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Chronic intermittent hyperoxia alters the development of the hypoxic ventilatory response in neonatal rats

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ABSTRACT

Chronic exposure to sustained hyperoxia alters the development of the respiratory control system, but the respiratory effects of chronic intermittent hyperoxia have rarely been investigated. We exposed newborn rats to short, repeated bouts of 30% O_2 or 60% O_2 (5 bouts h^{-1}) for 4–15 days and then assessed their hypoxic ventilatory response (HVR; 10 min at 12% O_2) by plethysmography. The HVR tended to be enhanced by intermittent hyperoxia at P4 (early phase of the HVR), but it was significantly reduced at P14-15 (primarily late phase of the HVR) compared to age-matched controls; the HVR recovered when individuals were returned to room air and re-studied as adults. To investigate the role of carotid body function in this plasticity, single-unit carotid chemoafferent activity was recorded in vitro. Intermittent hyperoxia tended to decrease spontaneous action potential frequency under normoxic conditions but, contrary to expectations, hypoxic responses were only reduced at P4 (not at P14) and only in rats exposed to higher O_2 levels (i.e., intermittent 60% O_2). Rats exposed to intermittent hyperoxia had smaller carotid bodies, and this morphological change may contribute to the blunted HVR. In contrast to rats exposed to intermittent hyperoxia beginning at birth, two weeks of intermittent 60% O_2 had no effect on the HVR or carotid body size of rats exposed beginning at P28; therefore, intermittent hyperoxia-induced respiratory plasticity appears to be unique to development. Although both intermittent and sustained hyperoxia alter carotid body development and the HVR of rats, the specific effects and time course of this plasticity differs.

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1. Introduction

Mammals typically respond to hypoxia by increasing pulmonary ventilation. In neonatal mammals, this hypoxic ventilatory response (HVR) is biphasic (Eden and Hanson, 1987; Bissonnette, 2000; Teppema and Dahan, 2010). Initially there is a rapid increase in ventilation (early or augmentation phase) that is mediated by excitation of the carotid body, the primary arterial O_2 chemoreceptor for the control of breathing. Although carotid body excitation continues, a secondary ventilatory decline occurs (late or depressive phase) that is generally attributed to the inhibition of neurons within the central nervous system (CNS) (Bissonnette, 2000; Teppema and Dahan, 2010). As mammals mature, this biphasic ventilatory pattern shifts toward a sustained increase in ventilation during hypoxia.

In addition to this ontogenetic change, the HVR can be modified by environmental conditions experienced during an individual's lifetime (Mitchell and Johnson, 2003; Bavis and Mitchell, 2008). Rats exposed to sustained hyperoxia (30–60% O_2) for the first 1–4 postnatal weeks of life exhibit an attenuated HVR as adults (Ling et al., 1996; Fuller et al., 2002; Bavis et al., 2013). This is an example of "developmental plasticity" (i.e., a form of phenotypic plasticity unique to developing organisms) since the HVR is not altered when individuals are exposed to equivalent hyperoxic exposures as adults (Ling et al., 1996; Bavis et al., 2002). Subsequent experiments revealed that the critical window for this plasticity (i.e., the time period during which the plasticity can be elicited) is limited to the first two postnatal weeks in rats (Bavis et al., 2002; Bisgard et al., 2003).

Attenuation of the HVR by chronic sustained hyperoxia is largely due to abnormal development of the carotid body. Postnatal exposure to hyperoxia markedly reduces carotid body size by decreasing cell proliferation and increasing cell death (Dmitrieff et al., 2012);

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these effects are evident after as few as 4 days in 60% O_2 (Dmitrieff et al., 2012) and appear to be permanent (Fuller et al., 2002). In addition to fewer O_2-sensitive glomus cells being present in the carotid body, individual glomus cells are less responsive to hypoxic stimuli when measured immediately after the hyperoxic exposure (Donnelly, 2005; Donnelly et al., 2009; Kim et al., 2013). This may further diminish carotid body function during the neonatal period, but glomus cell O_2 sensitivity recovers within a few days after return to room air (Bavis et al., 2011). Sustained hyperoxia also causes degeneration of primary carotid chemoafferent neurons as evidenced by fewer unmyelinated axons in the carotid sinus nerve (CSN) and fewer dopaminergic neurons in the petrosal ganglion (PG) (Erickson et al., 1998; Chavez-Valdez et al., 2012). Collectively, these changes to the carotid body and CSN result in life-long impairment of the CSN response to hypoxia (Fuller et al., 2002; Bisgard et al., 2003).

Rats reared in sustained hyperoxia also exhibit fewer dopaminergic cells in the nucleus tractis solitarii (nTS) (Chavez-Valdez et al., 2012), suggesting that hyperoxia elicits plasticity in the central limb of the carotid chemoafferent pathway. Indeed, recent studies indicate that developmental hyperoxia alters several aspects of the central neural regulation of breathing. For example, rats reared in sustained hyperoxia exhibit a sustained increase in ventilation at 4–7 days of age rather than the biphasic HVR expected in this age range (Bavis et al., 2010, 2014a). This may be due to reduced central nervous system (CNS) inhibition during hypoxia (Hill et al., 2013) and/or a shift in the balance between inhibitory and excitatory neuromodulation within the brainstem (Bavis et al., 2014a). Neonatal rats reared in 60% O_2 also hypoventilate when acutely returned to normoxia (Bavis et al., 2010, 2014b). While this hypoventilation may be explained partially by abnormal carotid body function (Bavis et al., 2014b), developmental hyperoxia also slows the frequency of respiratory bursts produced in isolated brainstems (Bierman et al., 2014; Bavis et al., 2014b). Taken together, these findings suggest that sustained hyperoxia impacts development of both peripheral and central components of the respiratory control system.

