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Reduced serum cholinesterase activity indicates splenic modulation of the sterile inflammation

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ABSTRACT

Background: Sterile inflammation is an immediate and well-coordinated immune response to surgical injury. The cholinergic system plays a pivotal role in the inflammatory response. Induced inflammation stimulates the vagus nerve, which in turn activates anti-inflammatory nonneuronal processes. Serum cholinesterase (butyrylcholinesterase [BChE]) is an enzyme that hydrolyzes acetylcholine. Measuring the activity of the BChE in blood might indicate the level of the nonneuronal cholinergic activity. The spleen is a major organ of the immune system playing an important role during inflammation. A functional connection of the neuroimmune reflex has thus far been described only in experimental settings.

Materials and methods: In 48 patients receiving major pancreatic surgery, BChE activity was measured by applying point-of-care-testing, in addition to standard laboratory tests.

Results: The BChE activity decreased in patients receiving surgery. This reduction emerged much earlier than changes in C-reactive protein concentration, an inflammatory biomarker broadly used in the clinical environment. A milder reduction in the BChE activity was observed in patients subjected to surgery with splenectomy than in those with a preserved spleen.

Conclusions: The use of the point-of-care-testing system for quick bedside diagnostics and the rapid effects of inflammation on BChE levels provide a method and a marker to facilitate the early detection of systemic inflammation. Furthermore, this study provides evidence that the experimentally documented neuroimmune interaction is part of the physiological response to surgery-induced sterile inflammation. Splenic function plays an essential role in modulating the cholinergic anti-inflammatory response.

Introduction

Systemic inflammation is an organized response to exogenous or intrinsic stimuli.[1] Inflammatory reactions rely on the immune system, consisting of a mixture of proinflammatory and anti-inflammatory mechanisms.[2,3] Sterile inflammation is a well-coordinated immunologic response to an injury resulting in the bimodal systemic reaction.[4] An initial systemic inflammatory response syndrome, lasting a few days or weeks, is succeeded by a compensatory anti-inflammatory

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response syndrome.[5] This bimodal response is mediated by an activation of multiple neurohumoral mechanisms.[6,7] This hypothesis has been challenged by Murphy *et al*., who have proposed that the systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome may occur simultaneously in response to the severe trauma and infection.[8]

The cholinergic system has been shown to play an important role in controlling the inflammatory response.[9,10] After initial immunologic stress, proinflammatory cytokine release directly activates vagal nerves. The acetylcholine (Ach) released by such vagal stimulation activates nonneuronal cholinergic receptors on immune cells (tissue-resident macrophages and other immunocytes) to inhibit the synthesis and release of proinflammatory cytokines. Thus, the cholinergic system maintains the immunologic equilibrium by basic vagal efferent activation. The cholinergic stimulation elicits a continuous inhibition of the extensive proinflammatory response in the absence of the pathogen-associated molecular patterns (e.g., bacterial toxins) and the damage-associated molecular patterns (released from damaged cells during sterile inflammation, e.g., proinflammatory cytokines). During the systemic inflammation, the increased activity of the proinflammatory mediators is associated with the increased cholinergic activity, forming the feedback loop of the cholinergic anti-inflammatory reflex. The anti-inflammatory effect of the cholinergic system during the systemic inflammation is achieved by limiting the acute escalation of the proinflammatory cytokine activation.

Earlier investigations have reported that the spleen, a major organ of the immune system, plays a pivotal role in the inflammatory response.[11-13] It has been widely shown that splenectomized patients are more prone to develop systemic inflammation and/or infection.[14] On the contrary, an experimental study by Huston *et al*. revealed that the spleen is the main source of circulating proinflammatory cytokines and the major target organ of the vagal efferent fibers in the animal sepsis model. Vagal stimulation fails to suppress synthesis of proinflammatory tumor necrosis factor (TNF)-alpha in splenectomized animals with endotoxemia.[15] Furthermore, this group has shown that splenectomy protects against sepsis lethality and reduces high-mobility group box 1 levels, improving sepsis survival in mice.[16] Rosas-Ballina *et al*. have suggested that the cytokine production during an inflammatory challenge could be modulated by the activation of cholinergic nonneuronal receptors in the rat spleen.[17] Nevertheless, an earlier clinical study suggested that splenectomy, before sepsis or septic shock caused by complex intra-abdominal infection, did not affect patient outcome.[18] Growing evidence indicates the importance of the spleen in the cholinergic control of the inflammation, however, the interdependence of the cholinergic anti-inflammatory pathway and the splenic function during an inflammatory challenge has so far only been described in animal models. The role of the anti-inflammatory cholinergic-to-splenic interaction on sterile inflammation in the controlled clinical environment remains to be determined.

Serum cholinesterase (butyrylcholinesterase [BChE]) is an enzyme synthesized in the liver. BChE is a nonspecific cholinesterase that hydrolyzes Ach. It is abundant in brain and liver and represents 99% of the soluble cholinesterases in the blood.[19] The abundance of the BChE in the serum and the fast activity dynamics renders this enzyme a biochemical monitor of extrasynaptic cholinergic activity. Reduced BChE activity, might signal an interruption in Ach hydrolysis, indicating an altered cholinergic homeostasis.[20] Monitoring BChE activity in blood might provide insight into cholinergic nonneuronal activity. Our previous study suggested that reduced BChE activity in blood could be associated with severe systemic inflammation.[21] Moreover, lowered BChE levels have been observed in the early stage of the mild traumatic injury,[22] rendering this rapid-acting enzyme an inflammation-specific and cholinergic activity–dependent indicator. Therefore, measuring BChE activity in patients receiving standardized surgical intervention (major pancreas surgery with or without splenectomy) might help better understand the interdependence of the cholinergic anti-inflammatory system and the splenic activity during sterile inflammation.

The aim of this study was to test whether the change in the BChE activity, measured by using a point-of-care-testing (POCT) system, might be used to early indicate a surgery-induced systemic inflammatory response. Furthermore, this study will test whether there is a functional connection between the spleen, as a major organ of the immune system and the cholinergic anti-inflammatory activity during a systemic inflammation.

Material and methods

Study design

The study was conducted in the Heidelberg University Hospital. Ethics Committee of the Medical Faculty of Heidelberg approved the study (Trial Code Number: S-196/2014). All patients included in the study signed written informed consent. In total, 50 patients admitted to the hospital for an elective major pancreatic surgery were recruited. Basic patient information including primary diagnosis, type of pancreatic surgery, comorbidities, demographic data, and medications have been documented. Exclusion criteria for this study were chronic inflammation (white blood cell count [WBCC] $> 10\ nL^{-1}$; C-reactive protein >5 mg/L) and disrupted liver function (three or more of the following tests: aspartate aminotransferase [AST]> 100 U/L, alanine aminotransferase [ALT] > 100 U/L, gamma glutamyl transferase [GGT] > 100 U/L, alkaline phosphatase [AP] > 200 U/L, total bilirubin >2 mg/dL, and international normalized ratio [INR] > 1.3). Two patients were excluded (because of the presence of chronic inflammation and documented disrupted liver function), which resulted in 48 patients included in the study. A summary of the patient data is listed in Table.

Measurements

Patients received a routine blood sample analysis 1 d before the scheduled surgery. Routine blood gas analysis was performed before as well as immediately after the surgery and at 12-h time intervals for the next 3 d, as a part of the standardized postoperative procedure. The median duration