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Physiological and Genomic Consequences of Intermittent Hypoxia

Invited Review: Respiratory plasticity following intermittent hypoxia: developmental interactions

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Gozal, Evelyne, and David Gozal. Invited Review: Respiratory plasticity following intermittent hypoxia: developmental interactions. *J Appl Physiol* 90: 1995–1999, 2001.—Intermittent hypoxia (IH) is the most frequent form of hypoxia occurring in the developing mammal. On one hand, the maturational process of neural, mechanical, pulmonary, and sleep state-dependent factors will favor the occurrence of IH during early postnatal life. On the other hand, it has also become clear that hypoxia, even when short lasting, can modify subsequent respiratory responses to hypoxia and induce a variety of genes whose consequences will persist for much longer periods than the duration of the hypoxic stimulus itself, i.e., functional and adaptive plasticities. The dynamic interactions between the overall duration and recurring frequency of IH, the severity of IH, and the level of neural maturity at the time of IH will modify the ventilatory, metabolic, and cardiovascular responses to hypoxia. We propose that the earlier IH will occur in the developmental course the more likely that the physiological responses to an ulterior hypoxic challenge will be altered even into adulthood. At this point in time, a critical examination of the field would suggest that the short-term alterations of the hypoxic ventilatory response (HVR) of the developing mammal to IH are qualitatively similar to those of the adult and display a biphasic pattern, namely, initial enhancement of the HVR followed by a reduction in HVR. However, the short- and long-term effects of IH on the modulation of neurotransmitter release, receptor binding and expression, intracellular signaling cascades, transcriptional regulation, and gene expression as a function of animal maturity are almost completely unknown. Further delineation of such complex responses to IH may permit the formulation of interventional strategies aiming at reducing the overall vulnerability of the young infant and child to apnea and sudden death.

maturation; neural plasticity; control of breathing; glutamate receptors; intracellular signaling; episodic hypoxia; repeated hypoxemia

RECENT TECHNOLOGICAL DEVELOPMENTS provide the opportunity for concomitant measurement of physiological responses and assessment of gene and protein regulatory changes underlying such phenotypic expression. These techniques have opened a new and exciting window of opportunity for identification and characterization of mechanisms underlying the postnatal development of brain function and, more specifically, the effect of perturbations during prenatal and early postnatal life on the maturation of the hypoxic ventilatory response (HVR) and on the adaptive strategies employed to promote neuronal survival and plasticity.

The HVR is a complex interplay of excitatory and inhibitory components in the temporal domain (32). The complexity of the HVR is further accentuated by

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the inherent plasticity of the neural substrates that underlie the neuronal discharge pattern characteristics of respiratory regions mediating HVR. Thus conditions such as obstructive sleep apnea, chronic lung disease, or apnea of prematurity, characteristically associated with intermittent hypoxic episodes, may not only impose immediate effects on HVR but may also modify both short-term and long-term characteristics of subsequent responses to similar hypoxic challenges. Such intermittent hypoxic events may also affect other neural regions and change their normal development to induce long-lasting functional and structural changes.

The clinical implications of an adequate HVR are immediately apparent. Apnea and hypoxia are very common problems in infants and children as well as in adults and often result in prolonged hospitalization. Delayed or abnormal development of defense mechanisms within critical brain structures underlying HVR could therefore lead to significant morbidity and mortality, underscoring the importance of understanding maturation of brain stem mechanisms from an organismal to molecular perspective (8).

In this paper, we will examine two major issues on the effect of intermittent hypoxic exposure, namely, how intermittent hypoxia (IH) acutely modifies HVR characteristics in the adult and developing mammal and the effect of IH during early postnatal development on the long-term responses of respiratory and nonrespiratory regions during adulthood. The definition of IH will be very liberal and will encompass any hypoxic challenge recurring within ≤24 h.

