Selective inhibition of carotid body oxigen sensing by genetic MCI disruption. Effect of NAD+ regeneration.

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The carotid body (CB) is essential for systemic acute O_2 sensing. The CB contains O_2 sensitive glomus cells, which have O_2-regulated K^+ channels that mediate transmitter release during hypoxia to elicit compensatory cardiorespiratory reflexes. How variations in O_2 tension (PO_2) are detected and the mechanisms whereby these changes are conveyed to membrane ion channels have remained unknown. We have recently reported the involvement of mitochondrial complex I (MCI) in acute O_2 sensing (Fernández-Agüera et al. Cell Metab 2015). Knockout mice lacking Ndufs2 (a MCI subunit required for ubiquinone binding) in catecholaminergic cells (TH-NDUFS2 mice) lost the hypoxic ventilatory response (HVR). Hypoxia-induced cellular responses (increase in NADH and reactive oxygen species (ROS), inhibition of K^+ channels, and increase in cytosolic Ca^{2+}) were also selectively abolished in Ndufs2-deficient glomus cell. Glomus cells from TH-NDUFS2 mice showed accumulation of NADH and a more oxidized state relative to control cells. To determine whether responsiveness to hypoxia result from a general metabolic disarrangement or a direct consequence of MCI dysfunction, we generated a conditional mouse model (ESR-NDUFS2), in which the *Ndufs2* gene was ablated during adulthood. In these mice the loss of the HVR occurred in parallel to the decrease in MCI activity. Glomus cells from ESR-NDUFS2 mice showed normal electrophysiology. Their basal NADH levels and redox state were close to those of wild type mice. However, Ndufs2-deficient glomus cells were unresponsive to hypoxia, although they were activated by hypercapnia and high potassium. The lack of responsiveness to hypoxia was maintained in Ndufs2-deficient cells treated with α-ketobutyrate, an agent that consumes NADH to regenerate NAD^+. These data support the notion that NADH and ROS produced in MCI mediates acute responsiveness to hypoxia in glomus cells.