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The preBötzinger complex (preBötC), in the lower brainstem, functions as the rhythm generator for breathing in humans and all mammals. Neurons of the preBötC comprise the respiratory central pattern generator, producing the rhythm for inspiratory breathing movements. Despite the evolutionary conservation and robustness of this neural oscillator, its Achilles heel is sensitivity to opioid drugs. Here, we present parallel projects assessing two aspects of preBötC function relevant to opioid-induced respiratory depression (OIRD).

Previously, we presented a firing rate activity model of the preBötC that exhibits episodic bursting mediated by the combination of recurrent excitation, synaptic depression, and cellular adaptation (Borrus et al., 2024). To investigate the pre-synaptic and post-synaptic effects of opioids on the preBötC, we extended this model to include two populations that either lack or express the mu-opioid receptor (μOR- and μOR+, respectively). Parameter studies explore how pre-synaptic suppression of excitation, post-synaptic decreases in excitability, and μOR+/- population sizes may contribute to OIRD.

Previous studies suggest that μORs may target G protein-coupled inward rectifiers (GIRKs), KCNQ channels that give rise to M-current (I_M), or a slowly inactivating A-current (I_A). GIRK and I_M have obvious roles in controlling baseline membrane potential. But how about I_A? To investigate the possible influence of I_A on OIRD, we developed a conductance-based network model of the preBötC in which I_A is included in the dendritic compartment of 500 Pinsky-Rinzel-type *in silico* neurons. Preliminary simulations with single-compartment neurons confirm that increased I_A conductance results in delayed excitation and lower burst frequency. Here, we present an extended analysis using a preBötC network model composed of two-compartment (somatic & dendritic) neurons, elucidating how opioid modulation of I_A can impact network rhythmogenesis.

These parallel projects provide a fresh perspective regarding basic biophysical mechanisms underlying OIRD, which is important foundational knowledge for developing resuscitation strategies and treatment of opioid addiction.

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