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

Muhammad Faizan[1], Niaz Muhammad[2]*

[1]Key Laboratory of Applied Surface and Colloid Chemistry MOE, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710062, China

[2]Department of Biochemistry, College of Life Sciences, Shaanxi Normal University, Xi'an 710062, China

*Correspondence should be addressed to Niaz Muhammad; niazpk@hotmail.com

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

one the exclusive feature of CORMats development. Although, at initial level there were some remarkable breakthrough but results need to be improved for the development of ideal CO pro-drug. In CORMats, several scaffolds/ conjugated formulation have been introduced, and are still under investigation using compatible conjugate CORM's (Fe-, Mn-, Ru-, Co-, metal carbonyl complexes) through different transporting services such as micellar system, Iron MOFs [9], co-polymer systems [10,11], protein [12], nano-fiber gel [13], metallodendrimers [14] and inorganic hybrid scaffolds [15-18].

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, osteoarthitis 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 infraction [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].

CO promotes the mitochondrial bio-genesis and compels mitochondria to enhance the reactive oxygen species (ROS) [7] and ATP generation as account for influences the cellular execution. That is the demonstration of ROS-contingent upregulation of hypoxia-inducible factor 1α (HIFα) and peroxisome proliferator-activated receptor-(PPAR-gamma) to save from inflammation and lung injury [42], and given performance against reducing TNF-α generation in ventilator induced injury [26]. CO participate the biological activity irrespective of mode of transportation and direct/indirect administration. CORMs/CO both have feature of exhibiting the re-endothelialization affected by wire-trauma injury [23].

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.

References

1. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning--a public health perspective. Toxicology 2000;145(1):1-14.

2. Haldane JBS. Carbon monoxide as a tissue poison. Biochem. J. 1927;21:1068-75.

3. Douglas CG, Haldane JS, Haldane JBS. The laws of combination of haemoglobin with carbon monoxide and oxygen. J. Physiol. (Oxford, U.K.) 1912;44:275-304.

4. Wang L, Yan L, Liu J, Chen C, Zhao Y. Quantification of Nanomaterial/Nanomedicine Trafficking in vivo. Analytical Chemistry 2018;90(1):589-614.

5. Jiang Y-h. Relationship between endogenous carbon

monoxide production and disease. Xiandai Jianyan Yixue Zazhi 2013;28(2):22-4.

6. Leffler CW, Parfenova H, Jaggar JH. Carbon monoxide as an endogenous vascular modulator. Am J Physiol Heart Circ Physiol 2011;301(1):H1-h11.

7. Faizan M, Muhammad N, Niazi KUK, Hu Y, Wang Y, Wu Y, et al. CO-Releasing Materials: An Emphasis on Therapeutic Implications, as Release and Subsequent Cytotoxicity Are the Part of Therapy. Materials 2019;12(10):1643.

8. Faizan M, Niazi UK, Muhammad N, Hu Y, Wang Y, Lin D, et al. The Intercalation of CORM-2 with Pharmaceutical Clay Montmorillonite (MMT) Aids for Therapeutic Carbon Monoxide Release. International Journal of Molecular Sciences 2019;20(14).

9. Diring S, Carné-Sánchez A, Zhang J, Ikemura S, Kim C, Inaba H, et al. Light responsive metal – organic frameworks as controllable CO-releasing cell culture substrates. Chemical Science 2017;8(3):2381-6.

10. Kunz PC, Brückmann NE, Spingler B. Towards Polymer Diagnostic Agents – Copolymers of N-(2- Hydroxypropyl) methacrylamide and Bis(2-pyridylmethyl)-4-vinylbenzylamine:Synthesis, Characterisation and Re(CO)3-Labelling. European Journal of Inorganic Chemistry 2007;2007(3):394-9.

11. Brückmann NE, Wahl M, Reiß GJ, Kohns M, Wätjen W, Kunz PC. Polymer Conjugates of Photoinducible CO-Releasing Molecules. European Journal of Inorganic Chemistry 2011;2011(29):4571-7.

12. Tabe H, Fujita K, Abe S, Tsujimoto M, Kuchimaru T, Kizaka-Kondoh S, et al. Preparation of a Cross-Linked Porous Protein Crystal Containing Ru Carbonyl Complexes as a CO-Releasing Extracellular Scaffold. Inorganic Chemistry 2015;54(1):215-20.

