Respiratory Physiology & Neurobiology 201 (2014) 1–6

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Learning to breathe? Feedforward regulation of the inspiratory motor drive

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ARTICLE INFO

Article history:
Accepted 26 May 2014
Available online 25 June 2014

Keywords:
Respiratory learning
Inspiratory drive
Occlusion pressure
Resistive loads
Interoceptive conditioning

ABSTRACT

Claims have been made that breathing is in part controlled by feedforward regulation. In a classical conditioning paradigm, we investigated anticipatory increases in the inspiratory motor drive as measured by inspiratory occlusion pressure (P100). In an acquisition phase, an experimental group ($N = 13$) received a low-intensity resistive load (5 $cmH_2O/l/s$) for three consecutive inspirations as Conditioned Stimulus (CS), preceding a load of a stronger intensity (20 $cmH_2O/l/s$) for three subsequent inspirations as unconditioned stimulus (US). The control group ($N = 11$) received the low-intensity load for six consecutive inspirations. In a post-acquisition phase both groups received the low-intensity load for six consecutive inspirations.

Responses to the CS-load only differed between groups during the first acquisition trials and a strong increase in P100 during the US-loads was observed, which habituated across the experiment. Our results suggest that the disruption caused by adding low to moderate resistive loads to three consecutive inspirations results in a short-lasting anticipatory increase in inspiratory motor drive.

1. Introduction

Behavioral control of breathing refers to the modulation of the breathing pattern that is not primarily related to metabolic requirements. This includes, for example, voluntary changes in breathing patterns such as during speech, and involuntary changes caused by variations in vigilance, emotions and cognitive activity (Gallego et al., 2001). Somjen (1992) proposed that learning mechanisms starting at an early age contribute to behavioral control. In early infancy breathing regulation is mainly controlled by feedback mechanisms in response to environmental or internal changes perturbing breathing, but with repeated perturbations the respiratory system would learn to anticipate and start responding to perturbations before they actually occur. Because of this anticipatory nature, Somjen (1992) used the term "feedforward regulation" to contrast it with feedback-based regulation of metabolic systems (see also Dworkin, 1993).

Anticipatory changes in breathing behavior have been documented for chemical perturbations, but studies on mechanical perturbations are sparse. An instance of the former may be the anticipatory increase in breathing when an increase in metabolism (CO_2 production) as a result of exercise is expected, the so-called "exercise hyperpnoea" (Fink et al., 1995; Mitchell et al., 1990; Tobin et al., 1986; Wood et al., 2003). During exercise, ventilation increases in proportion to O_2 consumption and CO_2 production, thus allowing a stabilization of blood gases. However, Wood et al. (2003) documented a decrease in PCO_2 starting already at onset of exercise, showing that the immediate respiratory response to exercise is not triggered by chemoreceptor feedback. Apparently, because of the narrow regulation of blood gas levels (Shea, 1997), a feedforward regulation mechanism triggers an adaptive ventilatory response by anticipation of a forthcoming increase in PCO_2. This view is further confirmed by studies on imagined exercise or activated emotions, in which an augmented ventilation is observed without any associated movement or increase metabolism (Gallego et al., 1996; Van Diest et al., 2001).

The development of anticipatory control of breathing can easily be understood from an associative learning framework, or, classical conditioning. During conditioning, a neutral stimulus (CS, conditioned stimulus) becomes associated with a motivationally relevant stimulus (US, unconditioned stimulus), which elicits an unconditional response (UR). As a result, the CS acquires predictive value for the occurrence of the US and starts to elicit a conditioned response that is similar to the unconditioned response. For example, perturbations in arterial blood gases can be viewed as unconditioned stimuli (US) and internal or external stimuli entailing a predictive value for such perturbations would function as

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http://dx.doi.org/10.1016/j.resp.2014.05.009
1569-9048/

conditioned stimuli (CS). Particularly interoceptive conditioning (IC) has been proposed as an important regulatory mechanism through which the body can anticipate and adapt to upcoming dysregulations (Dworkin and Dworkin, 1995). Interoceptive conditioning occurs when a sensation from within the body (CS) becomes a predictor of a significant disturbance (US). IC has been studied mainly in the context of drug tolerance and addiction (Sokolowska et al., 2002; Ramsay and Woods, 1997), of eating behavior and blood glucose regulation (Epstein et al., 2009; Dworkin, 1993; Woods and Ramsay, 2000) and in the context of blood pressure regulation (Dworkin and Dworkin, 1995; Razran, 1961, 2002). To date, no studies have investigated the potential role that conditioning to interoceptive cues may play in the regulation of breathing behavior.

A few studies have investigated respiratory conditioning to *external* cues, however. For example, Nsegbe et al. (1998) paired an odor (CS) with a hypoxic stimulus in rats. Their data show that the odor-CS, when presented alone in a subsequent test phase, elicited a conditioned increase in ventilation. In previous research, we have established a laboratory paradigm to study conditioning of human respiratory behavior in response to exteroceptive stimuli in humans. Predictable dysregulations of arterial pressure of CO_2 were established with a Pavlovian conditioning procedure in which inhalation of 7.5% or 20% CO_2 was used as the US (e.g., Fannes et al., 2008; Van den Bergh et al., 1995, 1997), reflexively triggering an increase in ventilation. When such increase in PCO_2 was preceded by an odor or a tone (CS), participants learned to increase their ventilation in response to the tone or the odor, that is, *in anticipation* to the metabolic dysregulation caused by inhaling CO_2. However, the observed effects were small and not consistent across studies, probably because of several methodological difficulties inherent to the use of CO_2-inhalation in a conditioning paradigm, such as the US qualities being dependent on the participants breathing behavior, the relatively slow rise of the aversive sensation and the long duration to wash out the increased PCO_2 levels after each trial.

