Int. J. Curr. Res. Med. Sci. (2020). 6(2): 9-12

International Journal of Current Research in Medical Sciences

ISSN: 2454-5716
P-ISJN: A4372-3064, E -ISJN: A4372-3061
www.ijcrims.com

Short Communication

Volume 6, Issue 2 -2020

DOI: http://dx.doi.org/10.22192/ijcrms.2020.06.02.002

How do hypoxic mechanisms play role in the carbon monoxide induced injury to the human body?

Dr Sunder S Samuel

Scientist, National Poisons Information Center, Department of Pharmacology, AIIMS, New Delhi, 110029, India.
E-mail: *sundersingh.samuel@gmail.com*

Abstract

In this Paper, how hypoxic mechanisms play role in Carbon Monoxide (CO) induced injury to Human body is discussed. CO exposure at levels producing hypoxia through hypoxic mechanisms will affect any tissue, particularly liver, brain, heart and kidney, tissues with high oxygen utilization requirements. Formation of carboxyhemoglobin (COHb), the principal hypoxic mechanism, decreases the oxygen carrying capacity of the blood. Although hypoxic mechanisms of action are well established, further research is needed in the area of biomarker profiles for CO poisoning to optimally treat patients who were exposed to this highly toxic gas.

Keywords: Carbon Monoxide, Poisoning, Hypoxia, Toxicity, Carboxyhemoglobin.

The toxic gas, Carbon Monoxide (CO) is colorless and odorless, and is produced as a by-product of incomplete combustion of carbon-based fuels and substances. Human beings are exposed to carbon monoxide usually through inhalation. No information is available on its absorption or toxicity resulting from oral or dermal exposures. Carbon monoxide affects cell metabolism through both hypoxic and non-hypoxic mechanisms. The effects produced by both mechanisms, are largely due to the ability of carbon monoxide to bind to heme and alter the metabolism and/or function of heme proteins.

Targets through non-hypoxic mechanisms include components of many physiological regulatory systems, such as brain and muscle oxygen storage and utilization (neuroglobin, myoglobin); prostaglandin cell signaling pathway (cyclooxygenase, prostaglandin H synthase); nitric oxide cell signaling pathway (e.g., nitric oxide synthase); steroid and drug metabolism (cytochrome P450), energy metabolism and mitochondrial respiration (cytochrome c oxidase, NADPH oxidase); and ROS (catalase, peroxidases); and various transcription factors. Carbon monoxide is also produced endogenously and participates in the physiological regulation of some of these systems. Most of these non-hypoxic mechanisms have been attributed to the binding of Carbon Monoxide to heme proteins other than Haemoglobin (Hb)[1].

Carbon monoxide exposure through hypoxic mechanisms is expected to affect any tissue, particularly tissues with high oxygen (O_2) utilization requirements like brain, liver, kidney, and heart. The brain and the heart, because of their high metabolic rates, are the organs most susceptible to CO toxicity. The degree of injury directly correlates with the duration and the severity of the exposure. Formation of Carboxyhemoglobin (COHb), the principal hypoxic mechanism, decreases the O_2 carrying capacity of the blood and also impairs the release of O_2 from Hb for its utilization in tissues. Carbon monoxide decreases O_2 storage in muscle cells through similar mechanisms by binding to myoglobin and displacing O_2 from it. Blood COHb levels have not been shown to be a reliable predictor of severity of acute toxicity, although binding of carbon monoxide to Hb is the primary component of the hypoxic mode of action of carbon monoxide. This can be due to the time elapsed between the removal of the subject from exposure to CO to COHb measurement.

