Peroxynitrite: Toxic or Protective in the Heart?

To the Editor:

The literature is somewhat controversial as to whether peroxynitrite (ONOO⁻) is either cytotoxic or cytoprotective. An Editorial by Vinten-Johansen recently suggested that deleterious effects of ONOO⁻ in the heart are predominantly observed in vitro or ex vivo crystalloid buffer-perfused systems; however, ONOO⁻ is cardioprotective if applied in vivo. Does the exogenous administration of ONOO⁻ accurately reflect pathological conditions in which the endogenous generation of ONOO⁻ within cells is enhanced?

Because of the short half-life of ONOO⁻ at physiological pH, it has very little chance to reach its cellular targets when it is applied via the blood, as it rapidly reacts with plasma proteins and thiols such as glutathione and cysteine. Thus, ONOO⁻ is likely to be detoxified before it has a chance to reach tissues downstream of the injection site, let alone the intracellular compartment. ONOO⁻ forms S-nitrosothiols when it combines with thiol groups, which then act as nitric oxide (NO) donors. Because NO itself is a cardioprotective and antioxidant molecule, protection from noxious stimuli may result when exogenous ONOO⁻ is administered intravenously. Accordingly, exogenously administered ONOO⁻ was shown to inhibit leukocyte-endothelial cell interactions and to protect against ischemia/reperfusion injury in rats in vivo. Intraventricular infusion of ONOO⁻ reduced myocardial infarct size and preserved coronary endothelium after ischemia and reperfusion in cats, an effect that was mediated by the intermediate formation of S-nitrosothiols.

Exogenously applied ONOO⁻, however, has been shown to be detrimental to cellular functions when it was applied in crystalloid buffer systems, in which the concentrations of extracellular antioxidants and both free and protein-bound thiols are limited. In this case, exogenous ONOO⁻ and its toxic metabolites have a greater chance to reach their cellular targets and cause injury. This is, of course, dependent upon the concentration of ONOO⁻ and the duration of exposure. We have shown that continuous infusion of 40 to not 4 μmol/L ONOO⁻ into isolated working rat hearts impaired cardiac contractile function within 45 minutes. Authentic ONOO⁻ inhibited contractile function of cardiac myocytes and isolated rat papillary muscle. Administration of the ONOO⁻ generator 3-morpholinosydnonimine (SIN-1) exerted either cardiodepression in crystalloid buffer-perfused or cardioprotection in blood-perfused rat hearts. Similar results were obtained using either crystalloid or blood cardioplegia in dogs. One can conclude that exogenous ONOO⁻ is toxic when applied in crystalloid perfused hearts; however, it can be protective under experimental conditions in which ONOO⁻ first reacts with thiol groups, thereby forming NO donors.

It is, however, questionable whether antioxidants such as thiols are of sufficient concentration to adequately detoxify ONOO⁻ at the site of its endogenous formation, especially under conditions of ischemia/reperfusion or after expression of inducible NO synthase. To our knowledge, there is no literature showing any tissue protective effect of endogenously formed ONOO⁻. In contrast, many studies show that enhanced formation of ONOO⁻ in the myocardium is cytotoxic to the heart and contributes to ischemia/reperfusion injury both in vitro and in vivo, the spontaneous loss of cardiac function as well as cytokine-induced myocardial contractile failure in isolated rat hearts and in dogs in vivo, myocardial dysfunction after doxorubicin treatment of mice in vivo, autoimmune myocarditis and acute allograft rejection in rats, myocardial inflammation in humans, and cardiomyocyte apoptosis. Many of these studies show a correlation between ONOO⁻ formation and deterioration of cardiac function. Taken together, there is a consensus that endogenously formed ONOO⁻ contributes to myocardial injury resulting from ischemia and reperfusion injury as well as systemic inflammatory response syndrome. Specific pharmacological targeting of ONOO⁻ is an exciting new strategy to protect the heart from oxidant stress injury.

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