

Commentary

Neuroimmune perspectives in sepsis

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Abstract

Physiologic anti-inflammatory mechanisms are selected by evolution to control the immune system and to prevent infectious and inflammatory disorders. Central-acting α_2 -agonists attenuate systemic inflammation and improve survival in experimental sepsis. This anti-inflammatory and therapeutic mechanism of central sympatholytics appears to be mediated by an unexpected vagomimetic potential of the α_2 -agonists to activate the vagus nerve. Recent studies, however, rule out a cholinergic anti-inflammatory mechanism based on a direct cholinergic interaction between the vagus nerve and the immune system. Since the nervous system is the principal regulator of the immune system, physiologic studies understanding the neuroimmune connections can provide major advantages to design novel therapeutic strategies for sepsis.

In the previous issue of *Critical Care*, Hofer and colleagues reported that central sympatholytics attenuate systemic inflammation and improve survival in experimental sepsis [1]. α_2 -Adrenoceptors close a negative feedback loop in the neuronal synapses to limit catecholamine production. α_2 -Agonists (clonidine and dexmedetomidine) therefore mimic a physiological condition of high levels of catecholamines and inhibit the noradrenergic neurotransmission in the medulla oblongata. The clinical implications of the central-acting α_2 -agonists reveal an unexpected sedative potential that is in part mediated by a proposed vagomimetic potential of these agonists to activate the vagus nerve [2]. The anti-inflammatory and therapeutic potential of central sympatholytics can therefore be mediated by the vagus nerve. This mechanism would be similar to that described for cholecystokinin, semapimod, ghrelin, leptin and melanocortin peptide, which control immune responses via the vagus nerve, as surgical vagotomy abrogates their anti-inflammatory potential [3]. Future studies with surgical vagotomy are needed to confirm that the vagus nerve mediates the anti-inflammatory potential of central sympatholytics.

The studies of Hofer and colleagues suggest that central sympatholytics may control systemic inflammation by inhibiting NF- κ B and cytokine production in the liver [1]. If the vagus nerve mediates the anti-inflammatory potential of the α_2 -agonists, however, central sympatholytics may modulate systemic inflammation through a mechanism mediated by the spleen [4]. Recent studies indicate that the spleen is a major source of inflammatory cytokines in experimental sepsis, as splenectomy attenuates systemic inflammation and protects against sepsis. The spleen is required for the anti-inflammatory potential of the vagus nerve. Vagus nerve stimulation inhibits systemic TNF levels in control animals but not in splenectomized animals [5]. Likewise, nicotinic agonists prevent systemic inflammation and improve survival in control animals but not in splenectomized animals. These studies might have clinical implications as they may not be beneficial for patients with a compromised or damaged spleen.

Rosas-Ballina and colleagues have recently demonstrated that there is no cholinergic connection between the vagus nerve and immune cells in the spleen [6]. The vagus nerve does not innervate the spleen, and vagal immunomodulation in experimental sepsis is mediated by postganglionic catecholaminergic fibers from the celiac mesenteric plexus traveling through the splenic nerve [6]. Unlike central-acting drugs, peripheral sympatholytics can prevent the anti-inflammatory potential of the vagus nerve and enhance systemic inflammation in sepsis.

Can NF- κ B predict the outcome of sepsis? Since NF- κ B is a key regulator of cytokine production, NF- κ B inhibition can modulate systemic inflammation [4]. A characteristic example is that the protection of RAGE-deficient mice from sepsis correlates with NF- κ B inactivation in the lung and peritoneum. NF- κ B, however, also protects parenchyma cells from

CLP = cecal ligation and puncture; NF = nuclear factor; TNF = tumor necrosis factor.

cytotoxicity and cell death [7,8]. The most characteristic example is that p65RelA and IKK knockout mice exhibit embryonic death resulting from extensive TNF α -mediated fetal hepatocyte apoptosis. Consistently, disruption of TNF α signaling – either by removing TNF α or TNF receptor 1 – prevents this hepatocyte apoptosis in *rela*^{-/-} mice, allowing embryonic development to birth. In agreement with these studies, inhibition of NF- κ B after partial hepatectomy results in massive hepatocyte apoptosis and impairs liver function. Conversely, NF- κ B activation in the liver prevents hepatic injury during ischemia and reperfusion. NF- κ B inhibition produces different effects in enterocytes, however, and can prevent intestinal derangements during sepsis. These studies suggest that the ubiquitous inhibition of NF- κ B may not generate an overall beneficial effect especially in the liver, unless the therapy targets specific organs or immune cells. Future studies are needed to determine the molecular and cellular mechanism by which central sympatholytics modulate the different NF- κ B pathways in sepsis.

What is the therapeutic time frame for experimental sepsis? Pre-emptive treatment with central sympatholytics started 12 hours before cecal ligation and puncture (CLP) provides survival benefits, but not if the treatment was started 1 hour after the surgical procedure [1]. One potential explanation for this is that the early phase of sepsis is characterized by high concentrations of circulating catecholamines, which can boost the initial inflammatory responses. The endogenous production of catecholamines decreases during the progression of sepsis, however, and can become insufficient for the homeostasis of the cardiovascular system (as indicated by the need for catecholamine administration during septic shock) [9]. Late inhibition of catecholamines can therefore be rather detrimental. Another consideration is that ketamine, the anesthetic used for CLP surgery by Hofer and colleagues, is a noncompetitive inhibitor of nicotinic receptors that can limit the anti-inflammatory potential of the vagus nerve. Since the half-life of ketamine is approximately 3 hours, this anesthetic may limit the effect of sympatholytics administered 1 hour after the CLP.

Previous studies from Hofer and colleagues also indicate that pharmacologic cholinesterase inhibition with physostigmine or neostigmine improved survival in experimental sepsis when the treatment was started immediately after the CLP [10]. A significant trend toward protection was observed when the treatment was started 6 hours after the surgical procedure. Yet the authors noted this protection was not statistically significant ($P=0.057$), probably due to the small sample size [10]. An important consideration is that these strategies can be limited by a potential cholinergic attrition that limits acetylcholine production by the vagus nerve during sepsis. Since vagus nerve stimulation requires α_7 -nicotinic acetylcholine receptors, direct activation of this receptor using nicotinic agonists may prevent this potential cholinergic attrition during the progression of sepsis. Indeed, nicotine

improved survival in experimental sepsis even when the treatment was delayed 24 hours after CLP [11]. Similar results have been confirmed by other investigators using selective α_7 -nicotinic acetylcholine receptor agonists. On the other hand, there are significant differences in these studies that can contribute to these late therapeutic benefits. The two studies use different models of sepsis (with or without antibiotics) and mice with different gender, age and genetic background (female C57BL/6 mice 12 to 16 weeks old versus male BALB/c mice 6 to 8 weeks old). Hofer and colleagues do not use antibiotics to prevent their interferences with the immune responses [1], whereas Wang and colleagues used antibiotics to mimic clinical settings [11]. It is possible that the use of antibiotics may limit bacteremia induced by CLP and may favor the benefits of delayed treatment with nicotinic agonists.

Future studies are needed to determine the therapeutic time window of central sympatholytics and how this window may be affected by genetic background, sex, gender and antibiotics both in clinical and experimental models.

Competing interests

The authors declare that they have no competing interests..

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