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Homeostasis of exercise hyperpnea and optimal sensorimotor integration: The internal model paradigm

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Abstract

Homeostasis is a basic tenet of biomedicine and an open problem for many physiological control systems. Among them, none has been more extensively studied and intensely debated than the dilemma of exercise hyperpnea – a paradoxical homeostatic increase of respiratory ventilation that is geared to metabolic demands instead of the normal chemoreflex mechanism. Classical control theory has led to a plethora of "feedback/feedforward control" or "set point" hypotheses for homeostatic regulation, yet so far none of them has proved satisfactory in explaining exercise hyperpnea and its interactions with other respiratory inputs. Instead, the available evidence points to a far more sophisticated respiratory controller capable of integrating multiple afferent and efferent signals in adapting the ventilatory pattern toward optimality relative to conflicting homeostatic, energetic and other objectives. This optimality principle parsimoniously mimics exercise hyperpnea, chemoreflex and a host of characteristic respiratory responses to abnormal gas exchange or mechanical loading/unloading in health and in cardiopulmonary diseases – all without resorting to a feedforward "exercise stimulus". Rather, an emergent controller signal encoding the projected metabolic level is predicted by the principle as an exercise-induced 'mental percept' or 'internal model', presumably engendered by associative learning (operant conditioning or classical conditioning) which achieves optimality through continuous identification of, and adaptation to, the causal relationship between respiratory motor output and resultant chemical-mechanical afferent feedbacks. This internal model self-tuning adaptive control paradigm opens a new challenge and exciting opportunity for experimental and theoretical elucidations of the mechanisms of respiratory control – and of homeostatic regulation and sensorimotor integration in general.

Keywords: Control of breathing; Homeostasis; Exercise hyperpnea; Chemoreflex; Optimality principle; Internal model paradigm; Sensorimotor integration; Learning and memory; Ventilatory load compensation

1. Introduction

The mechanism underlying the seeming constancy of arterial P_{CO_2}, P_{O_2} and pH (Pa_{CO_2}, Pa_{O_2}, pHa) from rest to moderate exercise (reviewed in Dempsey et al., 1995; Mateika and Duffin, 1995; Ward, 2000) has been a subject of continuing controversy (Eldridge et al., 2006; Secher et al., 2006; Waldrop et al., 2006). At the heart of the impasse is the enigma of homeostasis (Bernard, 1878–1979; Cannon, 1932), which pervades a host of similar physiological problems (Schmidt-Nielsen, 1994; Keesey and Hirvonen, 1997; Skott, 2003; McKinley and Johnson, 2004; Osborn et al., 2005; Boulant, 2006). At the root of this widespread conundrum is a wholesale and deep-seated reductionist view which predicates a singular, linear and static explanation of all biological phenomena including homeostasis (Ahn et al., 2006a, b). Here, we highlight a preponderance of counter-evidence, which points to an emerging 'internal model' paradigm for respiratory control – and homeostatic regulation and sensorimotor integration in general – that is far more elaborate than conventional wisdom prescribes.

Homeostatic regulation is as much an open physiological problem as an engineering challenge. Designing control algorithms that match up to the 'wisdom of the body' – as evidenced by the precision, robustness, versatility and reliability of brain control – is a holy grail in engineering (Wiener, 1948) and a far cry from the highly oversimplified schemes popularized in the biomedical literature. The internal model paradigm inspired by respiratory control suggests a novel principle of nonlinear

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adaptive control that is potentially applicable to a wide class of intelligent control problems in physiology and engineering.

2. Feedback, feedforward, and set-point models

The dilemma of exercise hyperpnea is that the supposedly homeostatic CO_2 "set point" (Oren et al., 1981) is readily abolished by CO_2 inhalation, which elicits a hypercapnic chemoreflex response instead. Similar set-point theories for other homeostatic systems (Keesey and Hirvonen, 1997; Osborn et al., 2005; Boulant, 2006) have also been variously challenged (Selye, 1973; Cecchini et al., 1981; Harris, 1990; Poon, 1996b; Romanovsky, 2004).

Another explanation of exercise hyperpnea is by postulating some "exercise stimulus" that feeds forward to the chemoreflex feedback loop (Grodins, 1950). Beginning in 1886 (Zuntz and Geppert, 1886) an extensive search for such a stimulus has revolved around three main groups of hypotheses regarding its origin: neurohumoral, somatic neurogenic, and central neurogenic (Dejours, 1964; Wasserman et al., 1986). The first two groups ascribe it to feedback control via specific central or peripheral reflexes. In neurohumoral feedback, respiration is thought to be stimulated by changes in certain exercise-induced blood-borne factors such as CO_2, $[H^+]$, plasma $[K^+]$, lactate, etc. that may activate peripheral or central chemoreceptors or possible venous chemoreceptors. In somatic neurogenic control, putative ergoreceptors or metaboloreceptors sensitive to tension or movement in working muscles, distention of their vasculature, or activity of metabolites therein supposedly may stimulate breathing, perhaps via Group III and IV somatic afferents (Kaufman and Forster, 1996; Haouzi and Chenuel, 2005; Haouzi, 2006). The third group of hypotheses postulates that forebrain signals that command locomotion may also concomitantly drive respiration and circulation in parallel. Such a central "irradiation" mechanism could potentially provide a feedforward stimulus matched to exercise intensity (Krogh and Lindhard, 1913; Henry and Whitehorn, 1959; Fink et al., 1995; Waldrop et al., 1996; Thornton et al., 2001).

