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Review article

Nitrite reduction and cardiovascular protection ☆

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ABSTRACT

Inorganic nitrite, a metabolite of endogenously produced nitric oxide (NO) from NO synthases (NOS), provides the largest endocrine source of directly bioavailable NO. The conversion of nitrite to NO occurs mainly through enzymatic reduction, mediated by a range of proteins, including haem-globins, molybdo-flavoproteins, mitochondrial proteins, cytochrome P450 enzymes, and NOS. Such nitrite reduction is particularly favoured under hypoxia, when endogenous formation of NO from NOS is impaired. Under normoxic conditions, the majority of these nitrite reductases also scavenge NO, or diminish its bioavailability via reactive oxygen species (ROS) production, suggesting an intricate balance. Moreover, nitrite, whether produced endogenously, or derived from exogenous nitrite or nitrate administration (including dietary sources via the Nitrate–Nitrite–NO pathway) beneficially modulates many key cardiovascular pathological processes. In this review, we highlight the landmark studies which revealed nitrite's function in biological systems, and inspect its evolving role in cardiovascular protection. Whilst these effects have mainly been ascribed to the activity of one or more nitrite reductases, we also discuss newly-identified mechanisms, including nitrite anhydration, the involvement of s-nitrosothiols, nitro-fatty acids, and direct nitrite normoxic signalling, involving modification of mitochondrial structure and function, and ROS production. This article is part of a Special Issue entitled 'Redox Signalling in Heart'.

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1. Introduction

In contrast to the structurally complex and chemically synthesised organic nitrates/nitrites, inorganic nitrite (NO_2^-) is a simple naturally occurring anion. Under normal physiological conditions, the majority (~70%) of circulating and stored nitrite is derived from the oxidation of nitric oxide (NO), endogenously produced via the L-arginine NO synthase (NOS) pathway [1,3]. The remainder (~30%) is acquired through dietary intake, via the recently described Nitrate–Nitrite–NO pathway [4]. Whilst concentrations in the circulation are low under basal conditions (90–350 nM) [5,8], nitrite accumulates substantially in tissues (1–20 μM) [9,11], with the highest concentrations in the liver, kidney, heart and topmost in the aorta [11,12].

Although nitrite is freely available in the environment, it is only found in trace amounts compared to inorganic nitrate (NO_3^-) [13]. Both are formed by the fixation of atmospheric nitrogen and oxygen, either directly through lightning, or indirectly through the actions of specialised bacteria; the latter being the more significant of the two processes. These anions are normally bonded to metal cations (commonly Na^+ or K^+) and exist as hydrophilic salts which permeate into water and soil [14,15]. Nitrate is taken up avidly by plants, especially green leafy vegetables and beetroot [4,13]. In turn the ingestion of these nitrate rich plants by mammals provides a major source of nitrite through the entero-salivary circuit [4]. Once ingested, nitrate is readily absorbed via the upper gastrointestinal tract avoiding first pass metabolism [7,16,17]. Within a 24 hour period ~75% of the absorbed nitrate is excreted by the kidneys; of the remainder, ~25% is taken up by the salivary glands with only trace amounts secreted via sweat glands [6,7]. The nitrate rich saliva is then excreted into the oral cavity where bacteria found on the dorsal part of the tongue convert it to nitrite via nitrate reductases. A number of bacterial species contribute to this process to varying extents, the most notable of these being the *Veillonella* species, *Actinomyces* species, and *Rothia* species [18]. Nitrite is swallowed, and absorbed via the upper gastrointestinal tract leading to a rise in circulating levels. However, a proportion of this nitrite is protonated under the acidic conditions normally found in the stomach, forming nitrous acid which in turn decomposes to NO and other derivatives (see Eqs. (1)–(4)) [19,20]. Although the entero-salivary circuit is the major pathway for nitrate reduction to nitrite in mammals, another possible mechanism described in a murine model and in rodent and human liver homogenates suggests direct reduction of nitrate to nitrite via the actions of hepatic xanthine oxidoreductase [21].

2. Nitrite in the circulation

As recently as 2001, nitrite was viewed as biologically inactive, and its only utility was as a marker of endogenously produced NO, thus reflecting NOS activity [5]. Furchgott demonstrated in 1953 that high concentrations of nitrite (100 and 1000 μM) relaxed strips of rabbit thoracic aorta [22]. Although lower concentrations were not tested, it was generally inferred that at physiological concentrations nitrite was biologically inactive. In 1994, Benjamin et al. and Lundberg et al. independently demonstrated for the first time that nitrite can be reduced to NO in a biological system — under the acidic conditions present in the human stomach [19,20]. A year later, in 1995, Zweier et al. suggested that nitrite, via a similar mechanism of direct reduction, may provide an alternative source of NO in the ischaemic heart, where NOS plays a diminishing role [23]. By looking at both NO metabolites (endogenous nitrate and nitrite) Cicinelli et al. suggested in 1999 that an arterial-to-venous (AV) gradient may exist [24]. A year later Gladwin et al. specifically investigated endogenous nitrite, and convincingly demonstrated the existence of an AV gradient, suggesting that nitrite is reduced to NO across the vascular bed under normal physiology [25]. However, others maintained the gradient in fact reflected differences in NOS activity and NO production in the arterial vs venous system [26]. In 2001, Modin et al. found that nitrite in physiological concentrations was an effective vasodilator of rat aortic rings under conditions of low pH (6.6) and normoxia (6.5% CO_2 and 93.5% O_2). With this finding, an active biological role for nitrite in vascular tone was hypothesised [27]. It was Cosby et al. who demonstrated in 2003, that intra-brachial infusion of minimally supra-physiological concentrations of nitrite caused a significant increase in forearm blood flow [28]. This discovery resulted in the acceptance of nitrite as a physiological source of biologically active NO, making nitrite the largest directly accessible storage pool for NO. Although nitrate is found in much higher concentrations in the circulation and tissues, nitrate requires a two-step reduction to NO, via nitrite. In 2008, Maher et al. demonstrated significant enhancement of nitrite-induced vasodilatation under hypoxic conditions in humans, suggesting greater rates reduction of nitrite to NO [29].

3. Mechanisms of nitrite reduction to NO

It has long been established that eNOS plays an important role in myocardial NO production [30,32], with an estimated ~1000 pM/s of NO being produced under normal physiological conditions [33]. Ischaemia however markedly reduces eNOS activity and NO production [33,34]. These same conditions of low oxygen tension and low pH significantly enhance nitrite reduction, releasing quantities of NO which far exceed those produced by eNOS under such conditions [35]. It has been estimated that under ischaemic conditions, NO production from nitrite (10 μM) in the heart is ~560 pM/s [33].

Under acidic conditions, nitrite exists in equilibrium with nitrous acid (Eq. (1)). Both exist in equilibrium with other oxygen intermediates (Eqs. (2) and (3)), including dinitrogen trioxide (N_2O_3), which breaks down to form nitrogen dioxide (NO_2) and NO (Eq. (4)) [28,35,36].

$$H^+ + NO_2^- \leftrightarrow HNO_2 \quad (1)$$

$$HNO_2 \leftrightarrow NOOH \quad (2)$$

$$NOOH + NO_2^- \leftrightarrow N_2O_3 + OH^- \quad (3)$$

$$N_2O_3 \leftrightarrow NO_2 + NO \quad (4)$$

Thus simple nitrite disproportionation, which increases under acidic conditions, with abundant availability of H^+ ions, favours the release of free NO. However, in tissues, this process accounts for only ~15–20% of the total NO produced from nitrite [35]; the remainder is derived from

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