Tissue hypoxia is the main cause for acute carbon monoxide poisoning. In general, signs and symptoms of acute carbon monoxide poisoning can be present at COHb levels ranging from 3 to 24% [2]. More severe signs of carbon monoxide poisoning are poorly correlated with blood COHb levels, with loss of consciousness occurring at a mean level of 24.3% (range: 2–70%); and fatality at a mean level of 32.1% (range: 3.0–60%)[2]. Exposures resulting in COHb levels >50% are frequently fatal[3]. Persistent neurologic sequelae, which can be delayed in onset, can also occur. Although severe carbon monoxide toxicity primarily derive from hypoxia, the relationship between blood COHb levels and signs indicative of life-threatening toxicity is highly uncertain (eg., cardiopulmonary depression, coma, and convulsions).

Adverse cardiovascular effects are associated with the carbon monoxide exposures that result in blood COHb levels ≥2.4%, in subjects with compromised cardiovascular function (e.g., coronary artery disease), with effects occurring at the lowest levels. And blood COHb levels between 2.4 and 5.9% exacerbates the underlying cardiovascular disease, including enhancing myocardial ischemia and increasing cardiac arrhythmias. Continuous exposure of healthy subjects, to carbon monoxide resulting in blood COHb levels of 2.4 and 5.1% produced many P-wave deviations under resting conditions[1]. Under conditions of cardiac ischemia, tissue hypoxia secondary to the elevated COHb levels is thought to be a contributing factor to the cardiac effects in patients with coronary artery disease. However, direct cellular effects of carbon monoxide on cardiac muscle are also important. These include modulation of coronary arteriole calcium-activated potassium channels. They are inhibited under hypoxic/ischemic conditions[4]. CO also binds with myoglobin, another heme protein. It has an affinity approximately 60 times greater than that of oxygen. Under hypoxic conditions this binding is enhanced. This binding may partially explain the myocardial impairment that occurs with low-level exposures in patients with ischemic heart disease[5].

Hematological effects of CO include compensatory responses to tissue hypoxia resulting from the binding of carbon monoxide to Hb. Because carbon monoxide has a much higher affinity for Hb than O_2 (>200 times that of O_2), with relatively low partial pressures of carbon monoxide, O_2 is displaced from Hb. Binding of carbon monoxide to Hb has two effects:(a) the amount of O_2 that can be stored on Hb for delivery to tissues, decreases; and (b) it impairs the release of O_2 from Hb for its diffusion into tissues. CO thus causes a leftward shift of the oxyhemoglobin dissociation curve[5]. At sufficient levels of COHb, the combined effect results in tissue hypoxia, the principal mechanism of many adverse effects of exposure to carbon monoxide. To maintain O_2 delivery to tissues under conditions of hypoxia, compensatory hematological responses like increased blood volume, erythrocyte count, hematocrit, and Hb occur.

Central nervous system toxicity is produced after acute exposure to high levels of carbon monoxide. Though mechanisms of acute and delayed adverse nervous system effects are not established conclusively, tissue hypoxia secondary to COHb formation may be a contributing factor, particularly in association with high levels of blood COHb (>60%)[1]. The hypoxic state also triggers release of nitric acid from platelets and endothelial cells, leading to the formation of the free radical peroxynitrate. This causes mitochondrial dysfunction with a marked decrease in cytochrome oxidase, capillary leakage and apoptotic cell death. Direct cellular effects of carbon monoxide like ATP depletion, excitotoxicity, oxidative stress and postischemic reperfusion injury also contribute to neurotoxicity. Cerebrovascular vasodilation and increased cardiac output occur as compensatory mechanisms to maintain O_2 delivery to the brain, under conditions of hypoxia induced by COHb formation[6].

Exposure to carbon monoxide at levels producing hypoxia would be expected to affect any tissue, in particular those tissues with high O_2 utilization requirements. The kidney is the greatest contributor to basal metabolic rate next only to the brain because of the use of ATP-dependent active transport processes. Carbon monoxide-induced hypoxia decreases the availability of oxygen to produce ATP in renal mitochondria, which produces adverse effects to the kidneys. In cases of acute carbon monoxide poisoning, acute renal failure secondary to rhabdomyolysis has been observed[7].Visual field deficits, retinal hemorrhage &optic atrophy have been associated with severe CO poisoning in humans. The fetus is particularly vulnerable to maternal carbon monoxide exposure. Carbon monoxide in the maternal system distributes to fetal tissues. Measurements of fetal COHb concentrations in fetal and maternal blood of nonsmoking women have found fetal COHb concentrations to be approximately 10–15% higher than maternal blood[8].