13. Matson JB, Webber MJ, Tamboli VK, Weber B, Stupp SI. A peptide-based material for therapeutic carbon monoxide delivery. Soft Matter 2012;8(25):6689-92.

14. Govender P, Pai S, Schatzschneider U, Smith GS. Next generation PhotoCORMs: polynuclear tricarbonylmanganese(I)-functionalized polypyridyl metallodendrimers. Inorg Chem 2013;52(9):5470-8.

15. Dördelmann G, Pfeiffer H, Birkner A, Schatzschneider U. Silicium Dioxide Nanoparticles As Carriers for Photoactivatable CO-Releasing Molecules (PhotoCORMs). Inorganic Chemistry 2011;50(10):4362-7.

16. Gonzales MA, Han H, Moyes A, Radinos A, Hobbs AJ, Coombs N, et al. Light-triggered carbon monoxide delivery with Al-MCM-41-based nanoparticles bearing a designed manganese carbonyl complex. Journal of Materials Chemistry B 2014;2(15):2107-13.

17. Dordelmann G, Meinhardt T, Sowik T, Krueger A, Schatzschneider U. CuAAC click functionalization of azide-modified nanodiamond with a photoactivatable CO-releasing molecule (PhotoCORM) based on [Mn(CO)3(tpm)]+. Chem Commun (Camb) 2012;48(94):11528-30.

18. Kunz PC, Meyer H, Barthel J, Sollazzo S, Schmidt AM, Janiak C. Metal carbonyls supported on iron oxide nanoparticles to trigger the CO-gasotransmitter release by magnetic heating. Chem Commun (Camb) 2013;49(43):4896-8.

19. Song R, Zhou Z, Kim PK, Shapiro RA, Liu F, Ferran C, et al. Carbon monoxide promotes Fas/CD95-induced apoptosis in Jurkat cells. J Biol Chem 2004;279(43):44327-34.

20. McDaid J, Yamashita K, Chora A, Ollinger R, Strom TB, Li XC, et al. Heme oxygenase-1 modulates the allo-immune response by promoting activation-induced cell death of T cells. Faseb j 2005;19(3):458-60.

21. Zuckerbraun BS, Chin BY, Wegiel B, Billiar TR, Czsimadia E, Rao J, et al. Carbon monoxide reverses established pulmonary hypertension. J Exp Med 2006;203(9):2109-19.

22. Hu CM, Lin HH, Chiang MT, Chang PF, Chau LY. Systemic expression of heme oxygenase-1 ameliorates type 1 diabetes in NOD mice. Diabetes 2007;56(5):1240-7.

23. Wegiel B, Gallo DJ, Raman KG, Karlsson JM, Ozanich B, Chin BY, et al. Nitric oxide-dependent bone marrow progenitor mobilization by carbon monoxide enhances endothelial repair after vascular injury. Circulation 2010;121(4):537-48.

24. Lee SS, Gao W, Mazzola S, Thomas MN, Csizmadia E, Otterbein LE, et al. Heme oxygenase-1, carbon monoxide, and bilirubin induce tolerance in recipients toward islet allografts by modulating T regulatory cells. Faseb j 2007;21(13):3450-7.

25. Ferrandiz ML, Maicas N, Garcia-Arnandis I, Terencio MC, Motterlini R, Devesa I, et al. Treatment with a CO-releasing molecule (CORM-3) reduces joint inflammation and erosion in murine collagen- induced arthritis. Ann Rheum Dis 2008;67(9):1211-7.

26. Freitas A, Alves-Filho JC, Secco DD, Neto AF, Ferreira SH, Barja-Fidalgo C, et al. Heme oxygenase/carbon monoxide-biliverdin pathway down regulates neutrophil rolling, adhesion and migration in acute inflammation. Br J Pharmacol 2006;149(4):345-54.

27. Chaves-Ferreira M, Albuquerque IS, Matak-Vinkovic D, Coelho AC, Carvalho SM, Saraiva LM, et al. Spontaneous CO release from Ru(II)(CO)2-protein complexes in aqueous solution, cells, and mice. Angew Chem Int Ed Engl 2015;54(4):1172-5.

