Nitrite in nitric oxide biology: Cause or consequence? A systems-based review

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Abstract
All life requires nitrogen compounds. Nitrite is such a compound that is naturally occurring in nature and biology. Over the years, the pharmacological stance on nitrite has undergone a surprising metamorphosis, from a vilified substance that generates carcinogenic nitrosamines in the stomach to a life-saving drug that liberates a protective agent (nitric oxide or NO) during hypoxic events. Nitrite has been investigated as a vasodilator in mammals for over 125 years and is a known by-product of organic nitrate metabolism. There has been a recent rediscovery of some of the vasodilator actions of nitrite in physiology along with novel discoveries which render nitrite a fundamental molecule in biology. Until recently nitrite was thought to be an inert oxidative breakdown product of endogenous NO synthesis but the past few years have focused on the reduction of nitrite back to NO in the circulation as a possible mechanism for hypoxic vasodilatation. Nitrite has evolved into an endogenous signaling molecule and regulator of gene expression that may not only serve as a diagnostic marker but also find its role as a potential therapeutic agent of cardiovascular disease. These data therefore warrant a reevaluation on the fate and metabolism of nitrite in biological systems. This review serves to encompass the history and recent evolution of nitrite, the compartment-specific metabolism of nitrite and its role in plasma as a biomarker for disease, the role of nitrite as a potential regulator of NO homeostasis, and the future of nitrite-based research.
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