Nitrite therapy for protection against ischemia-reperfusion injury

David J. Lefer
Division of Cardiology, Department of Medicine, Albert Einstein College of Medicine, Bronx, New York

RECENT EXPERIMENTAL EVIDENCE suggests that the anion nitrite represents an important storage form of nitric oxide (NO) that subsequently regulates a number of very important physiological activities (2–5, 10). This is a radical concept because nitrite was largely considered to be a biologically inert breakdown product of NO that served no physiological purpose. In fact, circulating nitrite levels were used as an indirect method to assess alterations in circulating NO levels in various animal models for many years. The nitrite anion forms as a consequence of oxidation of NO and then accumulates in the blood compartment as well as in tissues (5, 10) (Fig. 1). Under conditions of acidosis, hypoxia, and tissue ischemia-reperfusion, nitrite is reduced to form NO as a result of reduction by deoxyhemoglobin, myoglobin, tissue heme proteins, and nonenzymatic disproportionation (4, 5). In this manner, it seems highly logical that nitrite could very tightly regulate blood flow and tissue perfusion to maintain organs within the normal physiological ranges. This exciting series of discoveries has created an entirely new field of research that entails the investigation of the molecular, biochemical, and physiological activities of nitrite under a variety of physiological and pathophysiological states.

An improved understanding of the biochemical conversion of nitrite to NO under both physiological and pathophysiological conditions has resulted in a great deal of interest in the potential beneficial effects of nitrite therapy in animal models of injury. Nitrite has been shown to be a physiological vasodilator substance that regulates regional perfusion in humans (6) and to induce selective pulmonary vasodilation under conditions of hypoxia (8). Nitrite therapy has proven efficacious for the treatment of hemorrhagic stroke in primates in a recent study by Pluta and colleagues (9). In addition, a recent study by Duranksi et al. (4a) clearly demonstrated that sodium nitrite therapy significantly reduced the extent of both hepatic and myocardial ischemia-reperfusion injury. Treatment with very low levels of nitrite (i.e., 1–50 nmol) before reperfusion reduces hepatic enzyme release and hepatocellular apoptosis in a murine model of hepatic ischemia-reperfusion injury. Nitrite also markedly attenuated myocardial infarct size in a murine model of coronary artery ligation and reperfusion. Nitrite-mediated cytoprotection was dependent on the generation of NO from nitrite and signaling mediated via the soluble guanylate cyclase-cGMP pathway. These results are supported by earlier work by an earlier study by Webb and colleagues (11) that demonstrated protective effects of nitrite against myocardial ischemia-reperfusion injury in isolated, buffer-perfused hearts. Future studies are indicated to gain additional insights into the precise cellular and molecular mechanisms related to protection against ischemia-reperfusion injury afforded by nitrite therapy.

In the present issue of the American Journal of Physiology-Renal Physiology, Basireddy and colleagues (1) have investigated the effects of intravenous sodium nitrite administration on renal ischemia-reperfusion injury. Rats were subjected to a right nephrectomy followed by left renal ischemia, and sodium nitrite therapy was initiated at various times during the experimental protocol. In initial studies, nitrite therapy (0.12–12 nmol/g body wt) was initiated during renal ischemia, and in subsequent studies nitrite was injected before the onset of renal ischemia. In all experimental studies, the authors failed to demonstrate any protective effects of sodium nitrite therapy compared with saline or sodium nitrate. Renal injury was assessed using a number of methods including serum creatinine, histology, and renal function. The authors have very carefully performed the experimental studies, and the data are unequivocal. The present study by Basireddy et al. (1) does serve to raise a number of questions that need to be resolved. It is possible that the bioactivation of nitrite to NO did not occur under these experimental conditions, and therefore the authors failed to observe significant protection. It is very
difficult to measure NO levels in the circulation or in tissues in vivo under conditions of ischemia-reperfusion, and these studies may not be possible at present. Similarly, larger doses of sodium nitrite may be required for renal protection compared with other organs such as the heart and liver. Additional studies might involve an expanded dose range to determine the effects of higher nitrite doses in this model system. Studies investigating NO donors or inhaled NO would also add to our understanding of the results of the present study because NO therapy may not prove beneficial in this model of renal ischemia-reperfusion injury. Nonetheless, the study of Basireddy et al. does significantly extend our current knowledge regarding nitrite therapy in ischemic disorders and lays the foundation for additional studies to clarify the clinical potential of nitrite therapy for ischemia-reperfusion injury. It is important to determine which pathological states are amenable to nitrite therapy and to have additional confirmation of the protective effects mediated by nitrite in the heart, brain, liver, and lungs. Without question, the field of nitrite chemistry and biology is a truly exciting area of research that is certain to expand in the near future and lead to a dramatically improved understanding of the physiology of NO synthases and NO in terms of cytoprotection.

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