

Prospective Methods of Sepsis Treatment by Activation of the Cholinergic Anti-Inflammatory Pathway

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Abstract

Literature data, as well as the results of our experimental studies (after the cholinergic anti-inflammatory mechanism we established in 1987) allow us to suppose, that n-cholinomimetic ($\alpha 7$ nAChRs agonists, nicotine), acetylcholinesterase reversible inhibitor, adrenomimetics ($\beta 2$ ARs agonists) and M1-cholinomimetics, along with a range of therapeutic measures, in particular, with prescription of antibiotics, can be considered as promising agents for the treatment of sepsis and septic shock.

Keywords: *Cholinergic Anti-Inflammatory Pathway; Sepsis; $\beta 2$ ARs Agonist; $\alpha 7$ nAChR Agonist; Acetylcholinesterase Reversible Inhibitor; Proinflammatory Cytokines*

Introduction

Septicaemia and septic shock are a major public health problem. Every year, around the world, it causes the death of more than a million people. Mortality from sepsis, depending on various factors, ranges from 12 to 60% of all deaths associated with diseases and their complications [1] and there is an increase in the number of cases of sepsis and the mortality rate from it [2]. Sepsis is a clinical syndrome with the development of life-threatening organ dysfunction caused by impaired regulation of response to infection. In septic shock, there is a critical reduction in tissue perfusion; many organs, including lungs, kidneys and liver, can also be severely affected. The most common causes in immunocompetent patients are various types of gram-positive and gram-negative bacteria. Atypical bacterial or fungal infections may be contributing factors in immunodeficient patients. Symptoms include fever, hypotension, oliguria and blurred consciousness. Diagnosis is based on clinical studies combined with bacteriological sowing results indicating the presence of infection; early detection and treatment are crucial. Aggressive infusion resuscitation, antibiotics, surgical removal of an infected area or necrotic tissue, drainage of purulent secretions and maintenance therapy are used as treatment [3-5].

The following principles of antibiotic therapy for sepsis are currently recommended (International Guidelines for Management of Sepsis and Septic Shock: 2016) [6,7].

Cholinergic stimulation, as we established in 1987 [8] and in subsequent studies, significantly reduces the mortality of albino mice from sepsis caused by intraperitoneal or intrapulmonary administration, respectively of *E. coli* and *P. vulgaris* [8-12]. Thus, the cholinergic anti-inflammatory mechanism has been discovered in 1987 [8], named "cholinergic anti-inflammatory pathway" in 2000 [13] after the research its implementation at the organismal, cellular and subcellular levels [9,10,13,14]. It should be noted that in 1995 it was proved

the possibility of cholinomimetics for emergency activation of antimicrobial resistance of the organism in sepsis [9,10]. In the future, the study of the cholinergic anti-inflammatory pathway caused by the action of acetylcholine on $\alpha 7$ n-acetylcholine receptors ($\alpha 7$ nAChRs) cells of the monocyte-macrophage system (MMC), followed by inhibition of the production by the cells of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) and reduced mortality from sepsis were devoted hundreds of articles various authors [11-21]. Reduced production of TNF- α , IL-1 β , IL-6 (anti-inflammatory effect occurrence) for cholinergic anti-inflammatory pathway is provided kinase JAK2, transcription factor STAT3, NF- κ B transcription factor) [13,18-22].

We have established on outbred mice that that acetylcholine chloride in a dose of 20 mg/kg 6h after subcutaneous injection significantly reduces mortality of mice from sepsis induced by intraperitoneal injection of 2×10^9 CFUs diurnal culture of *E. coli* in 2.0 ml of saline and the blood levels of proinflammatory cytokines TNF- α , IL-1 β and IL-6 [18].