Studies on the effects of sustained hyperoxia have provided important insights into developmental plasticity of respiratory control, but few studies have considered the effects of chronic intermittent hyperoxia on breathing. In fact, preterm and low birth weight human infants routinely experience intermittent hyperoxia while undergoing supplemental O_2 therapy (Hagadorn et al., 2006; Sola et al., 2008; Claure and Bancalari, 2009; Bancalari and Claure, 2012; Lim et al., 2014). A previous study found that rats exposed to 60% O_2 every other hour for the first two weeks of life exhibit a modest blunting of their HVR at 6–10 weeks of age (Bavis et al., 2007), but the slow cycles of prolonged hyperoxia used in that study were not intended to approximate clinical intermittent hyperoxia.

The present study employed a model of chronic intermittent hyperoxia in which rats were exposed to five bouts of hyperoxia (30 or 60% O_2) per hour from birth through 4–15 days of age. Based on previous studies of chronic sustained hyperoxia (reviewed in Bavis et al., 2013), we hypothesized that intermittent hyperoxia would decrease normoxic ventilation, attenuate the HVR, and result in a sustained HVR (vs. biphasic) at an earlier age than in age-matched control rats. The results revealed age-dependent effects of intermittent hyperoxia on the HVR, so additional experiments investigated the potential role of the carotid body in this plasticity by examining the effects of intermittent hyperoxia on carotid chemoafferent responses to hypoxia and carotid body size. Finally, to determine whether the respiratory effects of intermittent hyperoxia are unique to developmental exposures, additional rats were exposed to intermittent hyperoxia beginning at 28 days of age (i.e., after the neonatal period).

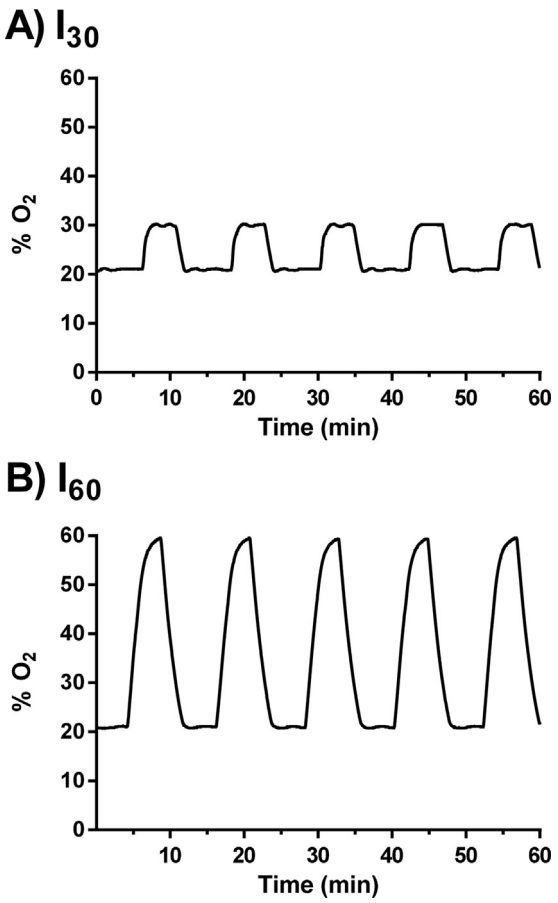

Fig. 1. Representative traces of O_2 concentration measured during (A) intermittent 30% O_2 (I_{30}) and (B) intermittent 60% O_2 (I_{60}) exposures. O_2 concentrations cycled continuously (24 h d^{-1}).

2. Methods

2.1. Experimental animals

All experimental protocols were approved by the Bates College Institutional Animal Care and Use Committee. Timed-pregnant Sprague–Dawley rats were obtained from a commercial supplier (Charles River Laboratories) and housed in room air. For the initial experiments, the resulting litters were assigned to one of three treatment groups on the day of birth (2–8 h after parturition): Control, intermittent 30% O_2 (I_{30}), or intermittent 60% O_2 (I_{60}). To determine whether a critical window exists for intermittent hyperoxia-induced plasticity, additional rats were reared in room air until 28 days of age (i.e., P28, where P0 is the day of birth) and then assigned to Control or I_{60} treatment groups; these rats were weaned at P21. Rat cages (pups housed with their mothers or P28 rats housed 2–3 per cage) were placed into chambers programmed to cycle between set oxygen levels at a rate of 5 cycles h^{-1} (4.5 min at 30 or 60% O_2, 7.5 min^{-1} at 21% O_2; 24 h d^{-1}) (OxyCycler A420C controller with A-30274A chambers; BioSpherix); because of the gas exchange dynamics of the system, rats actually spent approximately 5.4 min above 21% O_2 and 6.6 min at 21% O_2 per cycle (Fig. 1). Age-matched Control rats were housed in a large acrylic chamber (310 L) flushed with room air at flow rates sufficient to maintain approximately 21% O_2 (and less than 0.4% CO_2); the Control chamber sat adjacent to the I_{30} and I_{60} chambers. Chambers were opened briefly when animals were removed for study and for routine cage-cleaning as needed. Rats were exposed to a 12-h light: 12-h dark cycle and were provided food and water ad libitum.

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