Computational Modeling of Serotonin-Evoked Reorganization of the Brain Stem Respiratory Network

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The respiratory rhythm is modulated by a variety of serotonin receptors (5-HTR) including 5-HTR_{1A}. 5-HTR_{1A} activation induces a $G\alpha_{i3}$ mediated decline of cAMP levels that leads to de-phosphorylation of the co-expressed α3 glycine receptor (GlyRα3) causing an augmentation of its inhibitory chloride current (Manzke et al. 2010). The 5-HTR_{1A}–GlyRα3 signal pathway counteracts opioid depression and recovers breathing during opioid-based pharmacotherapy of pain. The effect seems to rely on an enhanced glycinergic inhibition of inhibitory neurons causing disinhibition of their target neurons. To evaluate this suggestion, an established computational model of the brain stem respiratory network (Smith et al. 2007) was used and extended by assigning the 5-HTR_{1A}-Gαi3-GlyRα3 signaling to specific populations of inhibitory respiratory neurons (glycinergic, GABAergic). We show that the model reproduces the effects of 5-HTR_{1A} agonists on the respiratory activity patterns, such as shifting the onset of post-inspiratory activity to inspiration and the conversion of the eupneic 3-phase pattern to a faster 2-phase pattern lacking the post-inspiratory phase. Importantly, the model gives a mechanistic explanation for the 5-HTR_{1A} induced recovery of the respiratory rhythm after opiate-evoked apnea.