It was established in experiments on noninbred mice that activation of $\alpha 7$ n acetylcholine receptors ($\alpha 7$ nAChR) by anabasine in single doses of 1.0 and 5.0 mg/kg for 2h before modeling sepsis (intraperitoneal injection of 2×10^9 CFUs diurnal culture of *E. coli*) cause a significant dose-dependent reduction of mortality of mice due to a decrease in the amount of proinflammatory cytokines TNF- α , IL-1 β and IL-6 in the blood [23]. The same action is taken by reversible inhibition of cholinesterase (proserine) and nicotine on mouse mortality and blood levels of proinflammatory cytokines during the early phase of sepsis [24]. Realization of the cholinergic anti-inflammatory pathway (stimulation of the peripheral nicotinic holinoreceptors ($\alpha 7$ nAChR) and central muscarinic cholinoreceptors (mAChR) was modulated by stimulation of the mAChR of the phagocytic monocytic system cells [25]. The activation of $\alpha 7$ nAChR with anabasine (0.5 LD50) and the use of antibodies to TNF- α (1 mg/kg) 2h before sepsis modeling significantly reduces mortality of mice from experimental sepsis due to a decrease in the blood concentration of TNF- α , IL-1 β , and IL-6. After combined administration of anti-TNF- α antibodies and anabasine, an additive effect was observed [19]. The same influence caused the effect of M1 muscarinic acetylcholine receptor agonist (TBPB) and $\alpha 7$ nAChRs agonist (GTS-21). Combined treatment with TBPB and GTS-21 determined their additive effect [21].

When the cholinergic anti-inflammatory pathway is realized, in addition to the excitation of $\alpha 7$ nAChRs [11,14,26,27], which cause the effects already mentioned, nAChRs activation of the brain substance of the adrenal glands and sympathetic ganglia occurs, which leads to the production of epinephrine and norepinephrine (NE), which activation of MMS adrenergic receptors and reduce the production of pro-inflammatory cytokines [27]. At this *n. vagus*, releasing acetylcholine (ACh) in the celiac ganglion, causes excitation of the spleen nerve, the action of NE through its efferent fibers on T lymphocytes, the production of ACh by these lymphocytes, activation of ACh of $\alpha 7$ nAChRs of MMS cells of the spleen [14,27]. Epinephrine and NE probably activating the adrenergic receptors of cells of the MMS (direct action) [27], $\beta 2$ -adrenergic receptors ($\beta 2$ ARs) of spleen T-lymphocytes (indirect effect) [15], cause the same effect as activation of $\alpha 7$ nAChRs, leading to reduction in the synthesis of proinflammatory cytokines by cells of the MMS [14,16,20].

Experiments on random-bred albino mice showed that of $\beta 2$ -adrenoreceptor agonist hexaprenaline sulfate significantly reduced mortality of mice from experimental sepsis (intraperitoneal administration of *E. coli*) in 4 and 24 h after modeling by reducing blood levels of proinflammatory cytokines TNF α , IL-1 β , and IL-6. The antagonist of $\beta 2$ AR ICI-118, 551 eliminated this effect [20]. The combined administration of NF- κ B inhibitor (BAY 11-7082) and $\beta 2$ -adrenoreceptors agonist have an additive effect [22]. Thus, n-cholinomimetic ($\alpha 7$ nAChRs agonists, nicotine), reversible inhibitor of acetylcholinesterase, adrenomimetics ($\beta 2$ ARs agonists) and M1-cholinomimetics, along with a range of therapeutic measures, in particular, with prescription of antibiotics, can be considered as promising agents for the treatment of sepsis and septic shock.

Bibliography

1. Pruetz SB., *et al.* "Innate immunity and inflammation in sepsis: mechanisms of suppressed host resistance in mice treated with ethanol in a binge-drinking model". *Toxicological Sciences* 117.2 (2010): 314-324.

