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Respiratory modulation of sympathetic activity is attenuated in adult rats conditioned with chronic hypobaric hypoxia

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ABSTRACT

Respiratory modulation of sympathetic nerve activity (SNA) depends on numerous factors including prior experience. In our studies, exposing *naïve* adult, male Sprague-Dawley rats to acute intermittent hypoxia (AIH) enhanced respiratory-modulation of splanchnic SNA (sSNA); whereas conditioning them to chronic hypobaric hypoxia (CHH) attenuated modulation. Further, AIH can evoke increased SNA in the absence phrenic long-term facilitation. We hypothesized that AIH would restore respiratory modulation of SNA in CHH rats. In anesthetized, CHH-conditioned (0.5 atm, 2 wks) rats (n = 16), we recorded phrenic and sSNA before during and after AIH (8% O_2 for 45s every 5 min for 1 h). At baseline, sSNA was not modulated with respiration. The sSNA was not recruited during a single brief exposure of hypoxia nor after 10 repetitive exposures. Further, the sSNA chemoresponse was not restored 1 h after completing AIH. Thus, CHH-conditioning blocked the short-term plasticity expressed in sympatho-respiratory efferent activities and this was associated with reduced respiratory modulation of sympathetic activity and with attenuation of the sympatho-respiratory chemoresponse.

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1. Introduction

The cardiovascular-respiratory control systems are coupled and this coupling is dynamic, varying in health and disease (Garcia *et al.*, 2013). For instance, cardiorespiratory coupling is increased in elite athletes (Aubert *et al.*, 2003) whereas it is decreased in sepsis (Dick *et al.*, 2012). Conditioning to hypoxia can evoke increases or decreases in sympatho-respiratory coupling depending on whether the exposure is intermittent or sustained. Chronic intermittent hypoxia enhances respiratory modulation of splanchnic sympathetic nerve activity (sSNA) (Zoccal *et al.*, 2009) with additional activity recruited specifically in late expiration (Abdala *et al.*, 2009). This type of sympatho-respiratory coupling is associated with hypertension (Zoccal et al., 2009; Abdala et al., 2009). In contrast, sustained or hypobaric hypoxia has not been associated with hypertension nor enhanced respiratory modulation (Ilyinsky *et al.*, 2003; Hsieh *et al.*, 2004; Ilyinsky & Mifflin, 2005). However recently, Moraes and colleagues (Moraes *et al.*, 2014) reported that after 24 h of sustained hypoxia, increased sympatho-respiratory coupling was associated with an increase in blood pressure. Our general working hypothesis is that mechanisms of plasticity for the control of the respiratory system also effect SNA. It is in this context that we address whether chronic hypobaric hypoxic (CHH) exposure impacts both sympathetic and phrenic plasticity.

1.1. Response to Hypoxia

In *naïve* adult male Sprague-Dawley rats, the hypoxic ventilatory response (HVR) has a stereotypic pattern, which consists of an asymptotic increase in phrenic nerve activity (PNA) burst amplitude whereas burst frequency acutely increases then decreases (Powell *et al.*, 1998). Immediately after hypoxia, PNA burst amplitude gradually returns to baseline whereas frequency decreases below baseline and recovers slowly. This period is referred to as post-hypoxic frequency decline (PHFD) (Coles & Dick, 1996). The HVR and PHFD depend on the duration and intensity of the exposure, the genetic background, the age of the animals as well as the prior exposure to hypoxia (Aaron & Powell, 1993; Dwinell & Powell, 1999; Ilyinsky *et al.*, 2003; Hsieh *et al.*, 2004; Ilyinsky & Mifflin, 2005). Conditioning rats with CIH increases baseline

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sympatho-respiratory coupling and accentuates the HVR (Baker & Mitchell, 2000; Fuller *et al.*, 2000; Xing & Pilowsky, 2010; Xing *et al.*, 2013). In contrast CHH conditioning attenuates both HVR and PHFD (Ilyinsky *et al.*, 2003; Hsieh *et al.*, 2004; Ilyinsky & Mifflin, 2005).

The sympathetic nerve activity has tonic and respiratory modulated components. During hypoxia respiratory modulation dominants and sSNA is activated during expiration and quiescent during inspiration. Further, sSNA is quiescent immediately after hypoxia. During PHFD, sSNA remains respiratory-modulated as it return to baseline levels (Dick *et al.*, 2004).

1.2. Plasticity Evoked by Acute Intermittent Hypoxia

In *naïve* rats, acute intermittent hypoxia (AIH) evokes sustained increases in both PNA and sSNA (Dick *et al.*, 2007), similar to long-term facilitation (LTF) as defined for respiratory motor activity (Millhorn *et al.*, 1980b,a; Baker & Mitchell, 2000; Fuller *et al.*, 2000; Baker *et al.*, 2001; Dick *et al.*, 2007). CHH conditioning blocked LTF in PNA and sSNA (Hsieh *et al.*, 2008). However, LTF in sSNA can occur in the absence of respiratory LTF (Xing & Pilowsky, 2010) and AIH facilitates motor function in general (*i.e.*, the recovery of function in spinal cord injured (hemisection) rats (Fuller *et al.*, 2003; Golder & Mitchell, 2005; Fuller *et al.*, 2006)).

