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Short Communication

Role of Carbon Monoxide in Mitochondrial Respiration

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DESCRIPTION

Mitochondria play two important functions in cellular function: (i) cell metabolism as the primary source of energy for the cell, and (ii) control of cell death *via* mitochondrial membrane permeabilization. Carbon Monoxide (CO) is a naturally occurring gaseous transmitter that has a variety of biological roles, including cell homeostasis and cytoprotection. The mitochondrion is discussed as the primary cellular target of carbon monoxide in this paper (CO).

Cellular oxygen consumption is an indirect approach of monitoring CO's effect on mitochondria and COX activity. Exogenous CO application or endogenous CO application marginally decreased cell respiration under normoxia (21 percent oxygen in gaseous phase), but the physiological significance of this suppression is unknown. Under hypoxia (1 percent oxygen), however, endogenous or exogenous CO significantly reduced cellular respiration [1]. As a result, tissue hypoxia and COX inhibition appeared to be synergistic. COX inhibition is thought to be relevant only when tissue oxygen transport is already reduced by large levels of carboxyhemoglobin and carboxymyoglobin. Furthermore, when the oxygen content is low, the electron transport chain is reduced, which is a better state for CO to bind to since CO may bind to reduced iron.

The respiratory control index was measured in isolated kidney mitochondria after introducing three distinct CO-releasing compounds (CORM-2, CORM-3, and CORM-A1) at 20, 30, and 100 M. The Respiratory Control Index (RCR) was calculated by comparing oxygen consumption in the presence (state 3) and absence (state 4) of ADP. The ratio between states 3 and 4 reflects the tightness of the coupling between respiration and phosphorylation. At this early time point CO decreased respiratory control index [2]. Furthermore, when the oxygen content is low, the electron transport chain is reduced, which is a better state for CO to bind to since CO may bind to reduced iron.

CORM-3 weakens the connection between ATP generation and respiration at low concentrations (up to 20 M). CO-treated heart-isolated mitochondria increased oxygen consumption in the absence of exogenous ADP (state 4). Complex II appears to be the target of CO in this context, as inhibiting complex II (malonate addition) reversed the CO-induced increase in oxygen demand. Second, 100 M of CORM-3 reduced oxygen consumption in the presence of ADP (state 3), which was attributed to complex IV inhibition. Third, CORM-3 lowered mitochondrial membrane potential (m) at concentrations of 20 or 100 M. The addition of inhibitors for Uncoupling Respiration Proteins (UCP) and Adenine Nucleotide Transporter (ANT) stopped this drop, showing that CO could open UCP and/or ANT to provide a mild uncoupling state. CO-induced cytoprotection was found to be associated with mitochondrial mild uncoupling activation, which reduces harmful mitochondrial ROS generation [3].

In a different experiment, astrocytes isolated from the cortex were exposed to CO for one brief period (by adding a CO-saturated solution with a final concentration of 50 M, from which the gas diffuses rapidly) and cell-specific oxygen consumption was measured for 36 hours. In intact astrocytes, acute exposure to CO boosted cellular oxygen consumption, which was explained by improvements in the mitochondrial respiratory chain and oxidative metabolism [4].

According to the two-step time response of cytochrome c oxidase activity to CO, an early or late reaction was detected, leading to a decrease or rise in COX activity. CORM-3 at 0.5 and 1 M enhanced the Respiratory Control Ratio (RCR) and mitochondrial transmembrane potential (m) in heart-isolated mitochondria, while at 5 and 10 M, RCR and m decreased. The tight mitochondrial balance and control of oxidative metabolism, particularly the influence of CO on COX activity, mitochondrial respiration, or cellular oxygen consumption, may be altered by experimental settings (concentration or exposure time).

This paper concludes that COX activity, oxygen consumption, mitochondrial biogenesis, and ROS formation are all controlled by CO, which improves cellular energy state through modulating mitochondrial function and oxidative metabolism. Additionally, CO also prevents cell death.

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