EFFECT OF IH ON HVR

Adult mammals. In adult anesthetized, vagotomized, mechanically ventilated isocapnic rats, exposure to an IH challenge consisting of 3 min of hypoxia [inspired O_2 fraction (F_{IO_2}) = 0.11] separated by 5-min hyperoxic intervals results in long-lasting increases of phenic nerve output, i.e., long-term facilitation (LTF) (1). LTF of phrenic nerve output cannot be induced by a similar exposure to continuous hypoxia, suggesting that it is the intermittent presentation of the stimulus that underlies the generation of phrenic LTF (1). Furthermore, Mitchell and colleagues (6) have accumulated a substantial body of evidence supporting a major role for serotoninergic pathways as a major mediator of this form of phrenic LTF. According to their proposed model, serotonin will activate postsynaptic 5-HT_{2A} receptors expressed in phrenic motoneurons, which in turn will increase intracellular protein kinase C (PKC) activity. PKC will either directly, or indirectly via mitogen activated protein kinase and possibly other tyrosine kinases, phosphorylate and potentiate inward currents mediated by the *N*-methyl-D-asparate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate glutamatergic receptors. As a result of the potentiated glutamate receptor currents, descending respiratory drive will be enhanced, leading to enhancements in phrenic nerve output in response to a similar presynaptic glutamate release (i.e., LTF) (6).

In a more intact animal preparation, that is, from available published data on IH in the dog (2), it is essentially confirmed that repetitive bouts of hypoxia will lead to increased normoxic ventilation. A putative equivalent of respiratory LTF was also observed in adult humans when they were exposed to IH. For example, when the ventilatory response to hypoxia or to exercise was assessed in normal subjects after 15 days of IH (2 h/day), subjects increased their HVR as well as their ventilatory response and arterial O_2 saturation to exercise (33, 34). Similarly, daily exposure to a F_{IO_2} of 0.13 for 2 h resulted in an increase of the HVR, which peaked at 5 days. However, this "LTF-like" ventilatory effect on the hypoxic drive progressively faded over time, such that, by 12 days of daily exposures to this IH protocol, the HVR had been reduced to values that were lower than the baseline HVR measured before initiation of the IH exposure (7). The temporal changes in HVR during repeated IH, as found in the latter study, are particularly intriguing because they suggest that the changes in HVR induced by IH may follow a biphasic pattern. In other words, short courses of IH (either a small number of frequent iterations or alternatively less frequent iterations over a short period of time) will enhance ventilatory drive and HVR. In contrast, recurrence of IH exposures over a longer period of time or an overall larger cumulative number of IH cycles will reverse such an effect and in fact will lead to decreased respiratory output and reduced HVR.

At the present stage, the paucity of available data precludes the formulation of a coherent model that will help predict how the frequency of IH cycles, their severity, and their duration will modify the response characteristics of the respiratory controllers during subsequent normoxia and acute hypoxia. We can only infer at this point that the overall respiratory response to IH appears to be strikingly similar to the more extensively characterized response to sustained noncycling hypoxia, at least from the conceptual standpoint (for review, see Ref. 32). Indeed, duration, magnitude, and stimulus presentation characteristics are all a priori major determinants of the overall effects of IH on respiratory drive and HVR characteristics (see Fig. 1).

Developing mammals. It has now been well established that the acute HVR in the vast majority of developing mammals exhibits substantial qualitative and quantitative differences compared with the adult (26). However, the ventilatory consequences of IH have only been summarily explored. Exposure of 2- to 3-day-old rat pups to a series of eight cycles of IH consisting of 5 min of hypoxia (F_{IO_2} = 0.10) and 10 min of normoxia revealed that the late phase of HVR but not the peak HVR was modified by such intermittent hypoxic exposure compared with unexposed littermates (10). Indeed, late ventilatory reductions were markedly attenuated when HVR was measured 6 h after IH, thereby indicating the presence of excitatory respiratory plasticity in the developing rat. Furthermore,

