ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY

Volume 551

POST-GENOMIC PERSPECTIVES IN MODELING AND CONTROL OF BREATHING

Edited by Jean Champagnat, Monique Denavit-Saubié, Gilles Fortin, Arthur S. Foutz, and Muriel Thoby-Brisson

Post-Genomic Perspectives in Modeling and Control of Breathing

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Preface

Since 1978, meetings of the Oxford Conference on Modeling and Control of Breathing are composed primarily of voluntary contributions from respiratory physiologists and modelers in order to promote interactions between these two domains and to stimulate interests of young researchers in modeling and physiological research in general. The first Oxford Conference was in September 1978 at the University Laboratory of Physiology in Oxford by the late Dr. D.J.C. Cunningham (Oxford), R. Hercynski (Warsaw) and others, who saw a need to bring physiologists and mathematicians together in order to address the critical issues in understanding the control of breathing. Four years later, a group at UCLA including respiratory/exercise physiologists, anesthesiologists and system engineers led by Drs. B.J. Whipp, S.A. Ward, J.W. Bellville and D.M. Wiberg organized a sequel meeting at Lake Arrowhead, California, USA, which proved to be as much a success as the first one. The next Conference was the first to be hosted in France: it was held in Solignac in 1985 and was organized by G. Benchetrit, P. Baconnier and J. Demongeot, from the University of Grenoble. Since then, the Oxford Conference has been continued every 3 years in the USA, Japan, U.K. and Canada with the most recent event in 2000 held at North Falmouth (Cape Cod, Massachusetts, USA) and co-chaired by Chi-Sang Poon (MIT) and H. Kazemi (Harvard).

This volume is dedicated to the memory of our colleague and member of the International Oxford Committee, Yoshiyuki Honda, MD, PhD, from the Department of Physiology at Chiba University School of Medicine (Chiba, Japan). Dr. Y. Honda passed away of acute heart failure on August 1st 2003, a little more than one month before the opening of the 9th Conference in Paris. This was just after he finished three of the seven days of an experiment on dyspnea induced by combination of hypercapnea and hypoxia with several co-workers. One could say that he fell in the battle which he had pursued to the very end of his 77 years. Dr. Yoshiyuki Honda was not only the scientist we know, working on many aspects of physiology, and particularly on the impact of life at high altitude, was also the organizer of the unforgettable 1991 Conference, at the foot of majestic Mont Fuji, the first of the series to be officially titled "Oxford Conference". We, his colleagues, express our deepest sympathy to his family and friends. The first section of this volume is specially dedicated to his memory. This section includes his chapter on ventilatory vs. respiratory sensation responses together with a tribute to Yoshiyuki Honda by John W. Severinghaus, and chapters on the breathing behaviour in humans. The second section of the volume is on central and peripheral chemoreceptive responses, to recognize the first *in vitro* studies identifying cells responsive to acidic perfusates in medullary slices (Fukuda, Y. & Honda, Y. pH-sensitive cells at ventro-lateral surface of rat medulla oblongata, Nature, 1975, 256: 317–318).

Close to the historical center of Paris, the 9th Oxford Conference presented a superb forum for formal and informal discussions. More than 140 participants from 16 countries attended this conference. The scientific program was comprised both of oral and poster

contributions. The hundred presented papers covered a wide spectrum of modeling and experimental studies of respiratory control ranging from genetics and ion channels to respiratory disease and respiratory perception. One of the highlights of the meeting was a research competition for pre- and post-doctoral trainees, in which four finalists made oral presentations in a dedicated session of the conference: Kevin J. Cummings from Calgary (Canada), Efstratios Kosmidis from Yale (USA), Philip N Ainslie from Calgary and Laura Guimarães from Porto (Portugal) who was congratulated by the International Organizing Committee for the best trainee presentation. The Committee stressed the difficulty of selecting these finalists in view of the high scientific quality demonstrated by all other trainee participants, whose work fill many chapters of this volume. At the business meeting of the Conference, the International Committee also decided on the venue of the next Oxford Conference which is to be organized by Marc Poulin from Calgary (Canada). We believe the long history of the Conference series and its past accomplishments will ensure its continued success in the upcoming meeting. We are very grateful to every participant who contributed scientifically and constructively to the fruitful discussions and congenial atmosphere of the Paris Conference.

