Review focus on inorganic nitrite and nitrate in cardiovascular health and disease

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Reviews and original articles in this focused issue of Cardiovascular Research address the topic of inorganic nitrite and nitrate in cardiovascular pathophysiology. It is well accepted that nitric oxide (NO) is a critical regulator of cardiovascular health that is routinely depleted during vascular disease and dysfunction. 

Since the original discovery of NO as a mediator of cardiovascular health, thousands of studies have focused on mechanisms of NO generation and function, largely addressing NO synthase (NOS) activity and NO-dependent signalling responses (e.g. soluble guanylate cyclase and nitrosylation reactions). From the beginning, a physiological role for inorganic nitrite or nitrate in mediating the biological effects of NO was briefly considered; however, early experimental data did not support a compelling role for these molecules in participating in NO physiology. Over the last decade, a handful of investigators have challenged this dogma through studies re-examining the relationship between NO, nitrite, and nitrate and have elucidated the newly described nitrite/nitrate/NO endocrine system. In the current review papers, the authors discuss how nitrite/nitrate serve as an important reservoir for NO and detail how under specific conditions nitrite/nitrate can be reduced back to NO to increase its bioavailability independent of classical NOS activity. The importance and mechanisms of this unique feature of nitrite/nitrate anion are further detailed with respect to cardiovascular health and potential therapeutic uses.

Historical and new, emerging evidence suggests that inorganic nitrite/nitrate can significantly alter blood pressure. In the article by Gilchrist et al., the authors discuss pharmacokinetic and pharmacodynamic properties of inorganic nitrite and nitrate consumption as well as elucidate on the entero-salivary circulation of nitrate, which can augment plasma nitrite levels through consumption of nitrate-rich foods. The authors also provide an update on the effect of nitrite/nitrate on blood pressure regulation and the possible importance of dietary nitrate contribution to cardiovascular health. Finally, the risk-to-benefit ratio for nitrate consumption is discussed, including the contribution of nitrate to carcinogenesis, which is presently equivocal.

Physical activity through regular exercise has long been associated with increased cardiovascular health and resistance to disease. In his review, John Calvert discusses how regimented exercise contributes to increased eNOS expression and activation, thus enhancing NO bioavailability and plasma nitrite levels. This article also posits the idea that nitrite generation and sequestration in tissues due to exercise may be a biologically important mechanism behind the cardioprotective effects of exercise, possibly by invoking preconditioning through an increase in antioxidant defences, heat-shock responses, or alteration of signalling mechanisms. This compelling idea could help explain the significant cardiovascular benefits of a healthy lifestyle consisting of the consumption of green leafy vegetables coupled with regular exercise. While several details of the link between nitrite and exercise remain unknown, the author clearly identifies important questions to consider that will undoubtedly expand our knowledge of the mechanisms behind exercise and cardiovascular protection.

Nitrite reduction back to NO is now known to occur in multiple tissues through several different mechanisms. However, the initial appreciation and understanding of a one-electron reduction of nitrite anion came from studies identifying deoxyhaemoglobin as an effective nitrite reductase. In the article by Patel et al., the authors recount this discovery as well as provide new insight into specific reductase mechanisms of deoxyhaemoglobin. The authors also discuss the conundrum around NO escape from the red cell after nitrite reduction, which still remains a strongly debated and poorly understood topic. Nonetheless, it is clear from numerous studies that haemoglobin-mediated nitrite reduction influences vascular tone in ex vivo experimental settings, reinforcing the idea that much work is needed to better understand the mechanisms of red cell-dependent, nitrite-mediated vasodilatation.

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Defective NO bioavailability is now well accepted as an aetiological factor contributing to metabolic and cardiovascular dysfunction during diabetes.13–15 The review by Yu et al.16 delivers clear and succinct insight into insulin regulation of eNOS activation and NO production. Moreover, the authors also discuss the effects of hyperglycaemia and hyperlipidaemia on insulin-mediated NOS signalling and NO bioavailability. While much still remains to be learned regarding the full ramifications of metabolic dysfunction on NO function and metabolism, NO-based therapeutic approaches remain a common goal for the treatment of cardiovascular disease in the setting of diabetes. In this regard, the review by Lundberg et al.17 addresses potential benefits of inorganic nitrate for cardiovascular health and disease. Recent work from the Lundberg and Weitzberg laboratories have shown that oral nitrate supplementation can confer protection against subsequent tissue ischaemia–reperfusion injury as well as correct pathological features of metabolic dysfunction in eNOS-deficient mice, including visceral fat accumulation and elevated triglyceride levels.18 These data are highly encouraging as nitrate/nitrate-based therapies may hold promise for alleviating NO deficiency during diabetes that could restore homeostatic metabolic function. Together, these reviews highlight the importance of NO and inorganic nitrite/nitrate during metabolism that is currently under investigation in a number of laboratories.

