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Review

Hydrogen sulfide and nitric oxide interactions in inflammation

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ABSTRACT

Together with carbon monoxide (CO), nitric oxide (·NO) and hydrogen sulfide (H_2S) form a group of physiologically important gaseous transmitters, sometimes referred to as the "gaseous triumvirate". The three molecules share a wide range of physical and physiological properties: they are small gaseous molecules, able to freely penetrate cellular membranes; they are all produced endogenously in the body and they seem to exert similar biological functions. In the cardiovascular system, for example, they are all vasodilators, promote angiogenesis and protect tissues against damage (e.g. ischemia–reperfusion injury). In addition, they have complex roles in inflammation, with both pro- and anti-inflammatory effects reported. Researchers have focused their efforts in understanding and describing the roles of each of these molecules in different physiological systems, and in the past years attention has also been given to the gases interaction or "cross-talk". This review will focus on the role of ·NO and H_2S in inflammation and will give an overview of the evidence collected so far suggesting the importance of their cross-talk in inflammatory processes.

Contents

1. Introduction

For many years, nitric oxide (·NO) and hydrogen sulfide (H_2S) have only been considered toxic gases, nonetheless present in the atmosphere at low concentrations. Their toxicity has been known for centuries [1], but despite this they have both been discovered to be produced endogenously and to regulate key physiological functions. First, ·NO was identified as the endothelium derived relaxing factor [2–5], and since then a variety of other biological functions have been ascribed to it [6]. Carbon monoxide (CO) was the second molecule to be identified as an endogenous gaseous transmitter and more recently H_2S was the third [7,8].

·NO and H_2S share several of the common features of gaseous mediators: they are small gaseous molecules; they are freely permeable to cell membranes and do not rely on membrane receptors to exert their functions; they are endogenously and enzymatically generated; their production is finely regulated and, finally, they have well-defined functions at physiologically relevant concentrations [8]. Besides these characteristics, ·NO and H_2S seem to

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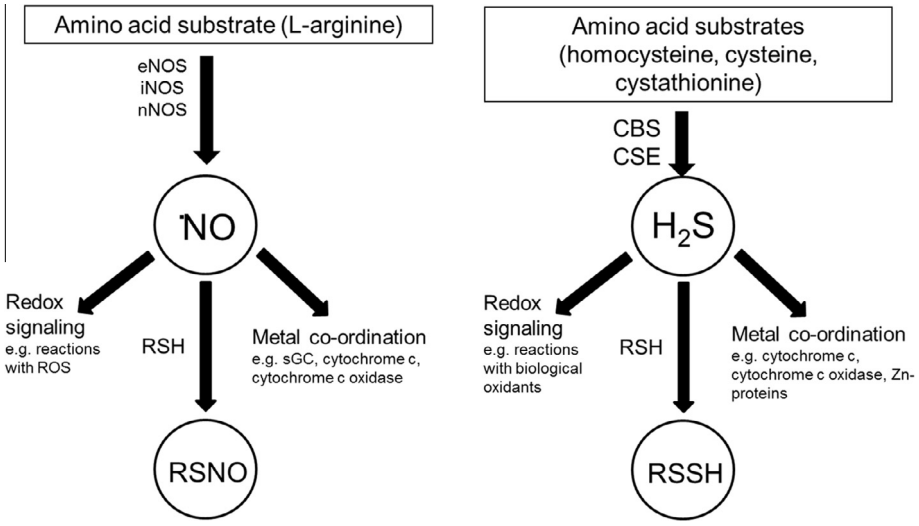

Fig. 1. Schematic representation of the similarities between ·NO and H_2S signaling pathways. ·NO and H_2S are both enzymatically synthesized from amino acid substrates (L-arginine and homocysteine, cysteine, cystathionine, respectively). ·NO and H_2S signaling mechanisms can be grouped into three main categories: redox signaling (to encompass redox reactions with ROS and biological oxidants); protein or low-molecular weight thiol (RSH) modifications (to form nitrosothiols, RSNO and persulfides, RSSH, from ·NO and H_2S respectively) and metal co-ordination (binding to transition metal ions in proteins, e.g. iron in soluble guanylate cyclase or copper in cytochrome *c* oxidase etc.).

regulate the same physiological functions through similar reaction mechanisms (Fig. 1) [9], in the cardiovascular and nervous systems and in inflammation. Experiments have suggested that these similarities do not rely only on "parallel" functions exerted by ·NO or H_2S, but that either molecule can also alter the functions (or levels) of the other [10–17]. Therefore, alongside studying the effects that ·NO and H_2S exert singularly, effort should be put into investigating the interplay, or so-called "cross-talk", between these molecules [9,18,19].