2. Martin GS. "Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes". *Expert Review of Anti-infective Therapy* 10.6 (2012): 701-706.
3. Singer M., et al. "The third international consensus definitions for sepsis and septic shock (sepsis-3)". *Journal of the American Medical Association* 315.8 (2016): 801-810.
4. Gyawali B., et al. "Sepsis: The evolution in definition, pathophysiology, and management". *SAGE Open Medicine* 7 (2019): 1-13.
5. Hotchkiss RS., et al. "Sepsis and septic shock". *Nature Reviews Disease Primers* 2 (2016): 16045.
6. Rhodes A., et al. "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016". *Intensive Care Medicine* 43.3 (2017): 304-377.
7. De Backer D and Dorman T. "Surviving Sepsis Guidelines: A Continuous Move Toward Better Care of Patients With Sepsis". *Journal of the American Medical Association* 317.8 (2017):807-808.
8. Zabrodskii PF. "Effect of armin on nonspecific resistance factors of the body and on the primary humoral immune response". *Farmakologiya I Toksikologiya* 50.1 (1987): 57-60.
9. Zabrodskii PF. "Variation in antiinfectious nonspecific resistance of the organism caused by cholinergic stimulation". *Bulletin of Experimental Biology and Medicine* 120.2 (1995): 809-811.
10. Zabrodskii PF. "Change in the non-specific anti-infection resistance of the body exposed to cholinergic stimulation". *Bulletin of Experimental Biology and Medicine* 120.8 (1995): 164-166.
11. PF Zabrodskii. "Immunotoxicology of organophosphorus compounds". Saratov (2016): 289.
12. Zabrodskii PF and Mandych VG. "Immunotoxicology of xenobiotics". Saratov Military Institute of Biological and Chemical Safety (2007): 420.
13. Borovikova LV., et al. "Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin". *Nature* 405.6785 (2000): 458-462.
14. Bernik TR., et al. "Pharmacological stimulation of the cholinergic antiinflammatory pathway". *Journal of Experimental Medicine* 195.6 (2002):781-788.
15. Bonaz BL and Bernstein CN. "Brain-gut interactions in inflammatory bowel disease". *Gastroenterology* 144.1 (2013): 36-49.
16. Fernandez R., et al. "Neural reflex regulation of systemic inflammation: potential new targets for sepsis therapy". *Frontiers in Physiology* 5 (2014): 489.
17. Reardon C. "Neuro-immune interactions in the cholinergic anti-inflammatory reflex". *Immunology Letters* 178 (2016): 92-96.
18. Zabrodskii PF. "Effect of acetylcholine on mortality of mice from sepsis and proinflammatory cytokine production". *Bulletin of Experimental Biology and Medicine* 150.3 (2011): 340-342.
19. Zabrodskii PF., et al. "Effect of $\alpha 7n$ -Acetylcholine Receptor Activation and Antibodies to TNF- α on Mortality of Mice and Concentration of Proinflammatory Cytokines During Early Stage of Sepsis". *Bulletin of Experimental Biology and Medicine* 159.6 (2015): 740-742.
20. Zabrodskii PF., et al. "Role of $\beta 2$ -adrenoreceptors in adrenergic anti-Inflammatory mechanism in sepsis". *Bulletin of Experimental Biology and Medicine* 163.6 (2017): 710-713.

21. Zabrodskii PF, *et al.* "Combined Effects of M1 Muscarinic Acetylcholine Receptor Agonist TBPB and $\alpha 7n$ -Acetylcholine Receptor Activator GTS-21 on Mouse Mortality and Blood Concentration of Proinflammatory Cytokines in Sepsis". *Bulletin of Experimental Biology and Medicine* 162.6 (2017): 750-753.
22. Zabrodskii PF, *et al.* "Combined Effect of NF- κ B Inhibitor and $\beta 2$ -Adrenoreceptor Agonist on Mouse Mortality and Blood Concentration of Proinflammatory Cytokines in Sepsis". *Bulletin of Experimental Biology and Medicine* 165.4 (2018): 445-448.
23. Zabrodskii PF, *et al.* "The effect of anabasine on mortality and concentration of proinflammatory cytokines in blood of mice at early stage of sepsis". *Ekspierimental'naia i Klinicheskaia Farmakologija* 77.11 (2014): 20-22.
24. Zabrodskii PF, *et al.* "Effects of reversible inhibition of cholinesterase and nicotine on mouse mortality and blood levels of proinflammatory cytokines during the early phase of sepsis". *Bulletin of Experimental Biology and Medicine* 152.5 (2012):600-602.
25. Zabrodskii PF, *et al.* "Role of nicotinic and muscarinic cholinoreceptors in the realization of the cholinergic anti-inflammatory pathway during the early phase of sepsis". *Bulletin of Experimental Biology and Medicine* 153.5 (2012):700-703.
26. Link A., *et al.* "Phosphodiesterase 4 inhibition but not beta-adrenergic stimulation suppresses tumor necrosis factor-alpha release in peripheral blood mononuclear cells in septic shock". *Critical Care* 12.6 (2008): R159.
27. Scanzano A and Cosentino M. "Adrenergic regulation of innate immunity: a review". *Frontiers in Pharmacology* 6 (2015): 171.

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