The Editors

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77 Massachusetts Avenue
Cambridge, MA 02139, USA

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Contents

1. VIEWS ON THE HUMAN BREATHING BEHAVIOR; MEMORIES OF Y. HONDA

2. MECHANISMS OF CENTRAL AND CAROTID BODIES CHEMORECEPTION

5. RESPIRATORY ACTIVITY DURING SLEEP AND ANESTHESIA

6. CARDIO-RESPIRATORY REGULATIONS AND CEREBRAL BLOOD FLOW

7. VENTILATORY RESPONSE TO EXERCISE

8. VARIABILITY AND PLASTICITY OF BREATHING

9. CONCLUSIONS AND PERSPECTIVES

1

Views on the Human Breathing Behavior

Memories of Yoshiyuki Honda

Different Profile in Ventilatory vs. Respiratory Sensation Responses to CO_2 with Varying Po_2

Atsuko Masuda, Yoshikazu Sakakibara, Toshio Kobayashi, Michiko Tanaka and Yoshiyuki Honda

1. Introduction

Recently, we[1] reported that the slope of the respiratory sensation response curve to CO_2 assessed by visual analog scale (VAS), exhibited a parallel leftward shift when combined with hypoxic stimulation. However, further analysis additionally elucidated the presence of significant upward shift of this VAS response curve in the same experimental condition. On the other hand, the CO_2-ventilation response curve increased its slope with increasing hypoxic stimulation, and the extrapolated response lines converged at the horizontal axis known as the so-called Oxford fan[2]. These contrasting change between ventilatory vs. VAS response curves led us to certain speculations and assumptions about the different control mechanisms and anatomical regions possibly responsible for our experimental findings.

2. Methods

Details of the experimental design and procedure were described in the preceding publication[1]. Briefly, 29 healthy young college students (11 males and 18 females) participated in the study. Their age, height and weight were 23 $\pm$ 5 yrs, 162.1 $\pm$ 9.0 cm and 54.2 $\pm$ 8.6 kg (mean $\pm$ SD), respectively. All subjects gave their informed consent before the experiment, and the study protocol was approved by the local ethics committee. The subjects were exposed to progressive hypercapnia by modified Read's rebreathing method using four different gas mixtures: A. 7% CO_2 + 93% O_2 or hyperoxia run, B. 7% CO_2 + 19% O_2 for normoxia run, C. 7% CO_2 + 13% O_2 for mild hypoxia run and D. 7% CO_2 +

Atsuko Masuda • Tokyo Med & Dent Univ, Tokyo, 113-8519, Japan. **Yoshikazu Sakakibara** • Kanazawa Inst Technol, Kanazawa. **Toshio Kobayashi** • Hiroshima Univ, Hiroshima. **Michiko Tanaka** • Miyazaki Pref Nurs Univ, Miyazaki. **Yoshiyuki Honda** • Chiba Univ, Chiba.

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11% O_2 for moderate hypoxia run. Amounts of 6–8 L of the above gas mixtures were put into a rubber bag and used for the rebreathing test. During rebreathing, by introducing a small amount of O_2 or N_2 gas to the inspiratory portion of the respiratory valve, the P_{ETO_2} level was consecutively adjusted to >300, 100, 80 and 60 Torr in the A, B, C and D runs, respectively. To avoid psychological intervention, a paper screen was placed between the subject and the experimenter. The magnitude of VAS was continuously recorded in a range of 0 to 10 degrees. Breath-by-breath V_T and P_{O_2} and P_{CO_2} signals in the airway gas were also detected and recorded by using a hot wire flowmeter (Minato, RF-H, Osaka, Japan) and a rapid response O_2 and CO_2 analyzer (NEC-Sanei, 1H21, Tokyo, Japan). Minute ventilation (V_E) was calculated from V_T and respiratory frequency (f) and normalized body surface area. Arterial O_2 saturation (S_{PO_2}) was continuously recorded by pulse oximeter (Ohmeda, BIOX·, USA). For each subject, four runs were randomly performed twice on the same day, once in the morning and once in the afternoon. Hypercapnic ventilatory and VAS response curves were obtained by linear regression analysis between P_{ETCO_2} and normalized minute volume or VAS, respectively.

