Neural Mechanisms of Breathing

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My collaboration with Christopher A. Del Negro at William & Mary brings mathematical biology and cellular biophysics together with experimental neuroscience to understand the neural control of breathing. Our work focuses on the preBötzinger complex (preBötC), a brainstem network that generates inspiratory activity. Two complementary lines of investigation address how this network produces normal breaths and sighs, and how μ-opioid receptor signalling reduces the excitability of neurons that support breathing.

Normal breathing and sighs

Our 2020 study examined how the rhythms underlying normal breathing (eupnea) and sighing are coordinated. Recordings from awake mice and neonatal brainstem slices revealed that sigh timing is more variable than previously appreciated: a sigh need not follow a normal inspiratory event. Blocking glycinergic and GABAergic inhibition did not abolish coupling or the post-sigh pause. These findings challenged inhibition-based explanations and supported excitatory coupling, with the pause reflecting refractoriness after a sigh.[1]

In 2024, we combined mathematical modelling with experiments to explain how one neuronal population can generate two rhythms on markedly different timescales. The model links recurrent excitation, synaptic depression and cellular adaptation to the faster inspiratory rhythm, while slower intracellular calcium dynamics generate sighs. It produces both rhythms without requiring separate dedicated neuron populations. Experiments validated key predictions: partially reducing calcium uptake into the endoplasmic reticulum accelerated sighs, whereas reducing calcium release slowed or stopped them. This work connects calcium homeostasis to respiratory network dynamics and explains how sigh frequency can be regulated separately from ordinary inspiration.[2]

μ-opioid receptors and respiratory depression

Our 2026 study with Eva Kalajian and Marco Stettler identified a cellular mechanism by which opioids can depress the breathing network in neonatal mouse brainstem slices. Although the μ-opioid receptor gene, Oprm1, was expressed in substantial fractions of excitatory and inhibitory preBötC neurons, the agonist DAMGO reduced excitability selectively in the glutamatergic neurons studied. Whole-cell and single-channel recordings showed enhanced Kir3 (GIRK) potassium-channel activity through a membrane-delimited signalling mechanism consistent with Gβγ action. The results identify a postsynaptic route by which opioids weaken excitatory respiratory drive and suggest downstream signalling targets for future interventions against opioid-induced respiratory depression. Such interventions remain a research direction.[3]

Selected joint publications

1. Borrus DS, Grover CJ, Conradi Smith GD, Del Negro CA (2020). Role of synaptic inhibition in the coupling of the respiratory rhythms that underlie eupnea and sigh behaviors. eNeuro 7(3):ENEURO.0302-19.2020. doi:10.1523/ENEURO.0302-19.2020.

2. Borrus DS, Stettler MK, Grover CJ, Kalajian EJ, Gu J, Conradi Smith GD, Del Negro CA (2024). Inspiratory and sigh breathing rhythms depend on distinct cellular signalling mechanisms in the preBötzinger complex. J Physiol 602:809–834. doi:10.1113/JP285582.

3. Kalajian EJ, Stettler MK, Conradi Smith GD, Del Negro CA (2026). μ-Opioid receptor signalling enhances Kir3 currents in glutamatergic preBötzinger complex neurons in mice. J Physiol 604:7351–7374. doi:10.1113/JP291442.

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