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CROSSTALK

# CrossTalk opposing view: Peripheral and central chemoreceptors have hypoadditive effects on respiratory motor output

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## Introduction

Breathing is all-important for survival, yet key aspects of the control system remain hidden from the gaze of consensus, not least the issue of central and peripheral chemoreceptor interaction. Activation (or inactivation) of either chemoreceptor alone will increase (or decrease) ventilation, but it remains unclear how the activation state of one chemoreceptor modality affects the chemoreflex magnitude of the other (i.e. how inputs interact). Recent investigations consider three possibilities (e.g. Day & Wilson, 2009; Blain *et al.* 2010; Forster & Smith, 2010; Smith *et al.* 2010; Cui *et al.* 2012; Tin *et al.* 2012). Below, we consider four possibilities, three of which implicate some degree of hypoadditive interaction.

## Additive interaction

Most models of respiratory control assume central and peripheral chemoreceptor inputs simply sum (e.g. Heeringa *et al.* 1979). Simple addition is supported by several animal studies (e.g. van Beek *et al.* 1983, Daristotle & Bisgard, 1989) and compelling evidence from characterization of human ventilatory response dynamics that assume a fast (peripheral) and slow (central) component (e.g. Clement *et al.* 1992; St Croix *et al.* 1996; Cui *et al.* 2012). However, conclusions of simple addition must take into account that (a) accuracy of using temporal dynamics to define contribution of chemoreceptors is limited to rapid changes (e.g. slow peripheral chemoreflex responses may be wrongly attributed to the central component), (b) systemic changes in blood gases affect multiple physiological systems beyond direct effects on chemoreceptors (including possible baroreflex-chemoreflex interactions; e.g. McMullan & Pilowsky, 2010) and (c) algebra dictates that simple addition observed in minute ventilation must necessitate a hypoadditive interaction in tidal volume and/or frequency (Mitchell, 1990).

## Hyperadditive interaction

A second possibility is hyperadditive (i.e. multiplicative) interaction, whereby activating (or removing) one chemoreceptor augments (or reduces) the response of the other. An example is provided by the well-established $O_2$–$CO_2$ interaction mediated by the carotid body, which translates to ventilation (e.g. Lahiri & DeLaney, 1975). A strong case for hyperadditive central–peripheral interaction was made recently by elegant experiments in awake dogs by Blain *et al.* (2010). Using a similar preparation to that used in awake goats to show an additive interaction (Daristotle & Bisgard, 1989), a single extracorporeally perfused carotid body (other carotid body denervated) was maintained at different levels of steady-state activation and inactivation, while systemic (assumed central chemoreflex) responses to increases in inspired $P_{CO_2}$ were tested. This stimulus order is reversed to that of intact animals where the peripheral chemoreflex has a faster response than the central, leading to suggestions that presentation order accounts for the observed hyperadditivity (Tin *et al.* 2012). In addition, in order to retrogradely perfuse the carotid sinus region, perfusion pressure was elevated above systemic blood pressure, apparently without arterial baroreflex activation, as systemic blood pressure was unchanged.

This required the authors to argue that any retrogradely perfused blood reaching brainstem and aortic chemoreceptors was negligible. Other concerns, also largely placated by the authors, include (a) having one perfused and one denervated carotid body is functionally different to having two intact carotid bodies (e.g. Fatemian *et al.* 2003) and (b) ventilatory responses to changes in inspired $P_{CO_2}$ may not be solely via direct effects on central chemoreceptors (e.g. McMullan & Pilowsky, 2010).

## Hypoadditive interaction

A third possibility is hypoadditive (i.e. negative) interaction, in which the sum of responses from each chemoreceptor compartment is less than the mathematical sum of independent responses. This is akin to a system with a high degree

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of redundancy, where the power of one chemoreceptor is most apparent when the influence of the other is reduced or eliminated. Redundancy is ubiquitous in biological systems crucial for homeostasis (Poon & Siniaia, 2000; Joyner, 2013).

Using the dual-perfused rat preparation (DPP; Day & Wilson, 2005), we demonstrated a robust hypoadditive interaction between carotid body and brainstem chemoreceptors. Reducing steady-state brainstem $P_{CO_2}$ increased phrenic responses to changes in specific carotid body $P_{O_2}$ or $P_{CO_2}$, and increasing brainstem $P_{CO_2}$ had the opposite effect (Day & Wilson, 2007, 2009).