3. Results

Figure 1 shows examples of CO_2-ventilation and CO_2-VAS responses. The CO_2-V_E response curve became steeper as the oxygen level decreased (left), the VAS response curves are not only shift in parallel to the left with increasing hypoxic stimulation (right). Figure 2 presents the averaged mean P_{ETCO_2}-V_E (left) and $PETCO_2$-VAS (right) response curves of all 29 subjects. The slopes of the ventilatory response curves were augmented by advancing hypoxia and the extrapolated response lines converged at the horizontal axis. On the other hand, the VAS response curve shifted to the left in parallel and simultaneously moved upward with intensifying hypoxia.

4. Discussion

The major finding in this study is the different profile in ventilatory vs. respiratory sensation responses to progressive hypercapnia with varying P_{O_2}. The former exhibited

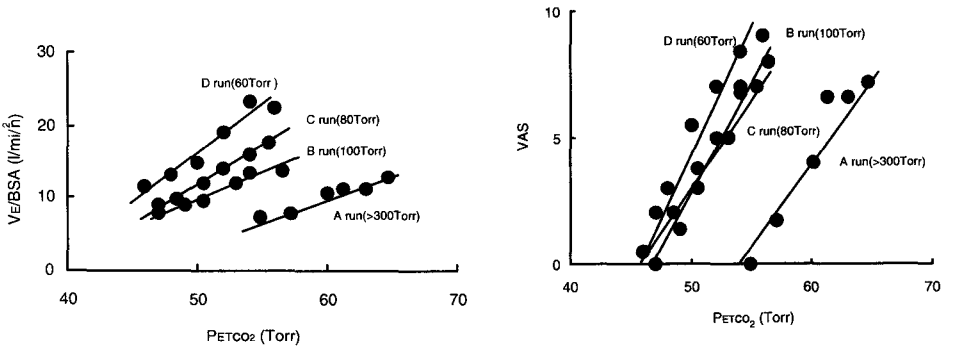

Figure 1. CO_2-ventilatory (left) and CO_2-VAS (right) responses obtained in one subject.

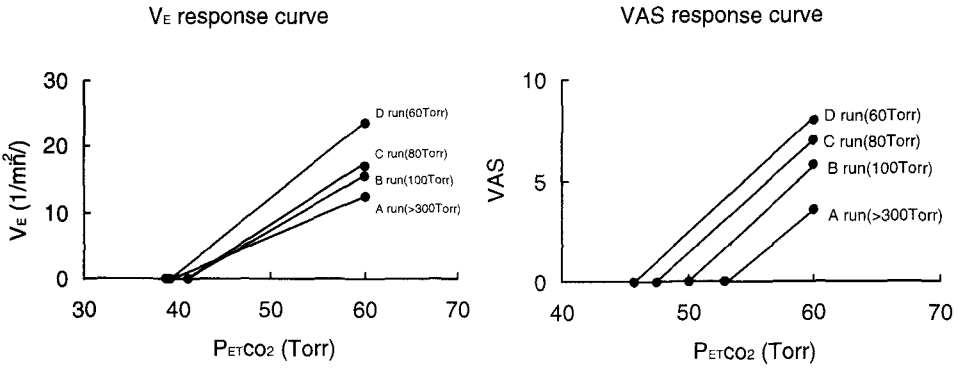

Figure 2. Average ventilatory and VAS responses of all subjects (n = 29).

increased response slopes, with extrapolated response lines converging at the horizontal axis. On the other hand, the latter showed parallel left and upward shifts with increasing hypoxic stimulation. We could verify that there was positive interaction between CO_2 and hypoxic stimulation in ventilatory response. Such strong positive interaction was not only seen in ventilatory response, but was also found in the discharges of the carotid body located in the brainstem[3]. On the other hand, no such positive interaction was detected in the present VAS response.

