Submitted: 01 April, 2024 Accepted: 10 May, 2024 Published: 08 January, 2025 DOI:10.22514/sv.2025.003

Open Access
Signa Vitae

MINI-REVIEW

α7nAChR-mediated cholinergic anti-inflammatory pathway of immune cells in sepsis induced cardiac injury

Yufan Yang[1,2,†], Yueqi He[1,†], Jiaotian Huang[1,2], Xiulan Lu[1,2], Zhenghui Xiao[1,2,*]

[1]Department of Intensive Care Unit, the School of Pediatrics, Hengyang Medical School, University of South China (Hunan Children's Hospital), 410007 Changsha, Hunan, China
[2]Department of Intensive Care Unit, the Affiliated Children's Hospital of Xiangya School of Medicine, Central South University (Hunan Children's Hospital), 410007 Changsha, Hunan, China

***Correspondence**
xiaozh@hnetyy.net
(Zhenghui Xiao)

† These authors contributed equally.

Abstract

Sepsis is a systemic syndrome characterized by widespread inflammatory responses induced by pathogenic microorganism invasion into the body, with increased susceptibility to major organs. Sepsis-induced cardiomyopathy is characterized by reversible myocardial depression or injury, primarily presenting as acute heart failure and/or arrhythmias triggered by sepsis. The mortality rate substantially increases when septic patients develop sepsis-induced cardiomyopathy. The cholinergic anti-inflammatory pathway (CAP) regulates inflammatory responses through the release of acetylcholine (ACh) via the vagus nerve and acts upon α7 nicotinic acetylcholine receptors (α7nAChR) on immune cells to suppress pro-inflammatory sytokines synthesis. In this review, we provide a concise overview of the current understanding of the α7nAChR-mediated CAP in sepsis-induced cardiac injury, with a primary focus on α7nAChR involvement in immune regulation.

Keywords

α7nAChR; Mediated cholinergic anti-inflammatory pathway; Immune cells; Sepsis; Cardiac injury

1. Introduction

Sepsis, a syndrome marked by systemic inflammatory responses triggered by the intrusion of pathogenic microorganisms, especially bacteria, threatens human health due to its elevated incidence and mortality rates [1]. It can lead to multi-organ damage, with the heart being particularly susceptible. Sepsis-induced cardiomyopathy is characterized by reversible myocardial depression or injury, primarily presenting as acute heart failure and/or arrhythmias triggered by sepsis. The mortality rate substantially increases when septic patients develop sepsis-induced cardiomyopathy [2]. Among septic patients, approximately 44% exhibit cardiac dysfunction, which has a mortality rate of nearly 70%. Comparatively, those without cardiac dysfunction have a lower mortality rate of only 20% [3]. Hence, effectively mitigating sepsis-induced myocardial damage and enhancing cardiac function are pivotal in preventing and treating sepsis. Recent studies highlight the inflammatory response provoked by sepsis as a primary contributor to sepsis-induced cardiac injury [4], and efficiently suppressing this cardiac inflammatory response is crucial for mitigating sepsis-induced myocardial damage and improving cardiac function. However, commonly utilized anti-inflammatory drugs in clinical practice, such as glucocorticoids, can not only suppress immune responses but also facilitate infection spread and complicate clinical treatment [5]. Thus, identifying novel interventions and targets to inhibit the cardiac inflammatory response in sepsis has become an urgent scientific challenge. Research suggests that inflammatory responses can be suppressed following the activation of the vagus nerve. In this regard, the effects of vagal nerve excitation on inhibiting sepsis-related inflammatory responses have garnered widespread attention from scholars globally [6]. This review summarizes the current understanding of the α7nAChR-mediated cholinergic anti-inflammatory pathway (CAP) during sepsis-induced cardiac injury, with a primary focus on the involvement of α7nAChR on immune regulation.

In sepsis experiments, vagus nerve stimulation has been demonstrated to effectively inhibit the release of inflammatory sytokines, such as tumor necrosis factor α (TNF-α), interleukin 1 (IL-1) and high-mobility group box 1 (HMGB1), which subsequently leads to the attenuation of the inflammatory response, reduction of sepsis-induced myocardial damage, and an associated improvement in survival rates. Thus, it is indicated that the vagus nerve assumes a pivotal role in the modulation of inflammation [7]. Research focused on the cecal ligation and puncture (CLP) model in septic rats showed that vagus nerve stimulation can significantly enhance survival rates during the early postoperative period, specifically within 8 hours post-surgery [8]. Moreover, investigations conducted by Huston *et al.* [9] emphasize that vagus nerve stimulation can ameliorate systemic inflammatory responses and improve

survival rates in a CLP sepsis model. Nonetheless, the precise mechanisms through which the vagus nerve mitigates sepsis-induced myocardial damage remain an area of ongoing investigation.

