O_2-SENSING DURING INTERMITTENT HYPOXIA: ROLE OF REACTIVE OXYGEN SPECIES AND HIF-TRANSCRIPTION FACTOR(s)

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Recurrent apneas resulting from sleep-disordered breathing is a major cause of morbidity that affects millions of people. In this condition, transient apneas (cessation of breathing) lead to periodic decreases in arterial O_2. Patients with chronic intermitting hypoxia (IH) as a consequence of sleep apneas have greatly increased risk for developing systemic hypertension. Studies on recurrent apnea patients and rodent models of chronic IH suggest that reflexes arising from the carotid body, the primary sensory organ for detecting systemic hypoxia, mediate increase in sympathetic activity and blood pressure. This presentation focuses on the mechanisms by which chronic IH affects O_2-sensing and the role of HIF-1 transcription factors. Chronic IH up-regulates O_2-sensing in the carotid body, and induces a novel form of plasticity manifested as sensory ”long-term facilitation” (LTF). The sensory LTF is characterized by long-lasting increase in sensory discharge that persists for hours after terminating the hypoxic stimulus. Chronic IH also induces hypoxic sensitivity in adult adrenal medullae, which otherwise are insensitive to low O_2. The effects of chronic IH involve increased generation of reactive oxygen species (ROS) arising in part due to inhibition of mitochondrial electron transport chain (ETC) at complex I. IH increases HIF-1α protein and HIF-1 dependent reporter gene activation, and require novel signaling pathway involving CaM kinase II. Physiological consequences of HIF-1 activation by chronic IH were assessed in mice partially deficient in HIF-1α, the O_2-regulated sub unit of the HIF-1 complex. In response to IH, *wild type* mice showed: a) augmented hypoxic sensitivity of the carotid bodies, b) sensory LTF, c) increases in blood pressure d) elevated plasma norepinephrine levels, and e) augmented hypoxic ventilatory response. By contrast, cardio-respiratory changes caused by IH were either markedly reduced or absent in HIF-1$\alpha^{+/-}$ mice.

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