Carbon Monoxide-Induced Alterations in the Expression of $K_{Ca}$ Channels in Pulmonary Artery Smooth Muscle Cells

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**CONTENTS**

INTRODUCTION
PHARMACOLOGICAL RELEVANCE OF CHRONIC CO EXPOSURE
CHRONIC CO EXPOSURE
CONCLUSION
REFERENCES

**SUMMARY**

Carbon monoxide (CO) is a generated gas and can regulate vascular tone. The two major sources of CO both exogenously and endogenously are automotive emissions and cigarette smoke, and the predominant biological source of CO is from degradation of heme by heme oxygenase. Accumulating data demonstrate that exogenous and endogenous CO are vasodilators, acting directly on vascular smooth muscle cells and on Ca$^{2+}$-activated K$^+$ channels. Surprisingly, there have been only a few experiments performed on the pulmonary circulation. Indeed, in this singular circulation, lying adjacent to the lung alveoli, CO could be directly delivered from the atmosphere and thus act directly on smooth muscle cells (SMCs) without delivery and by blood hemoglobin. Results from our laboratory have demonstrated that CO exposure can activate Ca$^{2+}$-activated K$^+$ channels of pulmonary SMCs. This review focuses on this point and also demonstrates that CO could induce a novel mechanism that we call “CO-induced CO increased sensitivity” in which K$^+$ channels are the main actor.

**Key Words:** Chronic carbon monoxide; large-conductance Ca$^{2+}$-activated K$^+$ channels; voltage-activated K$^+$ channels; chronic hypoxia; pulmonary hypertension; gasotransmitter.
1. INTRODUCTION

Carbon monoxide (CO) has often been presented as a “killer” or as a poison (1) because of its competition with oxygen for binding to hemoglobin (Hb), locking the compound in the oxy conformation and decreasing oxygen unloading to tissues. This toxicity is perhaps an unfortunate consequence of industrialization and the production of high quantities of exogenous CO. However, this action of CO has also provided a useful tool to support the hypothesis that oxygen sensors are heme proteins in oxygen-sensing cells (2,3). Recently, it was demonstrated that this diatomic gas may constitute the second member of a new class of transmitters called gasotransmitters (4). The physiological resurgence of CO (5) resulted in large part because of the demonstration that it could induce relaxation of vascular tissues (independently of hypoxia) and also because it could be endogenously produced by heme oxygenase (HO), which catalyzes the oxidative cleavage of heme to CO, iron, and biliverdin (6). Since the first evidence of a vascular effect of CO in the pulmonary circulation (7), only a few experiments have been performed on this circulation and almost none on the effect of chronic CO on isolated pulmonary myocytes.

This chapter summarizes some of the main findings obtained by ourselves and others on the effect of chronic CO on membrane K⁺ channels of pulmonary artery (PA) smooth muscle cells (SMCs).

2. PHARMACOLOGICAL RELEVANCE OF CHRONIC CO EXPOSURE

Global background concentrations of CO are in the range of 50–120 ppb (8). CO is produced by both natural and anthropogenic processes, and recent data suggest that human activities are responsible for about 60% of the CO in the nonurban troposphere (8). The concentration of CO shows a considerable variability depending on where the CO measurement was made. For example, CO concentration was found to be generally <25 ppm inside an automobile under typical driving conditions (9), average concentrations ranged from 2 or 3 ppm to 9 ppm in some US kitchens (10), and levels ranging from 10 to 50 ppm were found for pedestrians and street workers in Toronto (11). The highest peak indoor CO concentration measured was >600 ppm and was associated with emissions from geysers (12). Effects related to the production of hypoxemia for acute exposure to CO have historically been a basis of concern, and in recent years this has grown to include concerns for potential effects from chronic exposure as well. In addition, occupational exposure limits are utilized in numerous countries in which levels differ with the period of exposure. For example, this level ranges from 25 to 50 ppm for a typical 8-h working day and 9 ppm for the recommended multihour ambient air (8,13). The most common source of CO is tobacco smoke. The CO concentration in tobacco smoke is approx 45,000 ppm (4.5%), and a cigarette smoker may be exposed to 400–500 ppm of CO for the time it takes to smoke a cigarette (6 min) with a carboxyhemoglobin (COHb) of 4% (compared with 1% for nonsmokers and 15% for heavy smokers) (13). CO is, of course, not the only compound in cigarette smoke (see ref. 14), and it was demonstrated that 2% CO inhalation (inducing a COHb of 90%) is not a causative factor for cardiopulmonary dysfunction after smoke inhalation (15).

Claude Bernard (16) and John Haldane (17) described the first scientific studies of the hypoxic effects of CO. The hypoxic and pathological effects of CO result from the formation of COHb, a tight but slowly reversible complex with Hb. This decreases the