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Review

Gaseous mediators in resolution of inflammation

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ABSTRACT

There are numerous gaseous substances that can act as signaling molecules, but the best characterized of these are nitric oxide, hydrogen sulfide and carbon monoxide. Each has been shown to play important roles in many physiological and pathophysiological processes. This article is focused on the effects of these gasotransmitters in the context of inflammation. There is considerable overlap in the actions of nitric oxide, hydrogen sulfide and carbon monoxide with respect to inflammation, and these mediators appear to act primarily as anti-inflammatory substances, promoting resolution of inflammatory processes. They also have protective and pro-healing effects in some tissues, such as the gastrointestinal tract and lung. Over the past two decades, significant progress has been made in the development of novel anti-inflammatory and cytoprotective drugs that release of one or more of these gaseous mediators.

1. Introduction

Since the identification of nitric oxide (NO) as the substance accounting for the actions previously attributed to 'endothelium-derived relaxing factor' [1], there has been a burst of research into several gaseous mediators. NO, hydrogen sulfide (H_2S) and carbon monoxide (CO) have been the most studied gaseous mediators over the past three decades, and attempts have been made to develop novel anti-inflammatory drugs based on delivery of one or more of these gaseous mediators [2]. All three of these mediators have very low molecular weights, short half-lives, and can freely diffuse across membranes. They do not have specific receptors, per se, but can interact with a range of proteins and genes to produce a wide range of effects. Particularly in the case of NO and H_2S, suppression of synthesis can profoundly alter cell and tissue function.

The potential for the actions of these mediators to be exploited in the design of therapeutics is considerable. Of course, drugs that release NO have been in use for over a century (e.g., nitroglycerin). Development of drugs based on stimulation or suppression of H_2S or CO production has occurred mainly in the past decade. In this article, we review some of the key actions of these gaseous mediators with respect to their impact on inflammatory processes. We also review some of the drugs in development that are aim to exploit the anti-inflammatory actions of these mediators.

2. Nitric oxide

2.1. The importance of L-arginine-nitric oxide pathway

The acute inflammatory response is a self-limiting process that normally results in restoration of tissue homeostasis. Persistent inflammatory stimuli or deregulation of mechanisms of the resolution phase results in chronic inflammation, recognized to be a key underlying factor in the progression of a range of diseases, including atherosclerosis, arthritis, cancer and chronic neurodegenerative diseases. Alterations in NO synthesis by endogenous systems can influence these inflammatory processes.

The inorganic free radical, NO was first identified as an endothelium-derived endogenous messenger responsible for the regulation of vascular tone [3,4]. However, since then it has become clear that NO is the signaling molecule responsible for several diverse physiological and pathophysiological processes. NO is produced by three different forms of NOS, namely nNOS (NOS1), eNOS (NOS3), and iNOS (NOS2) [5].

A rather simple, not fully correct but traditionally useful classification discriminates inducible versus constitutively expressed NOS isoforms, which approximates low versus high production rates of endogenously generated NO [5,6]. Thus, it has been generally assumed that nNOS and eNOS are critical for a normal physiology, whereas iNOS is associated with injury. NOS isoforms not

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only produce NO, the primary reaction product, but also a number of species resulting from oxidation, reduction, or adduction of NO in physiological milieus, thereby generating various clinical species such as, S-nitrosothiols, peroxynitrite (ONOO—), and transition metal adducts [7]. The classical pathway by which NO exerts many of its actions is via activation of the enzyme soluble guanylate cyclase (sGC) [8] and resultant conversion of guanosine 5′-triphosphate (GTP) to the second messenger 3′,5′-cyclic guanosine monophosphate (cGMP) [9]. However, several studies have established that NO can also act via cGMP-independent pathways in various systems, particularly during the inhibition of platelet aggregation and regulation of inflammatory cell apoptosis [10–13]. In addition, NO modulates transcription/translation indirectly by affecting signaling pathways, such as mitogen activated protein kinases, G-proteins, the Ras pathway, glyceraldehyde dehydrogenase or phosphatidylinositol-3 kinase (PI3K) [14].

