

LETTER

Is Nitric Oxide Really the Primary Mediator of Pancreatic β -Cell Death in Type 1 Diabetes?

In their report (1), the authors strengthen doubts that peroxynitrite is a main culprit for β -cell dysfunction and death in type 1 diabetes, confirming previous studies (2).

Type 1 diabetes (T1DM) in humans and animal models is characterized by strong expression of the proinflammatory cytokines IL-1 β and TNF α (3). The reactive species generated by the cytokine action ultimately cause β -cell death through nitro-oxidative stress (2). The very low expression of the H₂O₂-inactivating enzymes in β -cells, even though physiologically sufficient, is insufficient to prevent toxicity under pathophysiological conditions (2).

IL-1 β alone with its dominant effect on NO generation causes β -cell dysfunction (4). Only together with TNF α , a strong stimulator of mitochondrial reactive oxygen species formation (2, 5), does it cause β -cell death in T1DM (3).

Cytokine-treated β -cells show high manganese superoxide dismutase expression in the mitochondria (5). Thus, there is little chance for the superoxide radical to generate peroxynitrite through interaction with NO (2). However, the authors ignore that these circumstances strongly favor the interaction between NO and H₂O₂, produced at

high concentrations in cytokine-treated β -cell mitochondria, the primary site of cytokine toxicity (2). This is the optimal precondition for formation of the highly toxic hydroxyl radical, because β -cell mitochondria express very little glutathione peroxidase (5), insufficient for quick H₂O₂ inactivation (2, 5).

The authors overlook the crucial role of TNF α in the pathogenesis of β -cell death in T1DM and therefore their conclusion that NO is the primary mediator of cellular toxicity is inadequate. Experiments performed with a combination of IL-1 β and TNF α confirm this (2).

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