28. Fujimoto H, Ohno M, Ayabe S, Kobayashi H, Ishizaka N, Kimura H, et al. Carbon monoxide protects against cardiac ischemia--reperfusion injury in vivo via MAPK and Akt--eNOS pathways. Arterioscler Thromb Vasc Biol 2004;24(10):1848-53.

29. Guo Y, Stein AB, Wu WJ, Tan W, Zhu X, Li QH, et al. Administration of a CO-releasing molecule at the time of reperfusion reduces infarct size in vivo. Am J Physiol Heart Circ Physiol 2004;286(5):H1649-53.

30. Bagul A, Hosgood SA, Kaushik M, Nicholson ML. Carbon monoxide protects against ischemia- reperfusion injury in an experimental model of controlled non heart beating donor kidney. Transplantation 2008;85(4):576-81.

31. Yoshida J, Ozaki KS, Nalesnik MA, Ueki S, Castillo- Rama M, Faleo G, et al. Ex vivo application of carbon monoxide in UW solution prevents transplant-induced renal ischemia/reperfusion injury in pigs. Am J Transplant 2010;10(4):763-72.

32. Sandouka A, Fuller BJ, Mann BE, Green CJ, Foresti R, Motterlini R. Treatment with CO-RMs during cold storage improves renal function at reperfusion. Kidney Int 2006;69(2):239-47

33. Nakao A, Faleo G, Shimizu H, Nakahira K, Kohmoto Sugimoto R, et al. Ex vivo carbon monoxide prevents cytochrome P450 degradation and ischemia/ reperfusion injury of kidney grafts. Kidney Int 2008;74(8):1009-16.

34. Chora AA, Fontoura P, Cunha A, Pais TF, Cardoso S, Ho PP, et al. Heme oxygenase-1 and carbon monoxide suppress autoimmune neuroinflammation. J Clin Invest 2007;117(2):438-47.

35. Fagone P, Mangano K, Mammana S, Cavalli E, Di Marco R, Barcellona ML, et al. Carbon monoxide-releasing molecule-A1 (CORM-A1) improves clinical signs of experimental autoimmune uveoretinitis (EAU) in rats. Clin Immunol 2015;157(2):198-204.

36. Zimmermann A, Leffler CW, Tcheranova D, Fedinec AL, Parfenova H. Cerebroprotective effects of the CO-releasing molecule CORM-A1 against seizure- induced neonatal vascular injury. Am J Physiol Heart Circ Physiol 2007;293(4):H2501-7.

37. Vitek L, Gbelcova H, Muchova L, Vanova K, Zelenka J, Konickova R, et al. Antiproliferative effects of carbon monoxide on pancreatic cancer. Dig Liver Dis 2014;46(4):369-75.

38. Chlopicki S, Lomnicka M, Fedorowicz A, Grochal E, Kramkowski K, Mogielnicki A, et al. Inhibition of platelet aggregation by carbon monoxide-releasing molecules (CO-RMs): comparison with NO donors. Naunyn-Schmiedeberg's Archives of Pharmacology 2012;385(6):641-50.

39. Nielsen VG, Chawla N, Mangla D, Gomes SB, Arkebauer MR, Wasko KA, et al. Carbon monoxide-releasing molecule-2 enhances coagulation in rabbit plasma and decreases bleeding time in clopidogrel/ aspirin-treated rabbits. Blood Coagul Fibrinolysis 2011;22(8):756-9.

40. Chung SW, Liu X, Macias AA, Baron RM, Perrella MA. Heme oxygenase-1-derived carbon monoxide enhances the host defense response to microbial sepsis in mice. J Clin Invest 2008;118(1):239-47.

41. Nobre LS, Seixas JD, Romao CC, Saraiva LM. Antimicrobial action of carbon monoxide-releasing compounds. Antimicrob Agents Chemother 2007;51(12):4303-7.

42. Bilban M, Bach FH, Otterbein SL, Ifedigbo E, d'Avila JC, Esterbauer H, et al. Carbon monoxide orchestrates a protective response through PPARgamma. Immunity 2006;24(5):601-10.