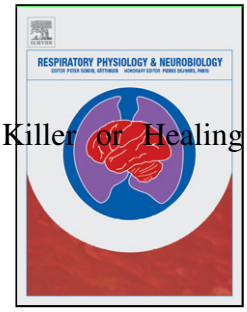

Title: Special Issue Title: “Intermittent Hypoxia: Pathologic Killer or Healing Tonic?¨113pt plus1fill

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Special Issue Title: "Intermittent Hypoxia: Pathologic Killer or Healing Tonic?"

-Tracy L. Baker, Stephen M. Johnson and Jyoti J. Watters

Disrupted breathing that exposes humans to repeated bouts of intermittent hypoxia induces widespread systemic disease with a high level of morbidity and mortality. However, administration of relatively mild intermittent hypoxia for shorter periods of time can produce beneficial and protective effects on physiological function. The key question as to whether intermittent hypoxia is beneficial or pathological depends largely on the degree of hypoxia and the duration of the exposure (Dale et al., 2014; Navarrete-Opazo and Mitchell, 2014). Thus, intermittent hypoxia triggers an array of changes in multiple physiological systems, but little is known regarding the factors that cause intermittent hypoxia to be beneficial and protective (*"friend"*) or pathological and deleterious (*"foe"*). The purpose of this Special Issue is to consider the dichotomous effects of intermittent hypoxia on neural and physiological functions. Review and primary data reports are featured that explore the complexity of intermittent hypoxia in the context of the behaving animal, while highlighting areas that require further research.

This Special Issue begins with a focus on a potentially beneficial effect of intermittent hypoxia; specifically, acute intermittent hypoxia is a profound inducer of plasticity in respiratory neurons. For example, acute intermittent hypoxia elicits a long-lasting enhancement of inspiratory motor output, a form of plasticity in respiratory control called long-term facilitation (LTF). Harnessing this property of intermittent hypoxia for use as a therapeutic tool continues to be explored with respect to improving breathing in a variety of devastating diseases that severely compromise respiratory motor function, such as spinal cord injury and amyotrophic lateral sclerosis. As such, it is important to understand mechanisms that give rise to LTF. Turner, Mitchell and Fuller and colleagues provide a comprehensive review of LTF with respect to current mechanistic models, and discuss potential pharmacological strategies to augment the magnitude and duration of LTF. New data are presented showing that augmenting glutamatergic synaptic transmission with exogenous ampakines allows mild hypoxic experiences, which normally are not sufficient for plasticity, to elicit LTF (Turner et al., 2017). These exciting data suggest that "priming" the respiratory control system with pharmacological approaches may boost the functional benefit of hypoxia-based therapies, while reducing the necessary hypoxia dose required to achieve functional benefits. An alternative strategy to augment phrenic inspiratory motor output while avoiding hypoxia altogether, is pharmacological activation of plasticity in the phrenic motor system. Devinney and Mitchell show that exogenous application of an activator of conventional/novel protein kinase C (PKC) isoforms to spinal regions encompassing the phrenic motor nucleus elicits a long-lasting enhancement of phrenic inspiratory activity. Interestingly, the authors show that the effect was mediated by a PKC isoform not previously implicated in phrenic motor plasticity, suggesting that we have much yet to learn about the many mechanisms that can induce long-lasting adaptations in respiratory motor control (Devinney and Mitchell, 2017).

Equally important in translating intermittent hypoxia-induced plasticity to a potential therapy is understanding mechanisms that constrain it. Wilkerson, Devinney and Mitchell discuss the sensitivity of LTF to the pattern of hypoxia in respiratory motor neurons controlling the upper airway, and discuss potential mechanisms whereby sustained exposures to hypoxia may interfere with plasticity expression. The authors compare and contrast features of neuroplasticity within different respiratory motor neuron pools, and discuss the potential clinical significance of LTF with respect to obstructive sleep apnea (Wilkerson et al., 2017). Huxtable, Mitchell and colleagues continue the discussion of plasticity constraints by considering the impact of neuroinflammation, which impairs LTF expression. New data are presented showing that constraints imposed on LTF by neuroinflammation are independent of COX enzyme activity, the rate limiting enzyme in the production of prostaglandins in the CNS (Huxtable et al., 2017). Neuroinflammation also impairs a distinct form of plasticity triggered by chronic sustained hypoxia: ventilatory acclimatization. De La Zerda and Powell and colleagues close our mechanistic view of hypoxia-induced plasticity by presenting new data suggesting that inflammation constrains the induction of ventilatory acclimatization to chronic hypoxia, but does not affect its maintenance once established. The authors discuss a potential role for microglia in inflammatory constraints to plasticity (De La Zerda et al., 2017).

We end our consideration of the beneficial effects of hypoxia with manuscripts addressing the potential of IH as a therapeutic strategy to improve outcomes in a range of disorders. Leading this theme is a comprehensive review by Mateika and colleagues on the impact of concomitant hypercapnia on hypoxia-induced plasticity, with