Baroreceptor modulation of cough motor pattern: computational network model and *in vivo* experiments

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We extended a computational model of the pontomedullary respiratory network capable of reproducing the cough motor pattern (Rybak et al. 2008). That previous model incorporated connectivity based on prior and coordinated *in vivo* experiments. It also instantiated speculative connectivity to support the earlier hypotheses that activation of airway cough receptors changes firing activity of 2nd order solitary tract nucleus (NTS) neurons that directly and/or indirectly affect several populations of respiratory neurons in the ventral respiratory column (VRC) and pontine respiratory group (PRG). These evoked changes reconfigure the respiratory network to produce cough motor pattern, acting (at least in part) through the same VRC neurons involved in providing drive to respiratory muscles during normal breathing. The new model incorporated a circuit "module" for baroreceptor modulation of breathing based on *in vivo* multi-array recordings and correlational linkages of baroresponsive neurons. This circuit included both excitatory and disinhibitory raphé neuron influences acting upon VRC decrementing expiratory (E-Dec) neurons, including a "tonic" E-Dec population with inhibitory actions on inspiratory premotor bulbospinal neurons. Other changes include *(i)* addition of a separate excitatory premotor population ("E-Dec-pre") to drive the expiratory laryngeal motoneurons and *(ii)* implementation of a speculative vagal afferent pathway for inhibition of the E-Dec-Phasic (E-Dec-P) population. This "deflation-sensitive" afferent pathway represents a class of possible network mechanisms that could contribute to a biasing inhibition of E-Dec neurons postulated to be lost with vagotomy. Repetitive cough-like motor patterns generated by the enhanced model were altered when evoked during concurrent activation of simulated baroreceptor reflex influences. Specific changes with co-activation of the two system inputs included reductions in the firing rates and integrated traces of model motor outputs, prolongation of individual phases of cough motor pattern, and fewer coughs. The model and simulations reported here predicted reductions in the frequency and amplitude of coughs evoked during elevated blood pressure that were confirmed in vivo. The results also suggest new predictions on the discharge profiles of network populations during coughing and altered baroreceptor drive. The model also produced changes in inspiratory and expiratory motor patterns observed experimentally. When disrupted by simulated "vagotomy", the deflation-sensitive afferent circuit operating in parallel with slowly adapting pulmonary stretch receptors contributed to a prolongation of both inspiratory and expiratory phases. Simulated baroreceptor stimulation prolonged the expiratory phase and reduced inspiratory motor drive, reproducing *in vivo* observations and prior modeling results. Supported by NIH HL 89104; HL 89071; HL 103415.

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