Among nicotinic receptors, α7 Nicotinic Acetylcholine Receptor (α7nAChR) is the predominant subtype reported in mammals and has been shown to be important in various diseases [10–13]. Research has shown an elevated expression of α7nAChR in monocytes and macrophages [14, 15]. ACh, a neurotransmitter released from vagus nerve terminals, activates α7nAChR on macrophages to inhibit the reticuloendothelial system and suppress macrophage activation, which subsequently reduces the production of inflammatory sytokines in both serum and tissues. This physiological process is recognized as CAP. It comprises the vagal nerve, Ach and its receptor (α7nAChR) and elicits a more rapid and direct response to systemic inflammatory reactions compared to humoral anti-inflammatory pathways. Consequently, it exerts pronounced anti-inflammatory effects and can attenuate cardiac inflammatory responses in sepsis. However, a comprehensive overview on α7nAChR-mediated CAP during sepsis-induced myocardial damage remains lacking [16].

2. α7nAChR-mediated CAP effects on immune cells in sepsis-induced cardiac injury

2.1 T lymphocyte

As previously described, α7nAChR is essential for inflammatory reactions and is overexpressed on T cell surface [17]. Both deficient and over-proliferation of T cells have been shown to be linked with inflammatory diseases. In addition, both nicotine and ACh have demonstrated the potential to inhibit T cell proliferation in response to mitogenic stimuli [18, 19], and increased infiltration of T lymphocytes has been shown to exacerbate sepsis-induced myocardial injury [20]. Additionally, it has been reported that the anti-proliferative effect of cholinergic agents on T cells is counteracted in the presence of α7nAChR antisense siRNA [21, 22], indicating the pivotal role of α7nAChR during T cell differentiation. Activation of α7nAChR leads to the functional suppression of Th1 and Th17 cells due to reduced synthesis of tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), interferon-γ (IFN-γ), interleukin-17 (IL-17) and interleukin-22 (IL-22) [23]. A previous research showed that in healthy individuals, the antagonism of α7nAChR may enhance Treg-mediated immunoinhibitory effects [24].

2.2 B cell

Regular B lymphocytes, as well as B lymphocyte-derived cell lines, possess a variety of ACh receptors, including α7nAChR [25]. Using single-cell sequencing, Martini *et al.* [26] identified inflammatory and immune cell subtypes in diseased myocardium, revealing an abundance of B lymphocytes in the heart of healthy mice. In addition, further research suggests that the stimulation of α7nAChR participates in calcium ion (Ca^{2+}) signal transduction, one of the important molecular events that facilitate the development of B cells [27]. Moreover, α7nAChR plays a role in negatively regulating adaptive immunity by suppressing the production and release of various pro-inflammatory cytokines, including TNF-α, IL-6 and IFN-γ, in B cells, which inhibits immunoglobulin G1 (IgG1) synthesis [28, 29]. Therefore, it is plausible to speculate that in the context of sepsis-induced myocardial injury, the IgG1 α7nAChR-mediated CAP may demonstrate anti-inflammatory effects by promoting B lymphocyte proliferation within the heart.

2.3 Macrophages

Throughout the course of sepsis, inflammation intensifies, leading to an increased release of inflammatory cytokines by innate immune cells, notably macrophages, upon their activation. This inflammatory response is a crucial factor triggering myocardial damage. Present literature indicates that macrophages, originating from monocytes, play a vital role in various aspects of myocardial injury repair. Macrophages exhibit two distinct phenotypes, categorized as M1 and M2. The M1 subtype releases pro-inflammatory cytokines, promoting pro-inflammatory effects, whereas M2 macrophages secrete anti-inflammatory cytokines, contributing to an anti-inflammatory milieu [30]. Maintaining a balanced polarization of macrophages is of paramount importance for efficient toxin clearance and tissue repair. Thus, the regulation of macrophage polarization holds substantial significance in ameliorating sepsis-induced myocardial damage.