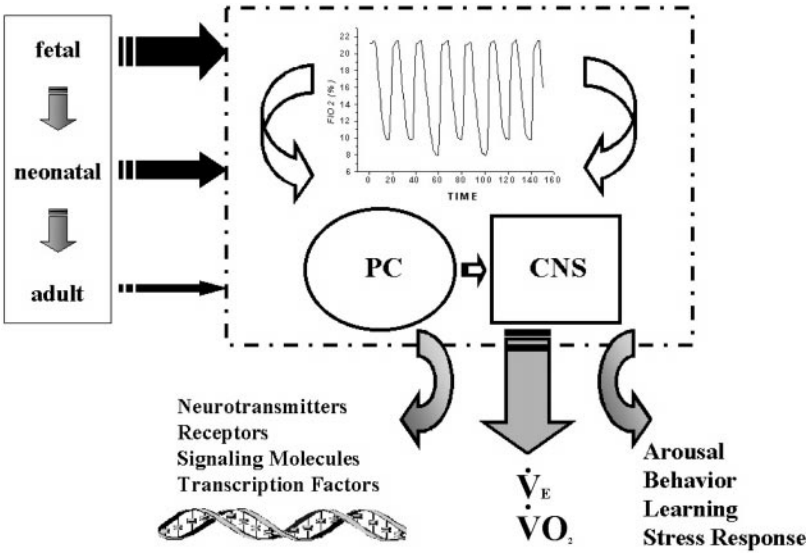

Fig. 1. Schematic diagram showing the potential interactions between intermittent hypoxia and its characteristics and the hypoxic ventilatory response pathways in mammals. Intermittent hypoxia can affect both peripheral chemoreceptor (PC) responses as well as those of centrally located neurons (CNS), the latter consisting of both respiratory and nonrespiratory neurons. Such interactions will be modulated to a greater or lesser extent by the developmental stage of the particular mammal of interest. Such global relationships will result in phenotypic changes of ventilation ($\dot{V}_E$), metabolism ($\dot{V}O_2$), as well as arousal, behavior, learning, and stress responses to include those of the autonomic nervous system. In addition, such modifications in phenotype will depend on alterations in expression and function of neurotransmitters and their receptors, intracellular signaling molecules, transcription factors, and genes.

overall IH-induced potentiation of the late phase of HVR was correlated to an increased expression of the neuronal isoform of nitric oxide synthase (nNOS) within the caudal brain stem, such that pharmacological inhibition of nNOS after the IH protocol resulted in a late HVR that was similar to the late HVR measured during control conditions (10). Thus IH elicits an excitatory form of neural plasticity that is mediated by altered expression of nNOS. These findings are in close agreement with a previous study by Trippenbach (36), who reported that repeated and successive hypoxic runs elicited enhancements of the HVR in rabbit pups during a subsequent hypoxic challenge. From these restricted data sets, it would appear that, despite substantial differences in the acute HVR between adult and immature mammals, IH will induce modifications of HVR that are qualitatively similar between immature and adult animals.

In contrast with such findings, however, Waters and colleagues (37) showed that in piglets repeated daily exposure to hypoxia (30 min/day) for 6 days induced attenuated respiratory responses to a subsequent acute hypoxic stimulus. Furthermore, such repeated hypoxic exposures also increased the interstitial concentrations of substance P within the nucleus of the solitary tract (nTS) (37). These are intriguing results because other investigators have suggested that the density of neurokinin type 1 (NK_1) receptors is markedly decreased in the nTS (by ~40%) after repetitive hypoxia without changes in the binding affinity for substance P (23, 24). Together, these studies suggest that afferent inputs from peripheral chemoreceptors may dynamically regulate the expression of those NK_1 receptors within brain stem nuclei that are involved in HVR. Thus the temporary reduction in NK_1 receptors within the nTS may account for the inability to sustain HVR during repetitive hypoxia, despite increased release of substance P during repetitive hypoxia within this neural region (37). The effect of IH on other neurotransmitter systems involved in HVR and their downstream signaling pathways has not yet been fully investigated.

Over the years, our laboratory has been interested in the ontogeny of signaling pathways mediating the acute HVR. A simplified and clearly noncomprehensive model was proposed whereby activation of the NMDA glutamate receptor, a critical receptor in the acute HVR (19, 25, 29, 30), will lead to downstream activation of an excitatory cascade of kinase systems, which include both serine-threonine (e.g., PKC) and tyrosine kinases (e.g., c-Jun NH_2-terminal kinase) (for review, see Ref. 11). Such pathways are then modulated at least in part by the activation of multiple receptors over time, including adenosine receptors (3), GABA receptors (16), and platelet-derived growth factor receptors (14), all of which occur subsequent to the NMDA receptor channel opening and account at least in part for the decreased ventilatory output that is so characteristic of the late phase of the acute HVR (11). In addition, activation of NMDA receptors leads to downstream activation of nNOS, and the latter plays a significant role in sustaining ventilatory output during sustained hypoxia (12). On the basis of the developmental biology of aforementioned receptors and their pattern of expression within neural regions underlying HVR, the proposed model could explain some of the singular differences between the acute HVR measured in developing and adult rats. Moreover, this model would predict the ventilatory behaviors reported by Waters and colleagues (37) in the piglet following IH. To further explore the implications of more sustained intermittent hypoxic exposures in the developing rat, 30-min hypoxic runs ($F_{IO_2} = 0.10$) were alternated with 30-min exposure to room air over time. We have found that this IH paradigm will induce an early potentiation of HVR after the initial 10–20 hypoxic-normoxic cycles in 10-day-old rat pups. Such HVR increases coincide with increased expression of the NMDA glutamate receptor (NR1 immunoreactivity) and of the PKC isoforms β and δ in the dorsocaudal brain stem, all of