Unique among preparations used in attempts to resolve the interaction controversy, the DPP allows the environment of the carotid body and brainstem chemoreceptors to be artificially perfused without non-specific ventilatory effects of anaesthetic or gas challenges on systemic circulation, descending influences, vagal input, or other nervous and endocrine effects. To accomplish this, the DPP is decerebrate and vagotomized, two key caveats that compromise sensory and descending inputs (including influence of hypothalamic chemoreceptors; Nattie, 2011), potentially changing the dynamic range of the system. However, data from other groups using conscious and anaesthetized rat preparations corroborate the existence of a hypoadditive interaction with the hallmark of redundancy. Tin *et al.* (2012) report that increasing systemic $CO_2$ blunts hypoxic responses in conscious and anaesthetized rats despite the known hyperadditive $O_2$–$CO_2$ interaction within the carotid body (Tin *et al.* 2012). Similarly, recent data from several groups suggest rat carotid bodies are not involved in systemic $CO_2$ chemosensitivity above eupnoea (da Silva *et al.* 2011; Mouradian *et al.* 2012), yet the fact that carotid body afferents are $CO_2$ sensitive appears unequivocal. Also consistent with a hypoadditive system, and reminiscent of observations of the dog extracorporeally perfused carotid body model (Smith *et al.* 2007), we recently found that increasing carotid body stimulation in the DPP translated to a powerful drive to breath during central hypocapnia (Fiamma *et al.* 2013). When stimulated with hypercapnic hypoxia, peripheral chemoreceptor activation was capable of maintaining phrenic activity even as brainstem $P_{CO_2}$ approached zero (Fiamma *et al.* 2013).

Similar observations have been made in anaesthetized cats (Berkenbosch *et al.* 1984). These observations are difficult to reconcile with a hyperadditive interaction, whereby if activation of one modality is miniscule, the influence of the other modality should also be miniscule.

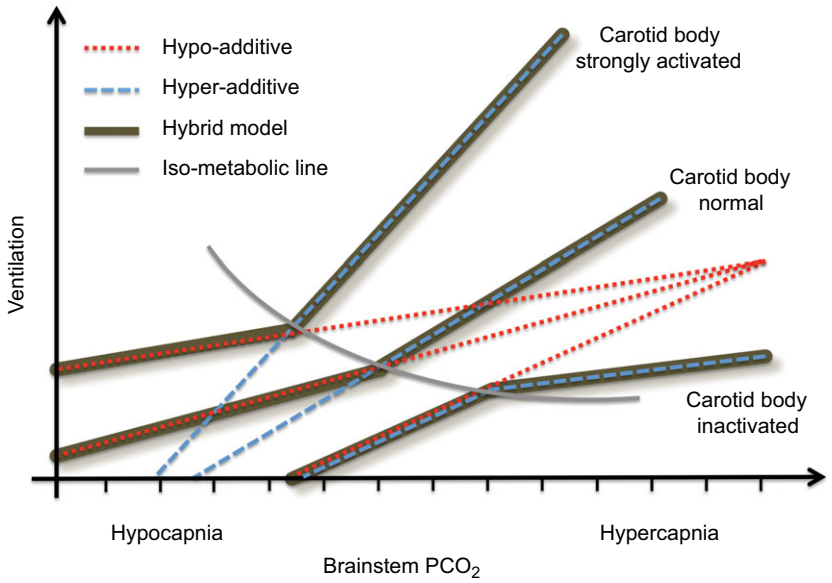


**Figure 1**
Using the dual-perfused rat preparation, we found evidence for a hypoadditive interaction between central and peripheral chemoreceptors, which was most pronounced when the brainstem was hypocapnic (converging red dotted lines; Day & Wilson, 2007, 2009; Fiamma *et al.* 2013). Using the extracorporeally perfused carotid body awake dog preparation, Blain *et al.* (2010) found evidence for a hyperadditive interaction when systemic $P_{CO_2}$ was above eucapnic levels (diverging blue dashed lines). Superimposing these findings (thick dark lines) yields a hybrid system, whereby the breaking point between interaction types is approximately the iso-metabolic line (grey arc). This hybrid model may offer new hope in resolving the interaction controversy.

## Hybrid model

A fourth possible form of interaction is a *hybrid model*, whereby additive, hyperadditive and hypoadditive interactions are all possible, with the form of interaction dependent upon behaviour and/or metabolism. For example, sleep, arousal, temperature, inflammation, exercise, experience and a host of other factors working through autocrine, paracrine and endocrine modulators likely have the ability to differentially affect chemoreflexes and how they are integrated. We note that a hybrid model is consistent with the principle of redundancy and a system that requires a large dynamic range. Thus, below eupnoea when the system is most vulnerable, central and peripheral chemoreceptors might form a redundant system to protect from and respond to apnoea, whereas above eupnoea they may act more synergistically, expanding the overall range of responses in time and magnitude domains to help maintain blood gases during diverse metabolic and behavioural demands (Fig. 1). We suggest this possibility may be a useful paradigm to design and interpret experiments.

## Conclusion

The observed interaction between chemoreceptors may depend upon factors such as species differences, preparation utilized (e.g. afferents intact or removed) and experimental protocol (e.g. order and duration of compartment stimulated). In addition, temporal domains (fast *vs.* slow), chemoreceptor stimulation or inhibition and the fact that physiological responses will have both a threshold and an asymptote (i.e. saturation), may also contribute to the range of observed responses. However, notwithstanding the importance of these considerations when interpreting or planning experimental work, we suspect that the solution to the interaction controversy lies in a hybrid model that

may favour hypoadditive interaction below eupnoea and hyperadditive interaction above eupnoea.

## Call for comments

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