2.2. NO apoptosis and resolution of inflammation

Progression of inflammatory conditions depends not only upon the recruitment and activation of inflammatory cells but also upon their subsequent removal from the inflammatory milieu. Apoptosis, or programmed cell death, can be considered as a "removal" mechanism, leading to resolution of inflammation, characterized by a series of morphological and biochemical features [15]. In inflammation-based diseases apoptosis is a fundamental process regulating inflammatory cell survival and it is critically involved in ensuring the successful resolution of an inflammatory response [15]. Dysregulation of apoptosis and phagocytic clearance mechanisms can have drastic consequences on resolution of inflammatory processes. Hence, apoptosis represents a mechanism to remove potentially damaging pro-inflammatory cells from the site of inflammation and is therefore critical to the successful resolution of inflammation. During this process, activated inflammatory cells generate reactive oxygen and nitrogen species, including NO. In this context it is of particular interest the ability of NO to regulate apoptosis of inflammatory cells [16]. What makes complex to evaluate the involvement of NO in the resolution phase is that NO has both pro-apoptotic and anti-apoptotic properties [17–19]. However, it is known that lower concentrations of NO produced by the eNOS and nNOS are cytoprotective, whilst supraphysiological concentrations produced by the iNOS trigger cell death. These apparent opposite effects are explained, at least in part, by the free radical nature of NO and hence its chemical interaction with other radicals present in the milieu to form various NO-related species in vivo. The pro- or anti-apoptotic effects of NO may thus be critically governed by the specific NO-related species generated. An example is represented by the ONOO— species that could account for the apoptotic resolving process [20]. However, the precise role of ONOO— in inflammatory cell apoptosis is still not clearly defined. Thus, it is intuitive that the ability of NO to induce apoptosis is particularly relevant during the resolution phase of inflammation. Several studies have demonstrated that activated macrophages infiltrating murine tumors induce apoptosis via a NO-dependent pathway in both activated anti-tumor T cells and in the tumor cells themselves [21,22]. Thus, it appears that macrophages induce apoptosis of nearby cells through NO that in turn enhances the clearance of apoptotic cells thereby promoting the resolution phase of inflammation.

It is widely accepted that inflammation drives development of some cancers that adapt to and use the oxidant-rich microenvironment [23,24]. This latter phenomenon provides a persistent and self-perpetuating oxidative stress composed of both reactive nitrogen species and reactive oxygen species [25]. Among the critical oxidant sources NO plays a major role in oxidative stress in melanoma and other cancers [25–29].

Also in cancer the effect of NO is dependent upon the concentration since it has been shown that angiogenesis, proliferation and metastasis can normally be stimulated by lower levels of NO (<100 nM), while higher concentrations of NO (>400–500 nM) promote cytotoxicity and cell apoptosis [30,31]. Thus, NO donors have been proposed as a novel therapy to various cancers [32,33]. The most interesting results have been obtained by the use of nitric oxide-releasing non-steroidal anti-inflammatory drugs (NO-NSAIDs). In fact, several studies have found a link between NSAIDs use and decreased risk of colorectal cancer [34–36], suggesting a possible chemopreventive role. NO-NSAIDs have been shown to be more effective in the inhibition of cancer cell growth and metastasis than the parent drug alone [33,37].

Atherosclerosis is another diseases where the concept of resolution of inflammation can be applied with regard to NO. It is now widely recognized that the inflammatory component of atherosclerosis contributes to plaque formation [38–40]. Plaque growth and development are driven by inflammatory cells, in particular monocytes and macrophages, representing the major driving force. Because apoptotic cells are ingested by phagocytes without initiating any further pro-inflammatory response, it has been suggested that apoptosis may represent a mechanism to regress the plaque. Therefore this process triggered by NO contributes to resolution of inflammation [41,42].

In conclusion NO plays a role in the resolution of inflammation but its activity depends upon the concentration of NO in the local environment, the timing of administration or the route of administration, as well as the NOS isoform targeted [43,44].

3. Hydrogen sulfide

3.1. H_2S as a mediator of inflammation

Kimura and colleagues were the first to identify physiological roles for H_2S through their studies of its actions in the nervous system [45,46]. Several years, later, Wang and colleagues demonstrated the H_2S was a potent endogenous vasorelaxant [47]. Together, these studies stimulated a burst of research into the role of this gaseous mediator in many cells and organ systems [47,48]. Zanardo et al. provided key evidence suggesting a role for H_2S an important endogenous anti-inflammatory and pro-resolution mediator [49]. They reported that H_2S exerted potent inhibitory effects on leukocyte adherence to the vascular endothelium. Using intravital microscopy to examine the mesenteric microcirculation in rats, they demonstrated that administration of H_2S (using donors such as Na_2S, NaHS and Lawesson's reagent) markedly and potently suppressed leukocyte adherence of leukocytes to the vascular endothelium and prevented extravasation of leukocytes [49]. They also observed that the inhibition of endogenous H_2S synthesis resulted in a very fast induction of leukocyte adhesion to the vascular endothelium. In models of carrageenan-induced sub-dermal inflammation, H_2S donors were found to suppress leukocyte infiltration and edema formation [49,50]. Inhibition of leukocyte-endothelial adhesion by H_2S is a consequence of suppression of the expression of cell adhesion molecules on both the endothelium (e.g., intercellular adhesion molecule (ICAM)-1 and P-selectin) and on the leukocyte (lymphocyte function-associated antigen (LFA)-1) [49]. Several other groups have also reported inhibitory effects of H_2S on these adhesion molecules [51–54]. Consistent with the findings of Zanardo et al. [49], mice that are heterozygous for the gene for cystathionine β-synthase (CBS), one of the major enzymes for synthesis of H_2S, exhibit reduced leukocyte-rolling velocity, increased vascular permeability, and increased numbers of adherent leukocytes in mesenteric venules [55].