Department of Pharmacology (II)

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General Summary

We have been focusing on the following areas: 1) verification of the hypothesis that coupled pairs of oscillators may generate the respiratory rhythm in vertebrates, 2) visualization of the spatiotemporal pattern of respiratory neural activities in the isolated frog brainstem, and 3) neural mechanisms of the vagal respiratory reflex.

Research Activities

Verification of the hypothesis that coupled pairs of oscillators generate the respiratory rhythm in vertebrates

The frog, with two distinct ventilatory acts, provides a useful model for investigating the prospective interaction of paired oscillators in generating the respiratory rhythm. Building on evidence supporting the existence of separate oscillators generating buccal ventilation and lung ventilation, we have attempted to uncouple the two rhythms in the isolated brainstem preparation. Opioids preferentially inhibited the lung rhythm, suggesting an uncoupling of the lung oscillator from the buccal oscillator. Reduction of the superfusate chloride concentration altered both the buccal rhythm and the lung rhythm. Joint application of opioids and reduced-chloride superfusate increased the variability of the buccal-burst-to-lung-burst intervals. This increase in variability suggested that chloride-mediated mechanisms are involved in coupling the buccal oscillator to the lung oscillator. Given the results of these interventions, we proposed a simple model of the frog respiratory rhythm generator, which consists of the coupling of the lung and buccal oscillators. This model can be used to explain various patterns in the breathing of all lunged vertebrates, although the mechanics of breathing differ fundamentally between amniotes and lower vertebrates (Collaboration with the Respiratory Research Group, University of Calgary).

Visualization of the spatiotemporal pattern of respiratory neural activities in the isolated frog brainstem

To identify the neural structures essential for the formation of respiratory motor-activity patterns (buccal and lung bursts) in frogs, we visualized the spatiotemporal pattern of respiratory neuronal activities in the isolated brainstem, using voltage-imaging techniques. We recorded optical signals from the ventral surface of the medulla using a voltage-sensitive dye and calculated cross-correlations between the integrated respiratory activity of the trigeminal nerve and each pixel. Lung-burst-related activities were visualized bilaterally as longitudinal columns in the ventrolateral medulla between the levels of the trigeminal and hypoglossal nerve rootlets. In contrast to that in neonatal

rats, the optically active area in frogs spreads in a caudal-to-rostral column during the lung burst. The optically identified area was verified with extracellular recordings of respiratory-related neurons. (Collaboration with the Department of Physiology, Hyogo College of Medicine, Hyogo, and the Department of Medicine, Keio University Tsukigase Rehabilitation Center).

Neural mechanisms of the vagal inspiration-promoting reflex and involvement of P2X receptors in nucleus of the solitary tract

To understand how respiratory movements are optimized in response to changes in internal and external environments, the research group for mammalian respiratory function has been studying neural mechanisms underlying various types of respiratory reflexes in mammals (in collaboration with the Laboratory of Neurophysiology, Department of Neuroscience). We have demonstrated that a local microinjection of pyridoxalphosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS), a P2X receptor antagonist, into the caudal nucleus of the solitary tract (NTS) of the anesthetized rabbit preferentially attenuates the "inspiratory promotion reflex," a response driven by the pulmonary stretch receptor and activated at a small lung volume. This year, we analyzed the site of action of PPADS by histological investigation and found that the marked reduction of the vagal inspiratory-promotion reflex occurred mostly when the site of PPADS injection, identified with staining, contained the caudal part of the lateral NTS. This result argues clearly for a pivotal role for the P2X receptors in the caudal NTS in the inspiratory-promoting responses activated by decreased inputs from the pulmonary stretch receptor.

Publications

Vasilakos K*[1]*, Kimura N, Wilson RJA*[1]*, Remmers JE*[1] *(*[1]*Univ Calgary). Lung and buccal ventilation in the frog: uncoupling coupled oscillators. *Physiol Biochem Zool* 2006; **79:** 1010–8.

Reviews and Books

Kimura N. Experimental animals, Frog (4): Physiology, pharmacology and anesthesiology in frogs (in Japanese). *LiSA* 2006; **13:** 378–81.