S-NITROSOTHIOLS: FROM DESIGN TO APPLICATIONS

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Primary S-nitrosothiols (RSNOs) carrying the S-NO moiety occur in the plasma and cells of mammals, where they have the same physiological functions of free nitric oxide (NO). We have synthesized primary RSNOs like S-nitrosocysteine (CysNO), S-nitroso-N-acetylcysteyne (SNAC) and S-nitrosoglutathione (GSNO). The physiological properties of such NO donors have been investigated in vitro and in vivo, using different animal models and different application forms, in order to obtain systemic and local effects. Oral administration of SNAC prevented the onset and progression of nonalcoholic fatty liver disease (NAFLD) in choline-deficient fed Wistar rats and reversed NAFDL induced by different diets in ob/ob mice. These effects were positively correlated with a decrease in the concentration of lipid hydroperoxydes in liver homogenate and with the ability of RSNOs in preventing lipid peroxidation of linoleic acid and LDL in vitro. Exogenous administration of GSNO induced in vivo S-nitrosation of the insulin receptor subunit (IR) and protein kinase B/Akt (Akt) and reduced their kinase activity in the muscle in two distinct animal models, showing that S-transnitrosation of proteins involved in insulin signal transduction is a novel molecular mechanism of iNOS induced insulin resistance. S-transnitrosation was also shown to be the major mechanism by which SNAC and GSNO exert leishmanicidal activity in cultured parasites, being thus potential therapeutic agents against cutaneous leishmaniasis. Topical RSNOs administration in hydrogel matrices can be used for this purpose and also to produce a consistent and sustained increase in the local blood flow in human skin.
Keywords: S-nitrosothiols, lipid peroxydation, transnitrosation