In the cardiac macrophages of mice, CAP primarily demonstrates anti-inflammatory effects via two distinct signaling pathways: the Janus kinase 2/Signal Transducer and Activator of Transcription 3 (JAK2/STAT3) and Phosphoinositide 3-kinase/Protein Kinase B (PI3K/Akt) [31, 32]. These signaling pathways can impede the activation of Nuclear Factor-κB (NF-κB) inhibitory protein kinase, thus preventing NF-κB inhibitory protein phosphorylation. As a result, NF-κB is inhibited, leading to the initiation of an anti-inflammatory response [33].

2.4 Dendritic cells (DCs)

DCs are recognized as the most proficient antigen-presenting cells (APCs) [34, 35], and they hold significant relevance in various ailments, including inflammatory bowel disease, autoimmune myocarditis, systemic lupus erythematosus, and sepsis [35–37]. The functional integrity and activity of DCs are intricately linked to septic patients' survival and prognosis, and related dysfunctions are considered a primary contributor to sepsis-induced immunosuppression, aligning with increased mortality and unfavorable outcomes [38, 39]. Given the notable expression of α7nAChR in DCs, their functions undergo inevitable alterations upon exposure to nicotine or ACh stimuli [40, 41]. The maturation of DCs in the presence of nicotine significantly impairs endocytosis and phagocytic activities, accompanied by a substantial reduction in their capacity to produce interleukin-12 (IL-12) and induce APC-dependent T cell responses [40, 41]. As ACh competitively antagonizes nicotine, CAP can, therefore, alleviate sepsis-induced myocardial damage by mitigating the functional impairments in DCs.

3. Conclusion

The uncontrolled inflammatory response in sepsis plays a crucial role in the development of sepsis-induced myocardial damage. CAP, serving as a natural anti-inflammatory mechanism, displays rapid and precise characteristics. It can enhance the regulatory response of various immune cells during sepsis, thus mitigating sepsis-induced myocardial damage. This proposition is supported by evidence from animal experimental models, offering a new avenue for potential treatments of sepsis-induced myocardial damage.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YFY and YQH—wrote the main manuscript. JTH and YQH—participate in discussion of the manuscript. XLL and ZHX—provide the supervision of the manuscript. All authors reviewed the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This work was funded by the grants from the National Natural Science Foundation of China (No. 82302428) and Hunan Provincial Science and Technology Department Project (No. 2022JJ40205, No. 2020SK2114, No. 2020SK1014-3).

CONFLICT OF INTEREST

All authors report no relationships that could be construed as a conflict of interest.

REFERENCES

[1] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016; 315: 801–810.

[2] Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, Huertos-Ranchal MJ. Sepsis-induced cardiomyopathy. Current Cardiology Reviews. 2011; 7: 163–183.

[3] Martin L, Derwall M, Al Zoubi S, Zechendorf E, Reuter DA, Thiemermann C, *et al*. The septic heart: current understanding of molecular mechanisms and clinical implications. Chest. 2019; 155: 427–437.

[4] Wang H, Cui W, Qiao L, Hu G. Overexpression of miR-451a in sepsis and septic shock patients is involved in the regulation of sepsis-associated cardiac dysfunction and inflammation. Genetics and Molecular Biology. 2020; 43: e20200009.

[5] Zahradnicka M, Saudek F, Lipar K, Skibova J. Hypoglycemia and glucocorticoid-free immunosuppression are related with low dehydroepiandrosterone sulfate level. Endocrine, Metabolic & Immune Disorders Drug Targets. 2017; 17: 63–70.

[6] Fernandez R, Nardocci G, Navarro C, Reyes EP, Acuña-Castillo C, Cortes PP. Neural reflex regulation of systemic inflammation: potential new targets for sepsis therapy. Frontiers in Physiology. 2014; 5: 489.

[7] Ulloa L. The vagus nerve and the nicotinic anti-inflammatory pathway. Nature Reviews Drug Discovery. 2005; 4: 673–684.

[8] Boland C, Collet V, Laterre E, Lecuivre C, Wittebole X, Laterre P. Electrical vagus nerve stimulation and nicotine effects in peritonitis-induced acute lung injury in rats. Inflammation. 2011; 34: 29–35.

