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NOVEL ROLE FOR REACTIVE OXYGEN SPECIES AS AMPLIFIERS OF
INTERMITTENT HYPOXIA

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Hypoxia (i.e., decreased O₂ availability) is a pervasive physiological stimulus that profoundly affects biological systems. Systemic responses to acute hypoxia occur within seconds, and are mediated entirely by reflexes originating from peripheral chemoreceptors especially the carotid bodies. Cellular mechanisms associated with acute hypoxia involve inhibition of certain classes of K⁺ channels leading to release of variety of neurotransmitters/modulators in the chemo-reflex pathway. On the other hand, chronic hypoxia persisting for several hours to days leads to phenotypic re-modeling and adaptation of physiological systems, which require activation of transcription factors most notably the hypoxic inducible factor-1 (HIF-1; Semenza, 2000). In work published in this issue of J. of Neurophysiology Griffioen et al (2006) demonstrate fundamental mechanistic differences in the effects of continuous versus intermittent hypoxia (IH), the most frequent form of hypoxic challenge to which humans are exposed.

People experience chronic IH as a consequence of sleep-disordered breathing manifested as recurrent apneas. The duration of hypoxic episodes associated with apneas are brief (each episode lasting no more than seconds) and the severity of hypoxia is rather modest. Yet, chronic IH leads to serious cardio-respiratory morbidity manifested as hypertension, persistent activation of sympathetic nervous system and abnormalities in breathing. The cardio-respiratory morbidity by chronic IH is in part due to induction of functional plasticity in chemo-reflex pathway manifested as long-term facilitation (LTF) of carotid body sensory activity as well as respiratory and sympathetic motor outputs (see Prabhakar et al., 2006 for ref). Chronic IH evoked LTF is not only seen at systemic level, but also reflected in the cellular responses as evidenced by long-lasting increase in transcriptional activation (Yuan et al. 2004). In striking contrast, LTF was not elicited by comparable, cumulative durations of continuous hypoxia either at the systemic or cellular level suggesting that long-lasting activation is a hallmark of functional plasticity selectively evoked by chronic IH. Despite being brief and of modest severity, how chronic IH evokes such long-lasting systemic and cellular responses? Recent studies have shown that chronic IH results in increased generation of reactive oxygen species (ROS) and anti-oxidant treatment prevents systemic (Kumar et al. 2006) and cellular responses (Yuan et al. 2004) to chronic IH. Patients with recurrent apneas also exhibit increased ROS generation and continuous positive airway pressure treatment not only prevents increased ROS generation but also reverses the autonomic morbidity (see Levi, 2003 for ref.). These observations lead to the proposal that ROS, the metabolites of molecular O₂, plays a novel role as amplifiers of brief hypoxic signals and mediate systemic and cellular responses to chronic IH resulting in morbidity associated with recurrent apneas (Prabhakar et al., 2006).

Unlike chronic IH, acute IH occurs in many physiological situations. For instance, it is well known that people experience acute IH during swimming as a consequence of apneas triggered by naso-pharyngeal reflex and exhibit bradycardia during apneic episodes. Does ROS also mediate physiological responses to acute IH? This question was addressed by Griffioen et al (2006) in this issue of J. of Neurophysiology. These authors using a brain slice preparation report that intermittent but not continuous hypoxia
facilitates excitatory glutamatergic neurotransmission at the vagal motoneurons. The effects of acute IH were associated with progressive increase in ROS, and ROS scavengers prevent neuronal responses to acute IH. Thus, this study gives us a new connection between ROS signaling and physiological responses to acute IH and also highlights the fundamental differences between continuous and intermittent hypoxia. However, this study also raises several important questions. For instance, how does acute IH generate ROS, and what are its cellular target(s)? Do antioxidants prevent bradycardic response to acute IH? Not withstanding these questions, the findings of this study are important in that they suggest that ROS are equally important in mediating physiological responses to acute IH similar to their role in evoking morbidity associated with chronic IH.

References