In contrast with inhalation of CO_2-enriched air, mechanical disruptions as induced by adding resistive loads to the external breathing circuit may offer interesting opportunities to investigate learned breathing control in a more controlled way. Resistive loads have been used repeatedly as a respiratory challenge (Milic-Emili and Zin, 1986), can be easily detected (Bloch-Salisbury and Harver, 1994; Davenport et al., 1986), and have a discrete on- and offset that can be tightly controlled in the laboratory. Resistive load breathing actually feels like one were to breathe through a straw. Adding them to an external breathing circuitry resembles a naturally occurring phenomenon, i.e., instances where our respiratory system must cope with obstructions and try to keep the airways open. The adaptive ventilatory response/reflex in response to inspiratory resistive loads is to augment the respiratory drive (UR) (Altose et al., 1976; Im Hof et al., 1986; Lopata et al., 1977; Poon, 1989). The dynamic response to loads is much faster than for CO_2-challenges: Altose et al. (1979) have reported an increase in respiratory drive from the second loaded breath onwards.

The central respiratory drive is the integrated output from the central nervous system (CNS) to the respiratory pump muscles, also called the summed motor output of the respiratory centers. A respiratory parameter generally used to measure the respiratory drive is P100 (Van Diest et al., 2008; Whitelaw and Derenne, 1993). P100 is the inspiratory occlusion pressure generated 100 ms after the onset of an inspiratory effort against a closed airway. P100 is the decrease in mouth pressure assumed to reflect the intra-thoracic negative pressure generated by the respiratory muscles. As mentioned previously, it reflects 'direct' cortical input to the respiratory controller. The more traditional respiratory parameters, like inspiratory volume or minute ventilation are influenced by mechanical factors involved in the transformation of respiratory motor neuron output into ventilation, such as airway resistance or elasticity of lungs and thorax (Whitelaw and Derenne, 1993). As the impedance of the system is changed, they no longer can be used to evaluate the output of the controller (Whitelaw and Derenne, 1993).

Mechanical perturbations such as breathing loads and occlusions were successfully introduced as CS or US in fear learning paradigms (Pappens et al., 2011, 2012a). In two experiments, Pappens et al. (2013) compared an interoceptive CS (non-aversive resistive load) with an exteroceptive CS (neutral picture) in a fear learning paradigm with an aversive, strong resistive load as the US. They found fear conditioned changes in volume-related breathing parameters. However, these effects were small and potentially confounded by the fear response itself, as fear typically augments ventilatory output. Whether anticipatory changes in breathing pattern for mechanical perturbations can be established also in a non-fearful context remains unexplored. Interestingly, recent evidence in animals has shown that anticipatory alterations (inspiratory-related phrenic nerve activity) can be established by repeated vagal stimulation or lung inflation in perfused brainstem preparations (Dutschmann et al., 2009), suggesting that anticipatory changes in the breathing pattern can occur without activation of higher brain structures involved in fear (learning).

The present study aimed to explore whether interoceptive conditioning of inspiratory motor drive could be established throughout the contingent pairing of a small inspiratory load with a stronger inspiratory load. To this end, during a learning phase (acquisition) three breaths loaded with a low intensity load preceded three breaths with a stronger intensity load in the experimental group while in a control group six breaths loaded with a low intensity load were presented. In a post-learning (post-acquisition) phase both groups received six breaths loaded with the low intensity load. We expected that participants in the experimental group would learn to anticipatorily adapt to the strong load by increasing their inspiratory motor drive to the low-intensity load during the learning phase and that this anticipatory response would wane during the post-learning phase.

2. Method

2.1. Participants

Thirty-three healthy participants (7 men and 26 women, mean age 18.7, range 18–21 years) volunteered to participate. Twenty-six participants were undergraduate students who participated in return for course credit. Seven other volunteers responded to local advertisements and were paid 10 €. A brief, custom-made health survey was administered to exclude participants when suffering from asthma or other respiratory diseases, cardiac diseases, epilepsy, anxiety disorders, and the use of medications that might suggest the presence of these conditions. No participants were positive on any of these. After exclusion due to technical problems ($N = 6$) or excessive variability in the P100 data ($N = 3$), the experimental and control group consisted of 13 and 11 participants, respectively. Each participant provided an informed consent. The experiment was approved by the ethical committees of the Faculty of Psychology and Educational Sciences and of the Faculty of Medical Sciences.

2.2. Materials

2.2.1. Subjective measures

Prior to the conditioning procedure, participants completed the Dutch version of the Claustrophobia Scale (Rachman and Taylor, 1993; Van Diest et al., 2010) to measure fear of suffocation. This was done because previous work has suggested that interindividual