Topic: Neuroscience

Hypoxia-induced Sighs Correlate with High Amplitude Bursts in Splanchnic Sympathetic Nerve Activity (SSNA): Role of Bombesin-Like Peptides in the PreBotzinger Complex

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Introduction: Hypoxia-induced sighs are widely studied and the actual research are trying to correlate the role of the inhibition of the paraventricular nucleus of the hyphothalamus.among other approaches.

Objective: To demonstrate that hypoxia-induced sighs correlate with high amplitude bursts in splanchnic sympathetic nerve activity and the role of bombesin-like peptides in the preBotzinger complex**.**

Results: Previous experiments in inactin anesthetized (100 mg/kg, i.v.) spontaneously breathing male SD rats found that hypoxia (HX, O2 saturation ~ 50%) increased frequency(F) and amplitude (amp) of phrenic (Ph) nerve activity (NA) during eupnea, but distribution of SSNA across eupneic Ph cycles was similar for normoxia and HX [inspiration (I1, I2) > expiration (E1, E2)]. HX produced high amp bursts in PhNA (~ 4 to 6/min), followed by brief apnea (sighs). Correlation analysis during sighs revealed that SSNA redistributed such that high amplitude bursts in SSNA occurred in late inspiration (I2 > I1, E1, E2). In the PreBotzinger Complex (PreBot) 2 bombesin-like peptides (Bom), neuromedin B (NMB) and gastrin-releasing peptide (GRP), generate sighs (Li et.al., 2016). Current experiments evaluated the role of NMB and GRP in the Pre-Bot in redistribution of SSNA during sighs. PhNA and SSNA were correlated before and after bilateral microinjections (100 nl) into the PreBot of a Bom receptor agonist cocktail [Bom-agonists) in rats breathing 100% O_2 (n = 3). Bom-agonists increased Ph amp and F during eupnea, but the distribution of SSNA across the eupneic Ph cycle was similar before and after PreBot Bom-agonists (I1, I2 > E1, E2). Bom-agonists in the PreBot

produced high amp bursts in PhNA (131% of eupneic; 4.6 ± 0.5/min) with prolonged expiration (0.90 ± 0.08 vs 0.74 ± 0.07 sec), indicative of sighs. However, unlike sighs due to HX, with PreBot Bom-agonists while rats breathed 100% O_2, the distribution of SSNA across the Ph cycle was similar for sighs and eupnea (I1, I2 > E1, E2). In 3 rats, sighs were evaluated during graded HX (18, 15 and 13% inspired O_2, 2 min ea) before and after a cocktail of Bom-antagonists was injected bilaterally (100 nl) into the PreBot (PreBot-bX). Both the number and amp of sighs tended to be less after PreBot-bX (P = 0.07), but the brief duration of action of the antagonists precluded evaluation of SSNA correlations using this protocol. In separate rats (n = 4), PreBot-bX was performed during HX after regularly occurring sighs were evident (13% O2). PreBot-bX tended (P = 0.08) to decrease the number (2.6 ± 0.3 vs 1.4 ± 0.4/min) and amplitude of PhNA sighs. Correlation of SSNA across the Ph cycle was not changed by preBot-bX during eupnea (I1, I2 > E1, E2), but HX-induced redistribution of SSNA during sighs (I2 > E1, E2) was eliminated by PreBot-bX. Thus, Bom-like peptides in the PreBot contribute to sighs, but correlation of sighs with high amp bursts in SSNA was evident only with HX-induced sighs.

Conclusions: Based on these results and our previous finding that inhibition of the paraventricular nucleus of the hypothalamus (PVN) resulted in uncoupling of SSNA with inspiratory sighs, we speculate that HX activates descending projections from the PVN which modulate cardiorespiratory coupling in the medulla during sighs (Heesch et al., 2018).

Keywords: Hypoxia, rats, hypothalamus, inspiratory sighs, splanchnic sympathetic nerve activity, bombesin-like peptides, preBotzinger complex

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