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Review

Chronic hyperoxia and the development of the carotid body☆

Ryan W. Bavis*, Sarah C. Fallon, Elizabeth F. Dmitrieff

Department of Biology, Bates College, Lewiston, ME 04240, USA

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ABSTRACT

Preterm infants often experience hyperoxia while receiving supplemental oxygen. Prolonged exposure to hyperoxia during development is associated with pathologies such as bronchopulmonary dysplasia and retinopathy of prematurity. Over the last 25 years, however, experiments with animal models have revealed that moderate exposures to hyperoxia (e.g., 30–60% O_2 for days to weeks) can also have profound effects on the developing respiratory control system that may lead to hypoventilation and diminished responses to acute hypoxia. This plasticity, which is generally inducible only during critical periods of development, has a complex time course that includes both transient and permanent respiratory deficits. Although the molecular mechanisms of hyperoxia-induced plasticity are only beginning to be elucidated, it is clear that many of the respiratory effects are linked to abnormal morphological and functional development of the carotid body, the principal site of arterial O_2 chemoreception for respiratory control. Specifically, developmental hyperoxia reduces carotid body size, decreases the number of chemoafferent neurons, and (at least transiently) diminishes the O_2 sensitivity of individual carotid body glomus cells. Recent evidence suggests that hyperoxia may also directly or indirectly impact development of the central neural control of breathing. Collectively, these findings emphasize the vulnerability of the developing respiratory control system to environmental perturbations.

1. Introduction

The respiratory control system is under strong genetic regulation which guides its development and determines much of the adult respiratory phenotype (Han and Strohl, 2000; Strohl, 2003; Tankersley, 2003; Borday et al., 2004, 2005). Even so, the respiratory control system also retains substantial capacity for phenotypic plasticity (Carroll, 2003; Mitchell and Johnson, 2003; Bavis and Mitchell, 2008). Phenotypic plasticity describes the ability of a single genotype to produce a range of phenotypes in response to environmental variation. This capacity may be greatest during development, with specific windows of environmental sensitivity (i.e., critical periods) in which plasticity is inducible. Plasticity is often adaptive because it enables individuals to cope with changing demands throughout their lifetime; however, this environmental sensitivity may also yield maladaptive responses to disease, injury, or novel stimuli.

Environmental hyperoxia (inspired $P_{O_2} > 160$ mmHg) occurs rarely in nature except, for example, in certain isolated systems like tidal pools. On the other hand, supplemental O_2 is a common therapeutic intervention in clinical settings which, in turn, leads to both acute and chronic hyperoxia in human and animal patients (e.g., Hagadorn et al., 2006; Claure and Bancalari, 2009; Finer and Leone, 2009). Moreover, it has been suggested that the earlier-than-normal rise in inspired O_2 associated with preterm birth induces a state of "relative hyperoxia" with respect to normal gestational P_{O_2} (Carroll, 2003). It is consequently important to understand the impact of hyperoxia (and relative hyperoxia) on critical homeostatic processes, such as regulation of blood gases.

The epithelium of the lungs and upper airways experience the highest P_{O_2} during clinical O_2 exposures and, consequently, may suffer direct oxidative injury through the overproduction of reactive oxygen species (ROS). The impact of hyperoxia may extend beyond these tissues due to elevated arterial P_{O_2}, however, and can include substantial morphological and functional plasticity in neural pathways critical to respiratory control. In this article, we review evidence that perinatal hyperoxia alters the development of the carotid body, the primary O_2 chemoreceptor for the respiratory control system. Although the mechanism of hypoxia transduction within the carotid body is not completely understood, it appears to be initiated in the glomus (type I) cells, neuron-like secretory cells that synapse with neurons projecting to the brainstem via the carotid sinus nerve (CSN). Decreasing arterial P_{O_2}

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* Corresponding author at: Department of Biology, Bates College, 44 Campus Ave., Carnegie Science Hall, Lewiston, ME 04240, USA. Tel.: +1 207 786 8269; fax: +1 207 786 8334.
E-mail address: rbavis@bates.edu (R.W. Bavis).

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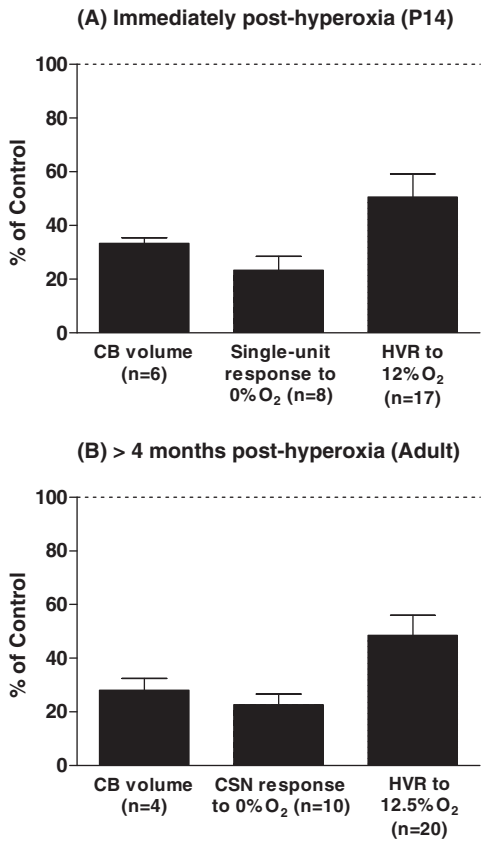

Fig. 1. Representative effects of developmental hyperoxia on carotid body (CB) volume, CB hypoxic response (single-unit or whole-nerve CSN response), and hypoxic ventilatory response (HVR). Rats were exposed to 60% O_2 for the first two postnatal weeks and studied (A) immediately (P13–P14) or (B) >4 weeks (Adult) after return to room air. Note that the HVR for P13–P14 rats represents the early phase of the response (i.e., first minute of hypoxia). Values (mean ± SEM) are expressed as a percentage of those measured for age-matched rats reared in room air (i.e., "Control" rats). All values are significantly reduced relative to Control (i.e., <100%; one-sample *t*-test, all $P < 0.001$). Data were compiled from previously published studies (Donnelly et al., 2005; Bavis et al., 2007, 2008, 2010; Dmitrieff et al., 2012).

depolarizes the glomus cells, increases intracellular calcium, and triggers the release of neurochemicals, ultimately enhancing afferent nerve activity and initiating the hypoxic ventilatory response (HVR) (Kumar, 2007; López-Barneo et al., 2008).