It is arguable that some if not all of these feedback or feedforward mechanisms may, in a way, contribute to respiratory control during volitional or simulated exercise under specific experimental conditions. At the same time, there exists an equal litany of counter-arguments which deem none of these candidate mechanisms obligatory for exercise hyperpnea (Mateika and Duffin, 1995; Ward, 2000; Eldridge et al., 2006; Secher et al., 2006; Waldrop et al., 2006; Yu and Poon, 2006) or cardiovascular regulation during exercise (Dampney et al., 2002). The lack of new and definitive insights or methodologies to help propel beyond this intellectual cul-de-sac has left many to wonder: *where do we go from here*? (Forster, 2000).

3. Sensorimotor integration in respiratory control

3.1. Synthesis as a rediscovered roadmap for physiology

The post-genomic renaissance of physiology research enlightens that, where 'naïve reductionism' ends, synthesis begins (Cherniack et al., 2001; Strange, 2005). M. Tenney once exhorted (Remmers, 2005): "The physiologist keeps the whole always in mind. He accepts the tactical necessity of reductionism to understand the parts, but, once done, it is for him only the beginning, never the end. Synthesis is his overriding strategy".

The exercise hyperpnea controversy is reminiscent of an archaic debate a century ago as to whether high P_{CO_2} or low P_{O_2} or pH alone constituted the 'ultimate' chemical stimulus to breathing (Remmers, 2005). Present-day understanding of the latter subject – though often taken for granted – owes much to the synthesis introduced by J.S. Gray in his 1946 'multiple factor theory' (Gray, 1946), which inspired subsequent models of central and peripheral chemoreflex that incorporated the proper integrative (additive or multiplicative) effects of changes in Pa_{CO_2}, Pa_{O_2} and pHa on ventilation (Grodins et al., 1954; Cunningham et al., 1986). Could exercise hyperpnea be explained by a similar synthesis of the variously proposed feedback/feedforward mechanisms alone (Yamamoto, 1980; Mateika and Duffin, 1995)?

3.2. Controller–chemical plant interaction

Feedback/feedforward models of respiratory control are premised on the general belief that the exercise hyperpnea and chemoreflex responses are simply additive and, hence, reducible and superposable (Fig. 1a). This reductionist (non-synthesis) assumption is questionable (Fig. 1b). On the contrary, the available evidence reveals a distinct multiplicative (synergistic) component in the ventilatory response to concomitant exercise and hypercapnia (elevated level of Pa_{CO_2} instead of end-tidal P_{CO_2}) particularly at low $\dot{V}_E$ levels when the effect of mechanical limitation on $\dot{V}_E$ is negligible (Clark et al., 1980; Poon and Greene, 1985; Poon, 1988, 1989b,c; Mitchell and Babb, 2006). Paradoxically, the multiplicative effect is more prominent when Pa_{CO_2} is servo-controlled at a constant elevated level at rest and during exercise (Poon and Greene, 1985; Poon, 1989c) than when the hypercapnia is administered by CO_2 inhalation at a constant elevated airway CO_2 level (Clark et al., 1980; Poon, 1992b); it is also more pronounced when the hypercapnia is caused by rebreathing with an external dead space than by CO_2 inhalation at a constant elevated airway CO_2 level (Ward and Whipp, 1980; Masuyama and Honda, 1984; Poon, 1992b; Sidney and Poon, 1995). Thus the "chemoreflex response" is not dictated by the level of chemical "drive" per se but may involve some dynamic interaction between the respiratory controller and the chemical "drive" and is influenced by respiratory mechanical constraints.

The ventilatory response to chemical or exercise inputs is also potentiated by increases in physiological dead space or shunt. For example, experimentally induced maldistribution of the ventilation–perfusion ratio in awake dogs elicits a compensatory increase in $\dot{V}_E$ restoring normal Pa_{CO_2} and pHa in the steady state (Juratsch et al., 1982). Interestingly, congestive heart failure patients with increased physiological dead space also demonstrate an augmented $\dot{V}_E - \dot{V}_{CO_2}$ slope such that Pa_{CO_2} remains normal from rest to maximal exercise (Wasserman et al., 1997), an effect which cannot be explained by an increase in resting chemoreflex gain per se (Johnson, 2001) but is consistent with