[9] Huston JM, Gallowitsch-Puerta M, Ochani M, Ochani K, Yuan R, Rosas-Ballina M, *et al*. Transcutaneous vagus nerve stimulation reduces serum high mobility group box 1 levels and improves survival in murine sepsis. Critical Care Medicine. 2007; 35: 2762–2768.

[10] Plummer HK 3rd, Dhar M, Schuller HM. Expression of the alpha7 nicotinic acetylcholine receptor in human lung cells. Respiratory Research. 2005; 6: 29.

[11] van Maanen MA, Stoof SP, van der Zanden EP, de Jonge WJ, Janssen RA, Fischer DF, *et al*. The alpha7 nicotinic acetylcholine receptor on fibroblast-like synoviocytes and in synovial tissue from rheumatoid arthritis patients: a possible role for a key neurotransmitter in synovial inflammation. Arthritis and Rheumatism. 2009; 60: 1272–1281.

[12] Macklin KD, Maus AD, Pereira EF, Albuquerque EX, Conti-Fine BM. Human vascular endothelial cells express functional nicotinic acetylcholine receptors. The Journal of Pharmacology and Experimental Therapeutics. 1998; 287: 435–439.

[13] Schliebs R, Arendt T. The cholinergic system in aging and neuronal degeneration. Behavioural Brain Research. 2011; 221: 555–563.

[14] Zhang Q, Lu Y, Bian H, Guo L, Zhu H. Activation of the α7 nicotinic receptor promotes lipopolysaccharide-induced conversion of M1 microglia to M2. American Journal of Translational Research. 2017; 9: 971–985.

[15] Wu CH, Inoue T, Nakamura Y, Uni R, Hasegawa S, Maekawa H, *et al*. Activation of α7 nicotinic acetylcholine receptors attenuates monocyte-endothelial adhesion through FUT7 inhibition. Biochemical and Biophysical Research Communications. 2022; 590: 89–96.

[16] Kong W, Kang K, Gao Y, Liu H, Meng X, Yang S, *et al*. Dexmedetomidine alleviates LPS-induced septic cardiomyopathy via the cholinergic anti-inflammatory pathway in mice. American Journal of Translational Research. 2017; 9: 5040–5047.

[17] Jiang Y, Ma H, Wang X, Wang Z, Yang Y, Li L, *et al*. Protective effect of the α7 nicotinic receptor agonist PNU-282987 on dopaminergic neurons against 6-hydroxydopamine, regulating anti-neuroinflammatory and the immune balance pathways in rat. Frontiers in Aging Neuroscience. 2021; 12: 606927.

[18] Schwaneck EC, Renner R, Junker L, Tony HP, Kleinert S, Gernert M, *et al*. T cells, natural killer cells, and $\gamma\delta$T cells in a large patient cohort with rheumatoid arthritis: influence of age and anti-rheumatic therapy. Scandinavian Journal of Rheumatology. 2020; 49: 8–12.

[19] Nizri E, Hamra-Amitay Y, Sicsic C, Lavon I, Brenner T. Anti-inflammatory properties of cholinergic up-regulation: a new role for acetylcholinesterase inhibitors. Neuropharmacology. 2006; 50: 540–547.

[20] Chen LR, Yang H, Liu L, Wang XX, Zhang XM, Wang HX. CD1d-dependent natural killer T-cells inactivation aggravates sepsis-induced myocardial injury via T lymphocytes infiltration and IL-6 production in mice. International Immunopharmacology. 2023; 120: 110256.

[21] Nizri E, Irony-Tur-Sinai M, Faranesh N, Lavon I, Lavi E, Weinstock M, *et al*. Suppression of neuroinflammation and immunomodulation by the acetylcholinesterase inhibitor rivastigmine. Journal of Neuroimmunology. 2008; 203: 12–22.

[22] Wu YJ, Wang L, Ji CF, Gu SF, Yin Q, Zuo J. The role of α7nAChR-mediated cholinergic anti-inflammatory pathway in immune cells. Inflammation. 2021; 44: 821–834.

[23] Nizri E, Irony-Tur-Sinai M, Lory O, Orr-Urtreger A, Lavi E, Brenner T. Activation of the cholinergic anti-inflammatory system by nicotine attenuates neuroinflammation via suppression of Th1 and Th17 responses. The Journal of Immunology. 2009; 183: 6681–6688.

