Sympatho-respiratory coupling: brainstem mechanisms

Y. I. MOLKOV[1], D. B. ZOCCAL[2], D. J. A. MORAES[3], D. M. BAEKEY[4], T. E. DICK[5], B. H. MACHADO[3], J. F. R. PATON[6], I. A. RYBAK[7]

[1]Dept. Math. Sci., Indiana University – Purdue University, Indianapolis, IN
[2]Dept. Phys. Sci., Federal University of Santa Catarina, Florianópolis, SC, Brazil
[3]Dept. Physiol., Univ. of São Paulo, Ribeirão Preto, São Paulo, Brazil
[4]Dept. Phys. Sci., University of Florida, Gainesville, FL
[5]Dept. Med. & Neurosci, Case Western Reserve Univ., Cleveland, OH
[6]Dept. Physiol. & Pharmacol., Univ. of Bristol, Bristol Heart Inst., Bristol, United Kingdom
[7]Dept. Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Hypertension, like that resulting from sleep-disordered breathing, is associated with elevated sympathetic nerve activity (SNA), which was found to be respiratory phase-dependent. Thus, hypertension may depend on specific interactions between the respiratory and sympathetic neural networks. Conditioning animals with chronic intermittent hypoxia (CIH) increases the late-expiratory (late-E) component in the SNA. In contrast, in naïve animals during eupnea SNA is typically most active in inspiration/post-inspiration and least active during late-E. Further, our recent studies in situ demonstrate that ponto-medullary transection significantly attenuates SNA respiratory modulation. Also, baro-stimulation facilitates post-inspiratory (post-I) activity in the Bötzinger Complex. However, the sources of respiratory modulation of SNA and the mechanisms responsible for the coupling between respiratory and sympathetic activities remain undefined.

To elucidate the mechanisms underlying these phenomena we extended our computational model of the brainstem respiratory network by incorporating neural populations representing rostral and caudal ventrolateral medulla (RVLM and CVLM). In this model, the RVLM and CVLM populations receive inputs from neural populations of the pons, Bötzinger and pre-Bötzinger Complexes and retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG), which together provide the respiratory modulation of SNA. Our simulations suggest that CIH-conditioning may evoke a late-E modulation of SNA similar to that produced by hypercapnia. This suggestion was experimentally confirmed in situ. We found that CIH-conditioned rats under normal conditions exhibit synchronized late-E discharges in the abdominal nerve (AbN) and SNA, which were similar to the late-E activity observed in both nerves in control rats during hypercapnia. With progressive increase of CO2 level in control rats, late-E discharges (in both AbN and SNA) appeared at a lower rate relative to phrenic nerve (PN), i.e. many respiratory cycles were skipped, and then quantally accelerated until they occurred in every cycle. The SNA late-E discharges appeared during the same breathing cycles as AbN late-E bursts. Similar behavior was observed in CIH-conditioned rats at normal CO2. We hypothesize that the mechanism for emergence of late-E modulation of SNA in CIH-conditioned animals is associated with an increase in the CO2 sensitivity of RTN/pFRG neurons as a consequence of intermittent hypocapnia resulting from tachypneic response to hypoxia. This suggestion is supported by a lower apnea threshold found in CIH-conditioned rats relative to naïve ones.