which have emerged as critical mediators of HVR (13, 15, 35, and Gozal and Gozal, unpublished observations). However, if such cycles are continued for 3 days, marked attenuation of the HVR will develop and will parallel decreases in NMDA receptor and PKC-β and PKC-δ expression as assessed by immunoblotting (Gozal and Gozal, unpublished observations). Thus, similar to the adult mammal, it is likely that the duration of IH will condition the changes in HVR associated with IH. In other words, short durations of intermittent hypoxic exposures will elicit increases in the magnitude of HVR, and such HVR enhancements will be subsequently followed by an attenuation of HVR over time if IH exposures are continued. However, the neural structures, neurotransmitters, and downstream signaling pathways underlying such biphasic changes in HVR as induced by IH are unknown and clearly need to be defined.

POTENTIAL IMPLICATIONS OF IH

Similar to the immediate consequences of IH on HVR, little attention has been paid to other short-term and long-term consequences of IH. In the lamb, repeated hypoxia became ineffective in stimulating protective arousal, as well as parallel ventilatory and blood pressure responses, when applied during active sleep but continued to elicit such responses during quiet sleep (5, 18). The failure to arouse in response to hypoxia developed very rapidly during active sleep and occurred after exposure to as few as 10 cycles of IH (17). Thus sleep state, particularly active sleep, emerges as an additional modifier of the putatively biphasic consequences of IH. The arousal response and the increased autonomic activation that occur during the initial cycles of IH will be followed by decrements in the effects of the intermittent hypoxic challenge on activation of arousal and autonomic pathways. Whether the biphasic pattern of physiological responses to IH exhibits species or age dependencies remains to be determined.

The long-term effects of IH on respiratory control have not been examined thus far. However, it has become apparent in recent years that exposures to either hypoxia or hyperoxia during early postnatal life may lead to significant modifications of neural function during adulthood. For example, suppression of peripheral arterial chemoreceptor activity induced by exposures to hyperoxia ($F_{IO_2} = 0.60$) during the first month of life leads to significant reduction in the number of unmyelinated axons in the carotid sinus nerve and petrosal ganglion in the adult rat (4) that are accompanied by substantial attenuation of the HVR at 3–5 mo of age but not at 15 mo (20, 22). In contrast, when adult rats are exposed to hyperoxia, no changes in HVR characteristics occur, indicating that the persistent plasticity changes in the pathways underlying HVR are unique to the interaction between an environmental stimulus and a critical developmental window (Ref. 21; see also Fig. 1). More recently, Peyronnet and collaborators (31) showed that prenatal hypoxia ($F_{IO_2} = 0.10$) between *days 5* and *20* of pregnancy in the rat induced marked changes in ventilatory and metabolic adaptations to acute postnatal hypoxia and that such effects were only reversed after 3 wk of age (31). Thus F_{IO_2} changes in either direction during development may result in long-lasting modifications of HVR. Again, the mechanisms mediating such respiratory plasticity changes are currently unknown.

Similarly, Nyakas and colleagues (27, 28) have shown that abnormal open-field, social, learning, and emotional behaviors as well as altered plasma corticosterone responses to stress occur throughout adulthood, including old age, in rats exposed to prenatal hypoxia. In these animals, prenatal hypoxia was associated with altered maturation of cholinergic and serotoninergic circuits within areas of the neocortex and hippocampus (27). However, other neurotransmitter pathways such as catecholaminergic or glutamatergic pathways were not explored. Thus hypoxia may not only affect components of autonomic responses, i.e., cardiorespiratory function, but may also extensively modify the development and function of other neural sites, even during adulthood. Indeed, we have recently found that recurrent IH imposes substantial cellular changes over time within cortical and hippocampal regions, resulting in impaired performance during acquisition of a cognitive spatial task (9).

Thus long-lasting alterations (i.e., plasticity) of neural networks underlying respiratory control are particularly likely to occur during early and therefore more plastic stages of development. A patchy yet exciting picture emerges from the IH experimental paradigms described above: application of IH during critical stages of development may not only permit insights into how the development of HVR pathways occurs but may also allow us to understand which genes regulate such adaptive processes and ultimately how such gene-function interactions can be used to our advantage such as to modify the phenotypic responses in at-risk individuals or populations.

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