PERSPECTIVES

The retrotrapezoid nucleus and the 'drive' to breathe

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The retrotrapezoid nucleus (RTN), unlike most neuroanatomical structures, was discovered rather recently. Retrograde tracing experiments designed to describe connections among groups of respiratory neurons uncovered a thin layer of not very densely packed neurons lying between the facial nucleus and the ventral surface of the medulla; it was labelled the RTN (Smith *et al.* 1989).

The maintenance of normal breathing at an appropriate level for metabolism depends on a variety of afferent inputs to clusters of respiratory neurons within the brainstem. The stimulatory inputs are viewed as a 'drive' to breathe, which importantly includes information that arises from multiple central chemoreceptor sites (sensing CO_2/pH) as well as from the peripheral chemoreceptor, the carotid body (sensing CO_2/pH and low O_2) (see Feldman *et al.* 2003). Much work has established that the RTN is one central chemoreceptor site (Nattie & Li, 2002; Feldman *et al.* 2003; Guyenet *et al.* 2005) and, recently, that the RTN chemosensitive neurons are glutamatergic (Guyenet *et al.* 2005).

In this issue of *The Journal of Physiology*, Takakura *et al.* (2006) further show that CO_2-responsive neurons in the RTN receive convergent input from neurons within the nucleus tractus solitarius (NTS) that are activated by carotid body stimulation. The effects of peripheral carotid body and local CO_2 stimulation on individual CO_2-sensitive RTN neurons are additive, a striking result in that prior experiments under anaesthesia had shown an absent respiratory response to both CO_2 and carotid sinus nerve stimulation after small, unilateral RTN lesions (Nattie & Li, 1990).

What is the physiological function of this small group of neurons? Under anaesthesia the impact of the RTN on the 'drive' to breathe and on the CO_2 response is substantial. An initial report showed in anaesthetized cats that a single, small, unilateral injection of kainic acid (an excitatory amino acid neurotoxin) into the RTN causes apnoea and virtually abolishes the response to increased CO_2 (Nattie & Li, 1990) and the paper by Takakura *et al.* (2006) in this issue shows in anaesthetized rats that bilateral inhibition at the RTN by muscimol has the same effects.

However, in the conscious animal the role and importance of the RTN is less clear. Lesions in conscious animals do not stop breathing but can diminish it and decrease the CO_2 response as well (Nattie & Li, 2002; Feldman *et al.* 2003). For example, bilateral lesions of ~40% of neurokinin-1 receptor-expressing neurons and processes in the RTN results in rats that hypoventilate while breathing air and have a 22% reduction in their ventilatory response to CO_2 (Nattie & Li, 2002). This hypoventilation while breathing air at rest is reminiscent of that observed following denervation of the peripheral chemoreceptors. In each case it seems that loss of a tonic 'drive' to breathe, either from the carotid bodies or the RTN, results in a control system that operates at a new level. An arterial CO_2 value above normal is accepted; the remaining chemoreceptors do not seem able to compensate.

Is the RTN quantitatively the most important of known central chemoreceptor sites? At present this question cannot be answered but the RTN does seem to provide an important 'drive' to breathe that may reflect this convergence of carotid body inputs to CO_2-sensitive RTN neurons. Is the RTN part of the parafacial nucleus involved in respiratory rhythm generation (Onimaru *et al.* 2006)? Again it is difficult to say at present but current evidence suggests that these are two functionally separate cell groups that lie adjacent to each other ventral and medial to the facial nucleus (with some anatomical overlap) (Onimaru *et al.* 2006). The parafacial neurons fire just before inspiration and provide rhythm generation in some conditions; the RTN neurons are chemosensitive, affected by carotid body stimulation and provide a 'drive' to breathe (future work will show if there is physiological overlap).

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