Ventilatory response is assumed to be mainly elicited by augmented peripheral as well as central chemoreceptor activities in the brainstem respiratory control system, but the VAS response likely originated from a somewhat different mechanism.

Figure 3 describes the possible implication of our results in schematic form. We speculate that the main respiratory sensation is produced in the sensory cortex as a response to the activated behavioral respiratory control system consisting of such emotion and behavior related systems as the limbic system. From the profile of the P_{ETCO_2}-VAS response

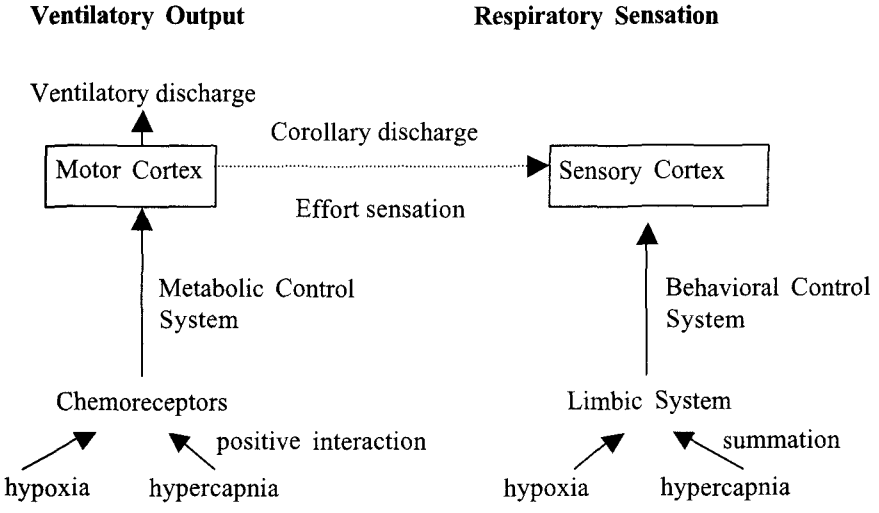

Figure 3. Possible implication derived from our experiment.

curve, we propose that respiratory sensation may have been induced additively by hypoxic and hypercapnic stimulation. Corollary discharge[4], which conveys the sense of ventilatory effort from the motor cortex, may have played a subsidiary role in our experiments. On the other hand, we surmise that stimulation of hypoxia and/or hypercapnia not only strongly drives ventilation by augmenting peripheral and/or central chemoreceptor activities[2], but also specifically arouses suprapontine CNS structures including the limbic system, thus eliciting additional VAS elevation.

A number of studies have indicated that the suprapontine brain structures elicit weak ventilatory, but appreciable behavioral response to hypoxic and/or hypercapnic stimulations. Horn and Waldrop[5] described in their review that they found studies from the early 90's that reported the presence of specific CO_2 and hypoxia-sensitive neural discharges in the caudal hypothalamus, both in vitro and in vivo. Chen et al.[6] reported in unanesthetized cats in 1991 that respiratory-associated rhythmic firing found in the mesencephalon, which is vulnerable to light anesthesia and is synchronous with EEG activities, was presumed to convey the dyspnea sensation. Corfield et al.[7] observed in awake humans in 1995 that in response to CO_2-stimulated breathing, dyspnea and regional brain blood flow in the limbic system were proportionally augmented. They used positron emission tomography (PET) to detect increased regional brain blood flows in their study, considering to indicate augmented local neural activities. More recently, similar PET studies observing CO_2 loading were also conducted by Brannan et al.[8]. They found not only activation, but also deactivation in some restricted areas. Since we found different VAS response feature when hypoxia was combined with hypercapnia, further exploration using PET deserves to be conducted. Furthermore, Curran et al.[9] recently demonstrated moderate tachpneic hyperventilation in unanesthetized dogs, in which the carotid body was maintained as normocapnic, normoxic and normohydric by separate extracorporeal perfusion and by specifically induced CNS hypoxia. They considered that this indicated the presence of hypoxia-sensitive respiratory-related neurons in the CNS, i.e., outside of the brainstem chemosensitive-ventilatory control system.