Both PHFD and LTF are forms of activity-dependent plasticity (Poon & Siniaia, 2000) and are abolished by conditioning with hypoxia (Ilyinsky *et al.*, 2003; Hsieh *et al.*, 2004; Ilyinsky & Mifflin, 2005; Hsieh *et al.*, 2008). The concept that the plasticity of a system is itself 'plastic' is termed *metaplasticity* (Abraham & Bear, 1996; Baker & Mitchell, 2000; Fuller *et al.*, 2000; Poon & Siniaia, 2000; Song & Poon, 2004). The effect of CHH-conditioning on the sympathetic chemoreflex is poorly understood. We hypothesized that CHH conditioning would unmask the tonic sympathetic chemoreflex because the HVR is blunted. Thus, we indirectly tested the hypothesis that AIH uses a common mechanism to evoke LTF in sSNA and PNA; in that AIH does not evoke LTF in tonic component of sSNA via the sympathetic chemoreflex in the absence of a strong HVR.

2. Methods

2.1. Experimental details

Surgical procedures and experimental protocols followed NIH guidelines and were approved by the Institutional Animal Care and Use Committee at Case Western Reserve University. The surgical and electrophysiologic methods for determining the hypoxic response was performed as previously reported (Dick *et al.*, 2004; Hsieh *et al.*, 2004; Dick *et al.*, 2007; Hsieh *et al.*, 2008). In brief, adult male Sprague-Dawley (Zivic Miller) rats (n = 16) were conditioned for 14 days to sustained hypoxia in a hypobaric chamber (0.5 atm); with ambient O_2 equal to 21% of the atmospheric gas, the inspired O_2 content is approximately that of 10% O_2 at 1 Torr. Throughout the 14 days, the chamber was opened every 2 days (< 5 min) for animal husbandry.

A small set of *naïve* rats (n = 3) were housed in a neighboring hypobaric chamber but remained at atmospheric pressure. Data from these rats were not different than those from experiments performed previously on *naïve* rats (Dick et al., 2004; Hsieh et al., 2008), so the *naïve* data set incorporated the previously obtained data (n = 12). The representative traces for the *naïve* rats are from previously unreported data.

Surgery and experiments were performed immediately following the conditioning period. Rats were anesthetized with equithesin (30 and 133 mg/kg sodium pentobarbital and chloral hydrate, respectively; administered intraperitoneally) and the initial and surgical anesthetic level was tested by paw pinch and evaluating withdrawal reflex. Once neuro-muscular blockade was administered, anesthetic effects were evaluated by observing the sympatho-respiratory neural response after painful paw pinch. If additional anesthetic was required, the 0.1 the original dose was delivered intravenously (iv).

The femoral artery was cannulated to measure blood pressure; the femoral vein, to administer pharmacological agents; and the trachea, to ventilate the animals. The cervical vagi were transected bilaterally and the animal was placed in a stereotaxic apparatus. The left phrenic and splanchnic sympathetic nerves were isolated, transected, and mounted on bipolar electrodes for recording. Rats were paralyzed with pancuronium bromide, (0.1 mg/100 g bw/h, iv) and ventilated with 100% O_2. A Novametrix 7000 Capnograph sensor was used to monitor end-tidal PCO_2 ($PETCO_2$) continuously. $PETCO_2$ for the entire group ranged between 35 and 38 mmHg, but within individual animals, $PETCO_2$ varied $\leq$2 mmHg about its mean, even including hypoxic episodes. The capnograph was calibrated weekly with a 5% CO_2 gas mixture. Arterial blood samples were analyzed for PO_2, PCO_2, and pH prior to hypoxic exposure, following the series of 10 hypoxic exposures, and at the end of the protocol; these parameters were maintained within normal limits (Radiometer ABL80).

2.2. Recorded Variables

Blood pressure, airflow, raw and integrated PNA and sSNA, as well as end-tidal PCO_2, were displayed on a chart recorder (Astro-Med Dash 8) and acquired on a computer (LabView data acquisition and analytical software written by Innovative Computer Engineering Inc.). Body temperature was maintained at approximately 37 °C throughout the experiment by a servo-controlled recirculating water blanket and infrared lamps.

2.3. Experimental Protocol

The hypoxic response was elicited by challenging with 8% O_2 for 45 s. The rats were ventilated with 100% O_2 before and after the hypoxic challenge to maximize response and all hypoxic exposures were poikilocapnic. A subset of rats (n = 10) received 10 successive hypoxic challenges (45 s of 8% O_2 followed by 5 min of 100% O_2), were allowed to recover for 1 h, and then were exposed to an 11th hypoxic challenge. As a control, CHH-conditioned rats (n = 3) received a single hypoxic challenge and another hypoxic challenge 2 h later.

2.4. Data Analysis

Changes in the timing of the breathing pattern were analyzed by plotting sequentially the duration of expiration (T_E) before, during, and after hypoxic exposure. Baseline values of T_E were the average of 10 consecutive cycles before a hypoxic exposure; peak frequency (Pkf_R), the 3-5 successive cycles with the shortest TE; and hypoxic ventilatory depression (HVD), the 3-5 cycles with the longest T_E at the end of hypoxic exposure; PHFD 3 consecutive cycles with the longest T_E immediately after hypoxia; and recovery (Rcvry) 10 consecutive cycles, which occurred 60 s after hypoxia. Cycles that contained fictive swallows were excluded.

Cycle-triggered averages (CTAs) were constructed to compare the coupling patterns of PNA and sSNA. Averaging increased the signal-to-noise ratio of sSNA that was time-locked to the respiratory cycle (Dick *et al.*, 2004). For averaging, the analog signal of sSNA was rectified, integrated (CWE, Inc.; Paynter Filter, 50 ms time constant), sampled at 200 Hz and summed (National Instruments, Analog-to-Digital board). The reference point (time zero) for cycle-triggered averages was the phase transition between

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