CO-Releasing Materials: Therapeutic Implications and Challenges towards Drug Discovery

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Abbreviations: CO: Carbon Monoxide; HO: Heme Oxygenase; COHb: Carboxy Hemoglobin; CORMats: CO-Releasing Materials; CORMs: CO-Releasing Molecules

Introduction

Since last century, carbon monoxide (CO) generally regarded as “silent killer” and life-threatening for living organisms because of its colourless, odourless and poisonous nature [1]. Haldane explored the poisonous nature of CO can be exerted as car-boxy hemoglobin (COHb) through hemoglobin dissociation parameters [2,3]. This study explains the biological role of the CO inside the mammalian systems.

As endogenously released gaseous messengers, or gas transmitters these particular molecules calibrated as nanomedicines (NMs) or nanomaterial (NMs) essential to physiology of all microorganisms’ postulates, responsible for intracellular and intercellular approaching [4]. The endogenous gaseous mechanism has attracted greater attention by the researchers for designing and developing such administration that could supply reserved CO at moderate rate such as vascular modulator [5,6]. To achieve the endogenous therapeutic activities, exogenous endeavor is the appropriate choice for the purpose of drugs.

Generally, there are two ways to classify the CO gas inhalation, i.e. direct inhalation and indirect inhalation. During direct inhalation carboxy hemoglobin level has been raised significantly beyond the therapeutic level because CO gas has great affinity with hemoglobin to form the carboxy hemoglobin (COHb). The percentage of COHb above 10% (therapeutic level) contains the oxygen movement along blood circulation [7]. This issue has been addressed properly through indirect inhalation. Indirect inhalation strategy has been further divided into two categories i.e. CO-releasing molecules (CORMs) and CO-releasing materials (CORMats) [8].

CORMs are organometallic carbonyl complexes good for solubility and shown good compatibility with mammalian system. The tissue selectivity and toxicity of organometallic complexes after degradation of CORMs is still a big challenge for the CO drug developers. Finding a specific target is quite impossible for CORMs because CORMs are soluble and can easily access every part of the body which makes it good for searching and reaching the effected organs, on the other hand might be harmful for the healthy organs because of their inhibiting characteristics. Slow kinetic profile is required for the therapeutic actions. Usually CORMs possess fast kinetic profile. The fast kinetic profile favors the ion-channel path rather than therapeutic dosage. The ion-channel path explained the complete biological route of CO. The already developed CORMs are: CORM-1, CORM-2, CORM-2, CORM-A1, ALF492, Re-CORM-1, ALF186, ALF794. The disused challenges and limitation moves the researchers towards CO-releasing materials (CORMats) [7].

CORMats have been introduced because they exhibit less toxicity and are excellent for tissue selectivity. The handling of the toxicity of organometallic complexes is
The major challenges for the development of CO precursor are: solubility, compatibility with biological system, tissue selectivity, kinetic profile, activation mechanism, cytotoxicity of the drugs (ability to kill the diseased organs), and toxicity of organometallic complexes before and after degradation of precursor. The half-life of CO precursor (t_{1/2}) is also defined the stability and sustainability of the drugs which is directly related to its performance. To improve the sustainability of CO precursor, the half-life (t_{1/2}) must be extended for few minutes. The half-life of CORM-1 and CORM-2 has very short interval up to 1 minute in PBS (phosphate buffered saline) at 37°C temperature and pH nearly 7.4 [7].

CO grants the pro-apoptotic behavior and acting as anti-apoptotic [19], by giving security to the cells and secure tissue from destruction, while being assertive to T- cells (strike and damage the tissue or cells), fibroblasts or cancer cells [20]. CO encompasses the broad scope as it influences the cellular proliferation. CO contains the cancer cells propagation, aggressive T cells and chronic vascular regeneration in pulmonary hypertension situation [21]. Surprisingly, CO encourages the proliferation of endothelial cells, progenitor cells and regulatory T-cells [22-24]. Self-regulatory mechanism of cell/organism (Homeostatic) are the beneficial aspects of CORMs or/and CO gas therapy in numerous animal disease model which are manifested by molecular and cellular functional mechanism of HIFα, iNOS, TNF, ROS, PPAR-gamma.

CORM-3 has good cure-ability for inflammatory disorders such as rheumatoid arthritis, osteoarthritis and collagen-induced arthritis (CIA) [25] whose illustrate of synergistic inflammatory variables PGE-2 (prostaglandin-2), (interleukin), RANKL, COX-2 (cyclooxygenase-2), IL10, IL6, IL2, TNFα and ICAM-1 (inter-cellular adhesion molecule-1) [26,27]. CORM-3 also inhibits the myocardial infarction [28,29], renal blood flow (RBF) restoration during Kidney transplantation [30-33] and alleviate cartilage destruction [25]. CORM-A1 provided ameliorated course in experimental auto immune uveoretinitis (EAU) [34], and also involved in experimental auto-immune encephalomyelitis (EAE) as moderate for inflammatory infiltrations of spinal cord [35]. CORM-1 came up with anti-inflammatory influence in the mesentery due to carrageenan [26] and while facing Epileptic seizures performed as cerebroprotective in newborn piglets [36]. CORM-2 attenuated the tumor proliferation [37], considerably, enhanced coagulation and slow-down the fibrinolytic bleeding [38,39] and improved survival in the liver injury affected by CLP [40]. CORM-3, CORM-2 and ALF-062 is corroborated with antimicrobial functions [41].

In summary, small concentration of CO is vital for different therapeutic purposes. Indirect inhalation is the appropriate choice for the CO drug administration. CORMs and CORMats are the two subcategories of indirect inhalation. For carbonyl complexes, organometallic element is the key component. Organometallic complexes are good for carbonyl reaction, unfortunately it is involved in toxicity. To some extent, different techniques are applied to overcome this dilemma. Tissue selectivity and cytotoxic effects are also prime objective of drug development.

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