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Editorial

The Future of Carbon Monoxide Releasing Molecules: A Message to the Pharmaceuticals to Manufacture these Compounds

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Carbon monoxide (CO) is one of the three gas transmitters (GTs) which is capable to regulate inflammation, cell survival and growth. Degradation of the haem molecule by haem oxygenase enzymes (HO-1, HO-2 and HO-3) leads to the generation of CO. Each cell in the body expressed haem oxygenase enzymes in which the HO-1 is the only inducible enzyme that expressed in the spleen and liver, while the HO-2 and HO-3 enzymes constitutively expressed and they are mainly present in the brain and testes.

The endogenous CO exerts multiple pharmacological actions including anti-inflammatory (due to its regulatory effect on the activity of T-lymphocytes and macrophages), antioxidant (due to its effect on the formation of the bilirubin), vascular smooth muscle relaxation including coronary artery and cryoprotection against ischemia or cytokines. It is impossible to manufacture the CO as a therapeutic medicine because it is a gas. Therefore, preparation of CO-releasing molecules (CORMs) is a novel approach that used specific CO carriers to release a measurable, controllable, and effective amount of CO in the specific organ or system in the body. The structure of the COMRs contains the metal core, the ligand (inner) coordination sphere and the drug (outer) sphere.

Therefore, the classification of CORMs is according to the metal transition into (a) Metal carbonyl complexes that contained ruthenium, manganese or molybdenum. In these complexes, CO bound to the transition metals and (b) Boron-carbonate complexes by which these molecules contained metalloid boron instead of transition metals and they spontaneously released CO in physiological conditions that depend on the pH of the milieu. According to the pharmacokinetics profile, these complexes are sub grouped into (a) lipophilic complexes such as CORM-1 ([Mn2(CO)10]) and CORM-2 ([Ru(CO)3Cl2]2). These complexes should be dissolved in the organic solvents e.g. dimethysulfoxide. In addition (b) water soluble CORMs such as CORM-3 (([Ru(CO)3Cl (glycinate]); CORM-A1 (Na2[H3BCO2]); and CORM-401 Mn(CO)4(S2CNMe[CH2CO2H]). Photo-CORMs are group of CORMs that activated by the light in which the photo-excitation of the metal-carbonyl bond lead to release of CO.

The pharmacological actions of these molecules were dependent on their interaction with the target tissue, and their potency is determined by the duration of CORM-target interaction. The optimum release of CO from these molecules is unknown due to the diverse nature of CORM.

Recent studies explored pleotropic pharmacological actions of CORMs including suppression of nitric oxide production in the pathological conditions e.g. inflammation, regulation of the mitochondrial respiration, activation of the potassium channels, blocking the entry of calcium through the L-type calcium channel, anti-apoptotic and cell survival via their effect on the different cellular signaling pathways.

Experimental studies explored the beneficial effects of CORMs in the treatment of rheumatoid arthritis, drugs induced gastric ulcer, as adjuvant in treatment of malaria, acetaminophen induced liver failure, prevent cardiac allograft rejection, increase blood flow in cerebral, coronary and other blood vessels due to their vaso-relaxant effect, and anti-cancer effect against several types of cancer. Moreover, CORMs were of benefit in alleviating the cancer related conditions, e.g. anti-neoplastic drugs induced cardiac toxicity and nephrotoxicity, and preventing the development of the secondary cancer due to radiation therapy.

The pharmaceutical companies were engaged in the discovery an optimum CORM and/or specific devices that carry the CO to the pathological site. The Ikaria, Inc. company has been developing the COVOX-delivery system for investigational use, which is the only device that designed specifically for inhaled carbon monoxide. The dose (mg/kg/hour) is delivered as a pulse at the beginning of each inspiratory period. In patients who are spontaneously breathing, CO delivered through a nasal cannula, whereas in patients who are mechanically ventilated, the gas is delivered through a flow trigger adaptor, which connects to the endotracheal tube of the patient. The desired delivery rate is maintained on a breath-by-breath

basis. The Alfama, Inc a pharmaceutical, company engages in the possible commercial benefit of COMRs. CO-donors or CORMs may be the future medicines for a variety of pathological conditions and intensive work is necessary to manufacture an optimum carrier of CO with suitable pharmacokinetics profile or looking for CO-donors as with nitric oxide donors e.g. Molsidomine and glyceryl trinitrate.

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