All these findings may support our speculation that VAS-related respiratory activity is present in the behavioral respiratory control system described above.

In conclusion, the contrasting profile between ventilatory vs. VAS responses to progressive hypercapnia with varying P_{O_2} led us to speculate that the behavioral respiratory control system may substantially contribute to the development of additional respiratory sensation in the sensory cortex.

Acknowledgments

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Amygdala and Emotional Breathing in Humans

Yuri Masaoka and Ikuo Homma

1. Introduction

According to many reports the amygdala plays a role in fear, attention and anxiety[1]. In addition to these emotional roles, the amygdala which is involved in the conditioning process projects to many anatomical areas to elicit physiological responses such as blood pressure elevation, skin conductance response and respiration as well as behavioral responses such as freezing and facial expression of fear. In an awake state, the amygadala evaluates a variety of environmental stimuli to determine whether the stimulation is harmful or safe; if it is harmful, the amygdala immediately elicits emotions of fear and anxiety simultaneously with physiological changes. In other words, measuring physiological responses could be an index to determine the level of emotion occurred in a situation.

Respiratory psychophysiology studies have reported that respiratory patterns are affected by fear and anxiety in humans[2]. The brainstem regulates respiration to adjust for a metabolic requirement but final respiratory output appears to be from interactions between maintaining homeostasis and input from many types of sensory information and emotions from the higher cortical and limbic structures. In animal studies, there have been reports on electrical stimulation of the amygdala which altered respiratory pattern[3]. Investigation of the relationship between respiratory output and the amygdala in humans is limited, but in this chapter we reports our studies investigating anticipatory anxiety in normal subjects and in two patients with epilepsy who had lesions of the left amygdala. We also give direct evidence concerning the effect of electrical stimulation of the amygdala on the total respiratory time, inspiratory time and expiratory time in a patient with epilepsy.

1.1. Measuring Respiratory Patterns and Metabolism in Anticipatory Anxiety

Our previous research on personality differences in breathing patterns during mental stress and physical load found that levels of individual anxiety affect respiratory frequency[4].

Yuri Masaoka and Ikuo Homma • Department of Physiology II, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, Japan, 142-8555.

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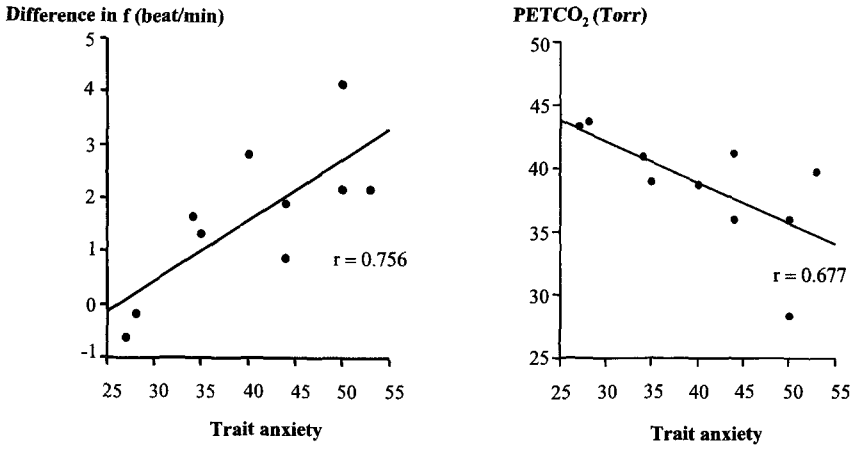

Figure 1. Relation between fR and trait anxiety scores (left), and between $PETCO_2$ and trait anxiety scores (right).

From this study we hypothesized that an increase of respiratory frequency might not be caused by metabolic changes but by input from higher centers related to anxiety. In a laboratory situation, anticipatory anxiety was produced in subjects while measuring V_E, V_T, fR, T_I, T_E and $PETCO_2$[5]. The subjects were informed that electrical stimulation attached to the forefinger would be delivered within two minutes after the onset of a warning light. "Anticipatory anxiety" was defined as the time between warning onset and stimulation. This increase of respiratory frequency correlated with trait anxiety scores, and $PETCO_2$ had a negative correlation with trait anxiety scores (Figure 1). There was no difference in VO_2 and VCO_2. The trait anxiety scores are used to evaluate how people generally feel, asking their tendency in various situations. Large increases of respiratory frequency in high trait anxiety subjects means that trait anxiety influences behavioral breathing independently from metabolic demands. What area is related to anxiety? That question prompted us to look into the amygdala.