2. Ventilatory control after developmental hyperoxia

The first indication that chronic hyperoxia alters carotid body development came from studies of the HVR in cats and rats reared in moderate hyperoxia. Hanson et al. (1989) observed that the acute HVR was severely diminished in kittens reared in 30% O_2 from birth. Later, Ling et al. (1996) demonstrated that the HVR remains blunted in rats reared in 60% O_2 for the first postnatal month even after being returned to normoxia (21% O_2) for several months; similar effects have been observed after only 1 or 2 weeks in 60% O_2 (e.g., Fig. 1) (Bavis et al., 2003, 2007, 2008). Interestingly, rats exposed to a similar duration of 60% O_2 as adults exhibit normal HVR (Ling et al., 1996, 1997a,c). Together, these data indicate that developmental hyperoxia induces a long-lasting reduction in the HVR and that this plasticity can only be elicited during development. Subsequent studies revealed that the critical period for long-lasting changes in the HVR is limited to the first two postnatal weeks in rats (Bavis et al., 2002). It is now known that developmental hyperoxia has similar effects on the HVR in several vertebrates species, including mice (Bavis et al., 2011a), quail (Bavis and Simons, 2008), chickens (Mortola, 2011), and zebrafish (Vulesevik and Perry, 2006); while fish do not have a carotid body *per se*, they have O_2-sensitive chemoreceptors in their gills that are considered homologous to those in the mammalian and avian carotid body (Milsom and Burleson, 2007). No controlled experiments have been conducted in human infants, but there is correlative evidence suggesting that ventilatory control is affected by supplemental O_2 in humans as well (Calder et al., 1994; Katz-Salamon and Lagercrantz, 1994; Katz-Salamon et al., 1996).

Although the eventual attenuation of the HVR is well documented in rats and other species exposed to developmental hyperoxia, recent studies indicate that changes to ventilatory control *during* the hyperoxic exposure are more complex than initially appreciated. The HVR is distinctly biphasic in newborn mammals, with an initial, carotid body-mediated increase in ventilation (early phase of the HVR) being followed by a secondary decline in ventilation linked to central neural inhibition (late phase of the HVR) (Eden and Hanson, 1987; Bissonnette, 2000; Teppema and Dahan, 2010). As individuals mature (over the first 7–14 postnatal days in rats), the overall magnitude of the HVR tends to increase and the biphasic response is gradually replaced with a sustained increase in ventilation. Bavis et al. (2010) assessed the ventilation of rats reared in 60% O_2 from birth until studied at one of three postnatal ages: 4, 6–7, or 13–14 days of age (P4, P6–P7, or P13–P14, respectively). When acutely exposed to hypoxia (12.5% O_2), the magnitude of the early phase of the HVR was similar to that of age-matched controls at P4, but became progressively diminished at P6–P7 and P13–P14 (Fig. 1A). Surprisingly, hyperoxia-treated rats exhibited a sustained increase in ventilation at P4 and P6–P7 in contrast to the expected biphasic HVR observed in controls (for potential mechanisms, see Section 5 below). Thus, when expressed as a percentage increase from baseline, the HVR was actually enhanced during the later stages of hypoxia in hyperoxia-treated rats at these ages. The magnitude of the late HVR increased with postnatal maturation in control rats, however, and an overall reduction in the HVR of hyperoxia-treated rats emerged by P13–P14 (Bavis et al., 2010).

In addition to changes in the HVR, Bavis et al. (2010) also noted changes to normoxic ventilation in neonatal rats exposed to developmental hyperoxia. Relative to age-matched control rats reared in normoxia, hyperoxia-treated rats exhibited substantially lower minute ventilation at P4 and P6–P7 when acutely returned to 21% O_2, but normoxic ventilation returned to normal in P14 rats despite their longer hyperoxic exposure. The reduced ventilation in hyperoxia-treated rats at P4 likely represents a true hypoventilation based on lower arterial O_2 saturations in these pups (van Heerden and Bavis, 2011). Inasmuch as the carotid body contributes to normoxic ventilatory drive, lower resting ventilation is consistent with abnormal carotid body function in hyperoxia-treated neonates. This is supported by recent experiments showing that minute ventilation decreases less in hyperoxia-treated rats during acute O_2 inhalation (Dejour's test) than in age-matched controls at P4 and P6–P7, but not at P13–P14 (van Heerden et al., 2011). Moreover, normalization of normoxic ventilation by P13–P14 could reflect a reduced contribution of carotid bodies to eupneic breathing with advancing age. Indeed, the ventilatory response to O_2 inhalation was lower in control rats at P13–P14 than at P4 (van Heerden et al., 2011).

3. Carotid body function after developmental hyperoxia

The carotid body responds to a decrease in arterial P_{O_2} by increasing action potential activity on the CSN which, in turn, stimulates breathing. Given the carotid body's primary role in initiating the HVR, it is a likely culprit in cases where the HVR is deemed abnormal. Indeed, direct measurements of CSN activity in cats and