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VIEWPOINT

Endogenous medullary raphé hydrogen sulphide facilitates the ventilatory response to hypercapnia

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Linked articles: This Viewpoint highlights an article by Sabino et al. To read this paper, visit https://doi.org/10.1113/EP089335.

The respiratory control network governs oxygen and acid–base balance. Breathing is exquisitely sensitive to changes in carbon dioxide, which are sensed by chemoreceptors located peripherally in the arterial circuit, as well as in multiple sites of the brain. Central chemoreceptors appear to operate as a functional syncytium allowing for dynamic cardiorespiratory modulation in response to perturbations of CO_2/pH. Whereas the retrotrapezoid nucleus has emerged as the critical nexus in CO_2 chemoreception, excitatory input from other classical chemoreceptor regions, such as the medullary raphé neurons, heavily informs the integrative homeostatic response to deviations in CO_2.

Hydrogen sulphide (H_2S) is one of three gasotransmitters known to affect neuronal excitability in the CNS. The modulatory effects of H_2S are widespread in the brain and extend to cardiorespiratory centres of the brainstem. Indeed, it is established that H_2S modulates inspiratory rhythm generation (da Silva et al., 2017) and ventilatory and thermoregulatory responses to hypercapnia (da Silva et al., 2014; Sabino et al., 2019). Interest has now focused on delineating the key site(s) of the brainstem chemoreceptor network wherein endogenous H_2S gasotransmission modulates ventilatory responsiveness to hypercapnic stress.

In this issue of *Experimental Physiology*, Sabino *et al.* (2021) examine the influence of pharmacological manipulations of H_2S in the rostral medullary raphé region on the ventilatory response to CO_2 in conscious rats. In separate groups of animals, microinjections of vehicle, aminooxyacetic acid (AOA; a cystathionine β-synthase (CBS) inhibitor), propargylglycine (PAG; a cystathionine γ-lyase (CSE) inhibitor), or sodium sulphide (a H_2S donor) were performed and ventilation was determined by whole-body plethysmography during normocapnia and 30 min exposure to hypercapnia (7% CO_2). CBS and CSE are enzymes critical in the production of endogenous H_2S. In vehicle-treated rats, exposure to CO_2 resulted in robust increases in respiratory frequency, tidal volume and minute ventilation. Compared with vehicle, rats microinjected with AOA, but not PAG, had lower ventilatory responses to hypercapnia due to reductions in respiratory frequency. The results are consistent with the known widespread expression of CBS in the brain, particularly in glia, whereas PAG is more commonly found in peripheral structures. However, whereas inhibition of H_2S synthesis by CBS blockade in the raphé magnus decreased hypercapnic ventilation, microinjection of the H_2S donor had no facilitatory effect, suggesting a ceiling effect of endogenous H_2S signalling on chemoreceptor firing. The novel findings reveal a critical role for the gasotransmitter H_2S in driving a substantial portion of the ventilatory response to CO_2 in conscious rats.

The reduction in the respiratory frequency component of hypercapnic ventilatory response is consistent with recent evidence that serotonergic projections to the retrotrapezoid nucleus are responsible for the elevated frequency component of the hyperpnoeic response to high CO_2 (Leirão et al., 2021); it appears that endogenous H_2S partly facilitates this drive. It would be interesting to extend characterisation of the role of H_2S in central CO_2 chemosensitivity of multiple brainstem sites across the sleep–wake cycle, during light and dark phases and in various disease models. Perhaps CBS-H_2S signalling is fundamentally important to global CO_2 chemoreception. The specific signalling mechanisms by which H_2S modulates brainstem network behaviour remain unclear and could plausibly extend beyond

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intracellular *S*-sulfuration of target proteins to actions of diffused H_2S and polysulfides on neighbouring cells. Thus, to better appreciate the mechanism of action, it will prove important to determine the modulatory effects of H_2S (and other gasotransmitters) on neuro-glial interactions, which are critical for chemosensitivity.

The authors demonstrated that exposure to 7% CO_2 for 1 h increased endogenous H_2S production in the medullary raphé region. The observation is supportive of a key signalling role for H_2S in CO_2 chemoreception, but experimental approaches that confirm increased H_2S production during acute exposures lasting just minutes, sufficient to raise ventilation, would provide superior evidence. Exposure to 7% CO_2 likely provokes alerting responses implicating supra-medullary networks capable of modulating cardiorespiratory outputs beyond the homeostatic control network of the medulla oblongata. It is therefore possible that the magnitude of the H_2S-dependent facilitation of chemoresponsiveness was underestimated in the study by Sabino *et al*. (2021). As such, it would be interesting to explore the influence of raphé CBS inhibition on ventilatory sensitivity to CO_2 across a broad range of gas challenges. Concerns regarding the specificity of AOA as a selective blocker of CBS are addressed by the authors in the article. Studies utilising conditional cell- and site-specific CBS knockout strategies to complement pharmacological approaches used to date would be most informative.

The study by Sabino et al. (2021) provides important insight into the central neuromodulatory mechanisms that shape the ventilatory response to hypercapnia. The fundamental role of gasotransmission in the homeostatic control of breathing is intriguing and evidently not something to be sniffed at!

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COMPETING INTERESTS

None declared.

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