1.2. EEG Dipole Tracing in Anticipatory Anxiety

Recent research on emotions has been investigated by neuro-psychologists using PET and fMRI. Among these methods, we have developed the EEG dipole method (DT) utilizing a realistic scalp-skull-brain head model (BS-navi, Brain research and Development, Japan)[6]. BS-navi is a method for estimating the source of brain activity from potentials recorded by electroencephalogram (EEG). The method has been used to evaluate patients with epilepsy showing the foci of the epileptic spike measured by deep electrodes corresponding to foci estimated by SSB/DT[7]. One feature of this method is that it can determine the source of the brain from averaged potentials which are triggered by physiological responses. Our hypothesis was that if the subjective feeling of anxiety enhances the respiratory rate, electric current sources synchronized with this onset of inspiration could be found somewhere in the limbic areas. During anticipatory anxiety, significant increases in anxiety state and respiratory rate were observed. The onset of inspiration during increased respiratory frequency was used as a trigger for averaging EEG. From 350 ms to 400 ms after the onset of inspiration,

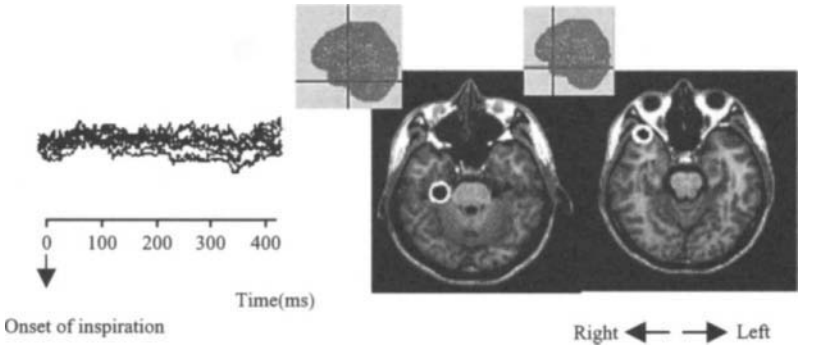

Figure 2. Respiratory-related Anxiety Potential (RAP) (right) and dipole location during RAP (left).

a positive wave was observed in the averaged potentials. This positive wave is referred to as "respiratory-related anxiety potentials" (RAP) (Figure 2 left)[8]. SSB/DT estimated the location of the sources from RAP which were found in the right temporal pole, and in the right temporal pole and the left amygdala in the most anxious subjects (Figure 2 right).

Anticipatory anxiety has been tested in patients with epilepsy who had a lesion of the left amygdala. The left amygdala lesion decreased state anxiety, respiratory frequency, skin conductance response during anticipatory anxiety, as well as trait anxiety [9].

In this chapter we give direct evidence of electrical stimulation on the left amygdala in patient who had deep electrodes installed to evaluate the location of the epileptic spike. All of the experiments reported here were approved by the Ethical Committee of Showa University School of Medicine and Tokyo Women's University.

2. Method

A patient (female, aged 26) had experienced epileptic seizures for more than ten years and had been diagnosed as having typical temporal seizures. Focus of the epileptic spike was located in the left amygdala confirmed with a intracerebral depth electrodes composed of six contact points, four electrodes from the tip placed in the amygdala had a 5 mm interval and the other two had a 10 mm interval (Figure 3) (Unique Medical Co., LTD). The location of

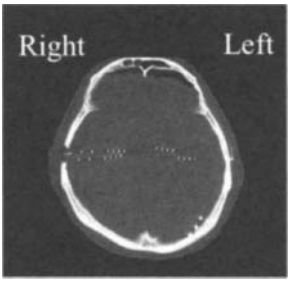

Figure 3. CT image with depth electrodes from a patient with epilepsy.