This review will focus on the role of ·NO and H_2S in inflammation and on the possible mechanisms behind their interaction either in physiological or inflammatory disease processes.

2. Inflammation

Inflammation can be defined as the protective response of tissues to noxious insults or tissue destruction. The five clinical signs of inflammation are redness, heat, swelling, pain, and eventually loss of function of the injured tissue [20]. At a molecular level the inflammatory response is driven by the production of soluble pro-inflammatory mediators such as: leukotrienes, histamine, bradykinin, platelet-activating factor, interleukins and reactive oxygen species (ROS) produced by inflammatory cells (e.g. neutrophils) [21]. The role of these molecules is to destroy the pathogen or the cause of inflammation, protect the injured tissue and to prevent spreading of the injury.

According to its duration it is possible to distinguish two types of response: acute or chronic inflammation. Acute inflammation is the immediate host response to the harmful stimulus. It is characterized by vasodilation and increased blood flow into the injured tissue; increased leukocyte and granulocyte chemotaxis; and increased expression of adhesion molecules on the vascular endothelium, followed by leukocyte adhesion and increased vascular permeability accompanied by edema (swelling) and neutrophil infiltration into the tissues [22]. Phagocytes are able to engulf pathogens, thereby releasing ROS and proteases, which are a potential cause of tissue damage [23]. These processes result in the production of several pro-inflammatory and anti-inflammatory mediators and cytokines, which are able to regulate lymphocyte function by either activating (e.g. IL-2, IL-4, IFN-α) or inhibiting (e.g. IL-10) the host immune response. Examples of acute inflammation are septic shock and pancreatitis [22,24]. The production of pro-inflammatory mediators is counteracted by the production of anti-inflammatory mediators (e.g. IL-10 and lipoxins) which are responsible for the resolution of inflammation [21,25]. The resolution of inflammation occurs through removal of the trigger of the inflammatory response, inhibition of the recruitment of neutrophils to the site of injury, induction of apoptosis of the infiltrated neutrophils and the subsequent clearance of the neutrophils by macrophages. During this process, the production of anti-inflammatory mediators prevails over the production of pro-inflammatory factors. Over-production of pro-inflammatory mediators, under-production of anti-inflammatory factors or impaired apoptotic clearance of infiltrated neutrophils can occur in pathological situations and can lead to the progression from acute to chronic inflammation.

Chronic inflammation is inflammation of prolonged duration, and although it can follow acute inflammation (impaired resolution of inflammation, as described above), it can also take place without initially showing any clinical symptoms [22]. It is characterized by a shift in the cell type present at the site of inflammation (usually from granulocytes to mononuclear and plasma cells), tissue destruction mediated by inflammatory cells and attempts to replace the damaged tissue by the connective tissue (angiogenesis and fibrosis). Examples of chronic inflammatory diseases are: rheumatoid arthritis, asthma and inflammatory bowel disease, but many other disease states involve a chronic low-level inflammation (atherosclerosis, autoimmune diseases, Alzheimer's disease, cancer, ischemia–reperfusion injury, diabetes, etc.).

Both ·NO and H_2S have roles in inflammation and both pro- and anti-inflammatory effects have been reported for each of these molecules. This dichotomy is probably dependent on the concentrations used in the different investigations, the delivery method, and on the particular system or disease model studied.

3. Biosynthesis and reactivity of ·NO

·NO is a short-lived free radical that is involved in diverse biological processes. It is most commonly known as the endothelium derived relaxing factor and it regulates vascular tone and blood flow (and therefore oxygen delivery) by causing vasodilation [2,26]. However, ·NO regulates many other processes, such as