The current understanding of principal mechanisms underlying the hypoxic mechanism of carbon monoxide are the higher affinity of carbon monoxide for Hb than O_2 and the increased binding affinity for O_2 from COHb. Binding of O_2 and carbon monoxide to the four heme moieties of Hb is actually cooperative[9]. With successive additions of carbon monoxide or $O_{2,}$ the associative reaction rate becomes faster, impairing the release of O_2 from Hb for utilization in tissues[10] . Although the blood COHb level reflects the current carbon monoxide body burden, measurement of blood COHb has not been shown to be a reliable predictor of severity of acute toxicity[2]. Cardiac enzyme markers are associated with elevated risk for long-term cardiac mortality following carbon monoxide poisoning; And the biochemical markers for brain injury, such as neuron-specific enolase and S-100 beta protein, have not been found to reliably correlate with severity of poisoning[11]. Although hypoxic mechanisms of action of carbon monoxide are well established (i.e., those related to formation of COHb), further research is needed in the area of biomarker profiles for carbon monoxide poisoning to optimally treat patients who were exposed to this toxic gas.

Conflict of Interest: None

References

1. Wilbur S, Williams M, Williams R, *et al*(2012). Toxicological Profile for Carbon Monoxide. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); Available from: https://www.ncbi.nlm.nih.gov/books/NBK153687/, accessed on August 30, 2018.
2. Hampson NB, Hauff NM (2008). Carboxy hemoglobin levels in carbon monoxide poisoning: Do they correlate with the clinical picture? Am J Emerg Med. 26(6):665–669.
3. Dolan MC (1985). Carbon monoxide poisoning. Can Med Assoc J.133: 392–399.
4. Wang R, Wu L (1997). The chemical modification of KCa channels by carbon monoxide in vascular smooth muscle cells. J Biol Chem. 272:8222–8226.
5. Christian T(2006). Carbon Monoxide. In: Neal EF, Mary AH, Lewis RG, Neal AL, Robert SH, Lewis SN. editors. *Goldfrank's Toxicologic Emergencies.* New York: McGraw-Hill; p.1689-1698
6. Gorman D, Drewry A, Huang YL, *et al* (2003). The clinical toxicology of carbon monoxide. Toxicology. 187(1):25–38.

7. Florkowski CM, Rossi ML, Carey MP, *et al* (1992). Rhabdomyolysis and acute renal failure following carbon monoxide poisoning: Two case reports with muscle histopathology and enzyme activities. J Toxicol Clin Toxicol. 30(3):443–454.
8. Longo LD.(1997) The biological effects of carbon monoxide on the pregnant woman, fetus, and newborn infant. Am J Obstet Gynecol. 129(1):69–103.
9. Alcantara RE, Xu C, Spiro TG, *et al*(2007). A quantum-chemical picture of hemoglobin affinity. Proc Natl Acad Sci USA. 104(47):18451–18455.
10. Perrella M, Di Cera E(1999). CO ligation intermediates and the mechanism of hemoglobin cooperativity. J Biol Chem. 274: 2605–2608.
11. Brvar M, Mozina H, Osredkar J, *et al* (2004). S100B protein in carbon monoxide poisoning: A pilot study. Resuscitation. 61:357–360.

Access this Article in Online	
	Website: www.ijcrims.com
Quick Response Code	Subject: Medicine

How to cite this article:
Sunder S Samuel. (2020). How do hypoxic mechanisms play role in the carbon monoxide induced injury to the human body?. Int. J. Curr. Res. Med. Sci. 6(2): 9-12.
DOI: http://dx.doi.org/10.22192/ijcrms.2020.06.02.002