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The therapeutic potential of carbon monoxide

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Carbon monoxide (CO) is increasingly being accepted as a cytoprotective and homeostatic molecule with important signalling capabilities in physiological and pathophysiological situations. The endogenous production of CO occurs through the activity of constitutive (haem oxygenase 2) and inducible (haem oxygenase 1) haem oxygenases, enzymes that are responsible for the catabolism of haem. Through the generation of its products, which in addition to CO includes the bile pigments biliverdin, bilirubin and ferrous iron, the haem oxygenase 1 system also has an obligatory role in the regulation of the stress response and in cell adaptation to injury. This Review provides an overview of the physiology of CO, summarizes the effects of CO gas and CO-releasing molecules in preclinical animal models of cardiovascular disease, inflammatory disorders and organ transplantation, and discusses the development and therapeutic options for the exploitation of this simple gaseous molecule.

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The pharmacodynamics evaluation of SGC-003, a novel soluble guanylate cyclase agonist, on pulmonary hypertension in rats

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Aim: The purpose of the present study is to evaluate the pharmacodynamics of SGC-003(Methyl-4,6-diamino-2-(1-(thien-2-yl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-pyrimidin-5-ylmethylcarbamate), a novel soluble guanylate cyclase agonist, synthesized by Beijing Institute of Pharmacology and Toxicology on hypoxia and monocrotaline (MCT)-induced pulmonary hypertension in rats.

Methods: The rats were exposed to chronic hypoxia (10% O2) in a ventilated chamber for three weeks or subcutaneously administrated monocrotaline (50 mg/kg) for two weeks to obtain Pulmonary Hypertension (PH) model. Pulmonary arterial pressure on anesthetized rats was measured by a blood pressure instrument.

Results: In chronic treatment of hypoxia in rats, SGC-003 (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, i.g., twice/day for 3 weeks) significantly inhibited the increase in the mean pulmonary arterial pressure (MPAP) ($P<0.05$), right ventricle systolic pressure (RVSP) ($P<0.001$) and right ventricular hypertrophy index (RVHI) ($P<0.01$) in dose-dependent manner, compared with model group, with the ratio of inhibition being 25.10%, 68.15% and 35.45%, respectively. In chronic treatment of MCT-injected rats with fully established PH, SGC-003 (0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, i.g., twice/day for 2 weeks) partially reversed the PH, with MPAP ($P<0.05$), RVSP ($P<0.01$) and RVHI ($P<0.01$), significantly decreasing in dose-dependent manner compared with model group with the ratio of inhibition being 59.82%, 55.20% and 30.19%, respectively. In addition, the experimental data from the noninvasive blood test indicated that systemic blood pressure did not significantly change after chronically administrating SGC-003 for eleven days. The above effects of SGC-003 were equivalent to BAY63-2521.

Conclusion: SGC-003, a novel soluble guanylate cyclase agonist, has the inhibition effect on PH induced by hypoxia and MCT, which is equivalent to BAY63-2521.

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