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Vasoplegia in septic shock: Do we really fight the right enemy?

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ABSTRACT

Vasoplegia is a key factor for the death of patients with septic shock in intensive care unit owing to persistent and irreversible hypotension. Impairment of vascular reactivity has been attributed to a combination of endothelial injury, arginine-vasopressin system dysfunction, release of other vasodilatory inflammatory mediators, and muscle hyperpolarizaton. Nitric oxide induced by a Ca^{+2} independent isoform of nitric oxide synthase has been suggested to play an important role in sepsis-induced vasoplegia. However, inhibition of nitric oxide synthase only partially restores the endotoxin-induced vascular hyporeactivity. The aim of this review is to discuss in detail the recent suggested alternative mechanisms of vasoplegia and to briefly outline the current therapeutic strategies and the novel therapeutic options based on those mechanisms.

1. Introduction

Vasoplegia is thought to be a key factor responsible for the death of patients with septic shock, due to persistent and irreversible hypotension [1-3]. Vasoplegia is a form of vasodilatory shock with low systemic arterial pressure despite high cardiac output and adequate fluid resuscitation and characterized by markedly low systemic vascular resistance despite adrenergic vasopressor administration [4,5]. Impairment of vascular reactivity, with imbalance between vasoconstrictor and vasodilator tone, will result in heterogeneous perfusion, which can alter blood flow to vital organs such that organ failure and death will eventually occur [6].

Vasoplegic syndrome has been attributed to a combination of endothelial injury, arginine-vasopressin system dysfunction, release of other vasodilatory inflammatory mediators, and muscle hyperpolarizaton [7,8]. Nitric oxide (NO) induced by a Ca^{2+}-independent isoform of NO synthase (iNOS) has been suggested to play an important role in activating soluble guanylyl cyclase (sGC), thus producing relaxation of vascular smooth muscle through rising in intracellular cyclic guanosine monophosphate (cGMP) levels and then causes hypotension and vascular hyporeactivity [9,10]. However, NO synthase (NOS) inhibitors were not uniformly successful in improving sepsis-induced hypotension outcome, and inhibition of NOS only partially restores the endotoxin-induced vascular hyporeactivity [11-14].

The aim of the present review is to discuss the most recent cited underlying mechanisms of decreased responsiveness to vasoconstrictors in sepsis and to briefly outline current therapeutic strategies and possible future approaches.

2. Nitric oxide bioavailability during sepsis

2.1. Time course profile of NO production during sepsis

Several human and animal studies reported the fluctuation of constitution and inducible NOS expression and NO production during sepsis with early increase in NOS expression and activity followed by decrease or return to the baseline level following sepsis in plasma and different investigated tissues (kidney, brain, small intestine, liver, heart, lung, and thoracic aorta) [15-20]. Thus, the previous therapeutic efforts directed at abolishing the production of NO by general NOS inhibition or selective iNOS inhibition under chronic infection may result in unavoidable NO deficiency (Fig. 1) [21-23].

2.2. Nitric oxide and reactive oxygen species balance and heterogeneous perfusion during sepsis

Reactive oxygen species (ROS) is a common term that is used for both oxygen radical (O_2^- and OH^-) and nonradical (H_2O_2, HOCl, O_3) compounds [24,25], produced by a variety of cell types, including vascular smooth muscle cells, endothelial cells, and mononuclear cells [26]. The main sources of ROS are mitochondria, NADPH oxidase, cytochrome P450, cyclooxygenase, and xanthine oxidase [24]. Moreover, NO synthase, through the depletion of suitable cofactors of the NO-producing enzyme (endothelial NOS [eNOS]), eg, L-arginine and tetrahydrobiopterin [BH4], during sepsis can enhance production of O_2^- and H_2O_2 by uncoupling endothelial NOS [27,28,25]. Decreased NO production due to uncoupling of endothelium NOS could limit the maximum NO production, since eNOS-induced NO production is an important factor in iNOS up-regulation [29,30].

In addition, NO can also be regarded as a free radical that interacts with ROS to form reactive nitrogen species such as nitrite, nitrate, nitrotyrosine, and peroxynitrite. The interaction between NO^- and