With our expanded understanding of nitrite recycling back to NO through various mechanisms, many in the field had long anticipated the development of nitrite/nitrate-based therapeutics for diseases involving hypoxia, including ischaemia–reperfusion injury, pulmonary hypertension, chronic ischaemic tissue disease, and others. The article by Pattillo et al.19 discusses the role and effect of inorganic nitrite on chronic tissue ischaemia. Previous studies have reported that NO bioavailability critically regulates ischaemia-mediated angiogenesis, and there is a recent appreciation that inorganic nitrite anion selectively stimulates angiogenesis only in ischaemic tissues.20,21 The ability of nitrite anion to induce vascular growth in a compartment-specific manner has reinvigorated the hope of targeted therapeutic angiogenesis strategies and represents an ideal modality in which to treat chronic ischaemic vascular disease, including peripheral arterial disease.22 The review by Zuckerbraun et al.23 reports current thoughts and efforts in nitrite therapy for pulmonary arterial hypertension (PAH). In this article, the authors provide a comprehensive evaluation of NOS/NOR contributions to clinical and experimental PAH as well as recent information on therapeutic approaches for PAH. It is now clear that NOS activity and NO bioavailability contribute to vascular tone and remodelling during PAH, with recent clinical trials focusing on interventions to augment NO bioavailability or signalling to downstream targets. The review also provides up-to-date developments of inorganic nitrite therapy for treatment of experimental PAH as well as clinical studies, including the development of inhaled nebulized nitrite. Finally, Cauwels and Brouckaert24 provide an interesting and compelling discussion regarding the effect of nitrite anion and shock. Previously, the authors reported the surprising finding that sodium nitrite therapy attenuated liver and kidney injury and mitochondrial dysfunction during tumor necrosis factor–lipopolysaccharide-induced sepsis.25 While these findings are at odds with some previous studies in this field, the authors propose that the beneficial effects of nitrite therapy may stem from attenuation of metabolic hypoxia originating from microcirculatory dysfunction. This hypothesis is consistent with other studies documenting nitrite-mediated effects on the microcirculation such as hypoxic angiogenesis and hypercholesterolaemia-mediated leucocyte recruitment.20,26 Together, this series of articles elegantly demonstrates that nitrite elicits protection against ischaemic tissue damage largely through effects on vascular function and remodelling. It will be exciting to see whether future clinical studies reinforce these conclusions and identify nitrite treatment as the long-awaited, selective, NO-based therapy.

Within the past decade, it has become overwhelmingly clear that nitrite/nitrate anion is no longer relegated to an ‘inert’ metabolic by-product of NO metabolism. It is now established that a nitrite/nitrate/NO endocrine system operates in conjunction with classical enzymatic sources of NO (i.e. NOS) to help maintain NO bioavailability. As such, nitrite/nitrate represents a novel salvage pathway for NO equivalents that are biologically important and appear to be attractive targets for therapeutic purposes. However, several key questions remain: What signalling mechanisms do nitrite influence? How is nitrite cellular uptake regulated, and is it compartmentalized upon entry into the cell? What are the molecular and biochemical targets of nitrite-mediated protection in disease models? Are there other conditions that do not involve hypoxia where nitrite may be influential? Are there adverse consequences to low levels of nitrite besides previous concerns regarding carcinogenesis at high concentrations? Additional studies within the field will certainly provide answers to these and many other questions while revealing a greater understanding of NO biology.

Conflict of interest: C.G.K. and D.J.L. are participants on pending US patents regarding the use of nitrite salts in tissue ischaemia. C.G.K. and D.J.L. have commercial interests in Theravasc, Inc.

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