Antihypertensive and antiatherogenic effects of novel nonoates based on metallic center

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At cardiovascular level, nitric oxide (NO) controls smooth muscle functions, maintains vascular integrity and exerts anti-hypertensive effect. Metal-nonoates are a recently developed class of NO donors, with NO release modulated through the complexation of the *N*-aminoethylpiperazine *N*-diazeniumdiolate ligand to metal ions. In this study, we characterized the vascular protective effects of the most effective compound of this class, Ni(PipNONO)Cl, compared to the commercial NONOate derivate DETA/NO. Ni(PipNONO)Cl induced a concentration dependent relaxation of pre-contracted rat aortic rings. When tested on cultured microvascular endothelial cells, Ni(PipNONO)Cl exerted a protective effect on the endothelium, promoting cell proliferation and survival in the range of pM. The administration of Ni(PipNONO)Cl to vascular smooth muscle cells reduced cell number, promoting their apoptosis at high concentration (10 μM). Inhibition of smooth muscle cell migration, a hallmark of atherosclerosis, was accompanied by cytoskeletal rearrangement and loss of lamellipodia. When added to isolated platelets, Ni(PipNONO)Cl significantly reduced ADP induced aggregation. Since atherosclerosis is accompanied by an inflammatory environment, cultured endothelial cells were exposed to interleukin-1 beta (IL-1β). In the presence of IL-1β, Ni(PipNONO)Cl inhibited cyclooxygenase.2 (COX-2) and inducible nitric oxide synthase (iNOS) upregulation, reduced endothelial permeability and the platelet and monocyte adhesion markers CD31 and CD40 at the plasma membrane. The acute and chronic administration of Ni(PipNONO)Cl to spontaneously hypertensive rats reduced systemic blood pressure, without the appearance of tolerance. Overall, these data indicate that Ni(PipNONO)Cl exerts vascular protective effects relevant for vascular dysfunction with antihypertensive properties and prevention of atherosclerosis and thrombosis.