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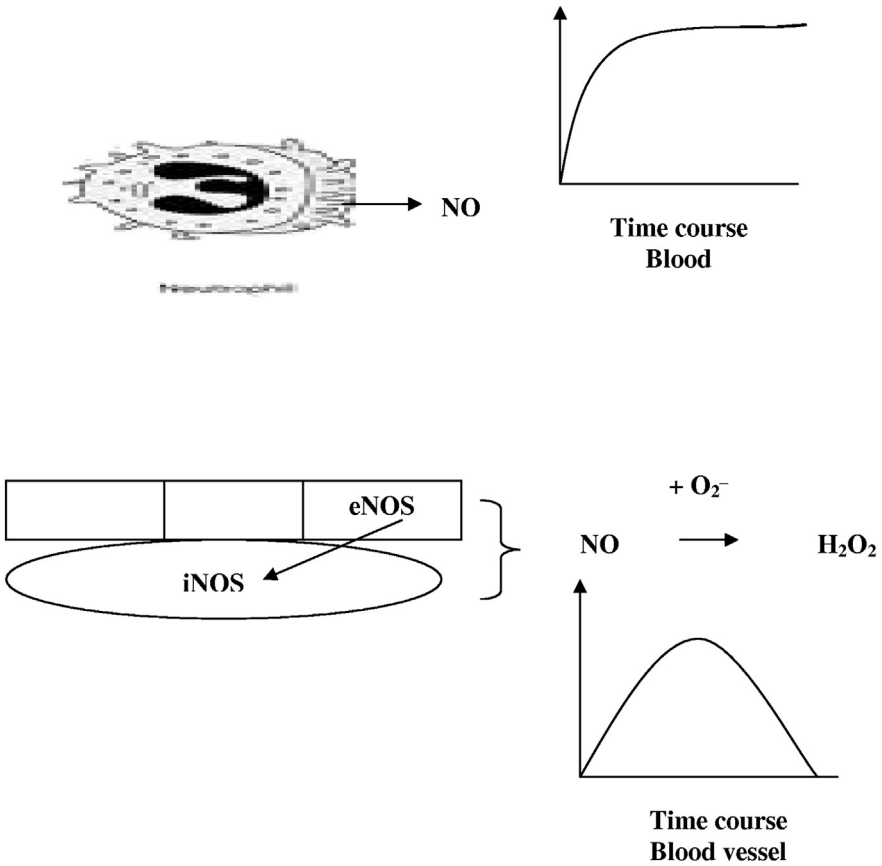

Fig. 1. Time course of NO in the blood and blood vessel.

O_2^- occurs faster than the reaction rate for O_2^- with superoxide dismutase (SOD), one of the endogenous enzymatic antioxidants in mitochondria [25]. Thus, the production and utilization of oxygen, NO, and ROS are intrinsically dependent on each other, and this delicate homeostasis is pathogenically altered during sepsis, with oxidative stress that could inactivate or destroy NO, with regional decrease in NO bioavailability in micociculation despite a state of total body NO excess, which could be produced by inflammatory cells, resulting in the heterogeneous tissue perfusion that characterizes sepsis in both experimental and clinical settings [31]. This could be supported by Tyml et al [32], who suggested that NADPH oxidase–derived superoxide rather than NOS is responsible for capillary blood flow impairment associated with sepsis.

Thus, NO-ROS interaction with reduced NO production in certain areas and the formation of another endothelium-derived hyperpolarizing factor (EDRF) that modulates the vascular tone especially in the small resistance vessel could be a major factor in the heterogeneity of tissue perfusion that characterizes both experimental and human sepsis, and may also help explain sepsis-induced vasoplegia. In support to this suggestion, the significant effects of ROS target therapies and tetrahydrobiopterin on the vascular hyporeactivity, endothelium dysfunction, and attenuation of the fall of blood pressure during sepsis [28,32-39] (Figs. 1 and 2).

3. NO/hydrogen peroxide (H_2O_2) as an alternative EDRF during sepsis

3.1. NO-sCG dependent and independent vasorelaxation pathway

NO produces relaxation by decreasing the smooth muscle cell Ca^{2+} levels through a cGMP-dependent pathway, which involves adenosine triphosphat (ATP)-activated potassium channels (KATP) and large conductance Ca^{2+}-activated K^+ channels, or through hyperpolarization due to increased conductance of the small-conductance Ca^{2+}-activated K^+ channels, which are also critical for other endothelium derived hyperpolarizing factor (EDHF)–dependent vasodilations [40-44].

3.2. NO as H_2O_2 generator: the alternative vasorelaxation pathway

EDHF is a distinct factor released by the endothelium and to some extent from vascular smooth muscle [45], that relaxes the blood vessels via a process of hyperpolarization. The predominant role of EDRF, mainly in small resistance vessels, were previously investigated [45,46].

Several candidates have been proposed as EDRF depending upon the species and vascular bed, including epoxyeicosatrienoic acids, K^+ ions, gap junctions, and H_2O_2 [45].

Since in situations where NO-mediated relaxation is reduced (eg, hypertension and hyperlipidemia), EDHF compensates for NO to cause endothelium-dependent relaxation, and that the correction of the underlying risk factors improves the relaxation mediated by EDHF as well as that mediated by NO, Matoba et al [47] demonstrated that a non-NO factor derived from eNOS, possibly ROS, may be an EDHF. Previous studies demonstrated also that endothelium derived H_2O_2 is an EDHF in mouse, human mesenteric arteries and coronary microvessels, and that NOS-derived superoxide anions are a major source of H_2O_2, in addition to superoxide anions that are derived from cyclooxygenase, lipoxygenase, cytochrome P-450 enzymes, and NAD(P)H oxidases, where copper and zinc SOD, plays an important role to dismutate eNOS-derived superoxide anions to synthesize H_2O_2 in animals and humans [45,47-54]. Then H_2O_2 is eliminated by glutathione peroxidase and catalase to water [26].