mainly related to COX-2 in the carrageenan-induced acute inflammation model (93,95). Augmented expression of cyclooxygenase-2 (COX-2) has been shown in LPS induced in-vitro sepsis model in macrophages (96,97).

Considering the interaction between cholinergic system and cyclooxygenase pathway; citicoline, as choline donor, inhibited the activation of phospholipase A2, decreased the production of arachidonic acid in necrotic tissue when administered orally (98). Acetylcholinesterase inhibitor tacrine has been inhibited the increase in COX-2 expression and PGE2 production in LPS-induced RAW macrophage cell culture by decreasing the degradation of acetylcholine (99). Conflicting results were obtained in an in-vitro study that COX2 expression and prostaglandin E2 synthesis have been shown to increase when the α7nAChR selective agonist nicotine is applied to primary culture of microglial cells (68). Although it has been showed that PGE2 may have a part in reduction of microglial activation and TNFα production in the cerebral endothelium and brain parenchyma (100). Co-administration of choline and aspirin in carrageenan and LPS-induced acute inflammation models in mice produced a synergistic anti-inflammatory effect. In the study, it was observed that choline significantly decreased the level of inflammation induced PGE2, PGI2, TXA2 and other inflammatory cytokines. It has been emphasized that diminishing effect on prostanoid and cytokine levels is mediated by α7nAChR activation. Taken together that cholinergic agonists might be a part of prospective treatment approach in inflammatory diseases such as sepsis and arthritis (52).

2. CONCLUSION

The specialized function of cholinergic system in order to produce an anti-inflammatory action in the body have been described in last few decades and cholinergic agonists have been widely investigated to modulate the release of inflammatory cytokines. As a part of the cytokine family prostaglandins are one of the main contributors of the cardinal signs of inflammation. Further investigations on the control of cholinergic anti-inflammatory pathway in the release of prostaglandins may provide us a novel treatment strategy in case of inflammatory response syndrome and sepsis.

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