[24] Gowayed MA, Rothe K, Rossol M, Attia AS, Wagner U, Baerwald C, *et al*. The role of α7nAChR in controlling the anti-inflammatory/anti-

arthritic action of galantamine. Biochemical Pharmacology. 2019; 170: 113665.

[25] Kawashima K, Fujii T. Expression of non-neuronal acetylcholine in lymphocytes and its contribution to the regulation of immune function. Frontiers in Bioscience. 2004; 9: 2063–2085.

[26] Martini E, Kunderfranco P, Peano C, Carullo P, Cremonesi M, Schorn T, *et al*. Single-cell sequencing of mouse heart immune infiltrate in pressure overload-driven heart failure reveals extent of immune activation. Circulation. 2019; 140: 2089–2107.

[27] Skok MV, Kalashnik EN, Koval LN, Tsetlin VI, Utkin YN, Changeux JP, *et al*. Functional nicotinic acetylcholine receptors are expressed in B lymphocyte-derived cell lines. Molecular Pharmacology. 2003; 64: 885–889.

[28] Skok M, Grailhe R, Changeux JP. Nicotinic receptors regulate B lymphocyte activation and immune response. European Journal of Pharmacology. 2005; 517: 246–251.

[29] Fujii YX, Fujigaya H, Moriwaki Y, Misawa H, Kasahara T, Grando SA, *et al*. Enhanced serum antigen-specific IgG1 and proinflammatory cytokine production in nicotinic acetylcholine receptor alpha7 subunit gene knockout mice. Journal of Neuroimmunology. 2007; 189: 69–74.

[30] Orecchioni M, Ghosheh Y, Pramod AB, Ley K. Macrophage polarization: different gene signatures in M1(LPS+) *vs.* classically and M2(LPS−) *vs.* alternatively activated macrophages. Frontiers in Immunology. 2019; 10: 1084.

[31] de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerloo DJ, Bennink RJ, *et al*. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nature Immunology. 2005; 6: 844–851.

[32] Bencherif M, Lippiello PM, Lucas R, Marrero MB. Alpha7 nicotinic receptors as novel therapeutic targets for inflammation-based diseases. Cellular and Molecular Life Sciences. 2011; 68: 931–949.

[33] Piovesana R, Salazar Intriago MS, Dini L, Tata AM. Cholinergic modulation of neuroinflammation: focus on α7 nicotinic receptor. International Journal of Molecular Sciences. 2021; 22: 4912.

[34] Lin W, Liu T, Wang B, Bi H. The role of ocular dendritic cells in uveitis. Immunology Letters. 2019; 209: 4–10.

[35] Chudnovskiy A, Pasqual G, Victora GD. Studying interactions between dendritic cells and T cells *in vivo*. Current Opinion in Immunology. 2019; 58: 24–30.

[36] Ganguly D, Haak S, Sisirak V, Reizis B. The role of dendritic cells in autoimmunity. Nature Reviews Immunology. 2013; 13: 566–577.

[37] Wang G, Li X, Zhang L, Elgaili Abdalla A, Teng T, Li Y. Crosstalk between dendritic cells and immune modulatory agents against sepsis. Genes. 2020; 11: 323.

[38] Kumar V. Dendritic cells in sepsis: potential immunoregulatory cells with therapeutic potential. Molecular Immunology. 2018; 101: 615–626.

[39] Poehlmann H, Schefold JC, Zuckermann-Becker H, Volk HD, Meisel C. Phenotype changes and impaired function of dendritic cell subsets in patients with sepsis: a prospective observational analysis. Critical Care. 2009; 13: R119.

[40] Nouri-Shirazi M, Guinet E. Evidence for the immunosuppressive role of nicotine on human dendritic cell functions. Immunology. 2003; 109: 365–373.

[41] Guinet E, Yoshida K, Nouri-Shirazi M. Nicotinic environment affects the differentiation and functional maturation of monocytes derived dendritic cells (DCs). Immunology Letters. 2004; 95: 45–55.

How to cite this article: Yufan Yang, Yueqi He, Jiaotian Huang, Xiulan Lu, Zhenghui Xiao. α7nAChR-mediated cholinergic anti-inflammatory pathway of immune cells in sepsis induced cardiac injury. Signa Vitae. 2025; 21(1): 21-24. doi: 10.22514/sv.2025.003.