Model of inspiratory rhythm generation and maintenance by parafacial respiratory group and pre-Bötzinger complex pacemakers

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The mammalian respiratory rhythm has been hypothesized to be generated by intrinsically rhythmic pacemaker neurons located in two subregions of the ventrolateral medulla: the parafacial respiratory group (pFRG) where pre-inspiratory (pre-I) neurons are found, and the pre-Bötzinger complex (pBötC) that comprises mainly inspiratory (I) neurons. There is general consensus that both are bona fide respiratory rhythm generators and that the pFRG is important for expiratory rhythm generation. Controversy remains, however, as to whether the pBötC per se is sufficient to drive the inspiratory rhythm independent of pFRG. Here we present a dual pFRG-pBötC pacemaker model of inspiratory rhythm generation in which pFRG excites the pBötC and is inhibited by it. The pacemaker network is configured such that in brainstem slice preparations where pFRG is absent, the pBötC generates spontaneous rhythmic bursts that sustain inspiration whereas in en bloc brainstem-spinal cord preparations or intact animals, the pBötC rhythm is entrained by the faster endogenous pFRG pre-I activity. This model configuration explains why the inspiratory rhythm in vivo is more severely disrupted by lesions of the pBötC than those of the pFRG. The model mimics the experimental resetting of respiratory rhythm induced by electrical pFRG stimulation during expiration. More importantly, it predicts that during opioid-induced quantal slowing of respiratory rhythm (i) quantal increases in pBötC cycle duration occur whenever the probabilistic pFRG excitation of the opioid-depressed pBötC neuron fails to reach the firing threshold; and (ii) pBötC cycle durations are randomly distributed between quantum levels that are separated by ~70% of the control cycle duration, as found experimentally. In contrast, such quantal effects are not reproduced by the model when the pBötC is set as an independent rhythm generator. These results are consistent with the view that pFRG neurons normally generate the inspiratory rhythm by periodically triggering pBötC bursts which, once activated, sustain inspiration independent of the pFRG.

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