the focus also confirmed with an estimation of the SSB/DT[7]. Epileptic patients are routinely tested to determine the location of the focus of the spike by electrical stimulation on the amygdala and by asking the patient whether or not this stimulation causes a feeling which is similar to that before an epileptic seizure. The stimulation was delivered through the depth electrode by a cortical stimulator (Ojemann, Radionics). Stimulation of 0.5 mmA was delivered for 60s. During the stimulation on the left amygdala, chest and abdominal movements were measured with a respiratory induction plethymography using Respitrace transducer (Amburatory Monitoring) and volume was measured by a transducer connected to a flow meter (Minato Medical). Data was stored on a digital recorder (PC208AX, Sony) and analyzed with a PowerLab (ADInstruments).

3. Results

Figure 4 (top) shows Ttot, TI and TE during baseline, 0.5 mA of stimulation and 1 mA of stimulation. Rib and abdominal movements, and volume during the 0.5 mA of stimulation on the left amygdala are shown in Figure 4 (bottom).

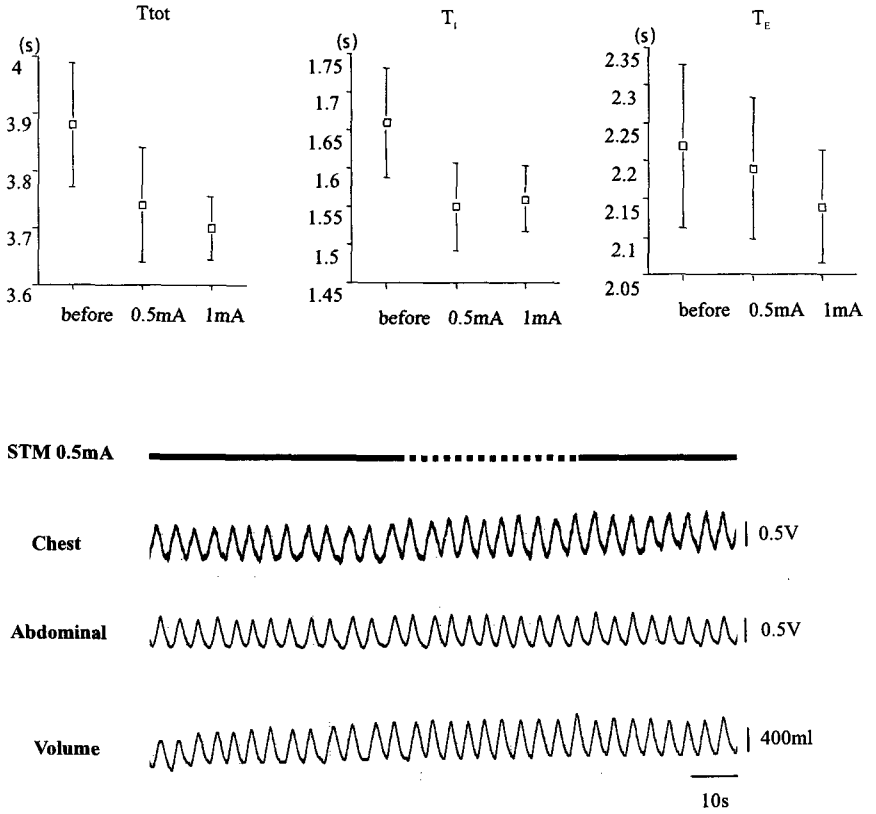

Figure 4. Ttot, TI and TE during baseline, 0.5 mA of stimulation and 1mA of stimulation (top). Chest and abdominal movements and volume during stimulation of the left amygdala (bottom).

4. Discussion

In this chapter, we have focused on the role of the amygdala during anxiety and anxiety related respiratory changes in humans. A number of investigators have studied neuroanatomical correlates of anxiety using various modality in humans[10]. In animals, many reports show the effect of the electrical stimulation of the amygdala on respiratory timing. These studies prove that the amygdala has a role for fear and anxiety, and the physiological outputs related to these emotions. From these studies and our data, our interest focuses on three questions. The first two are related to the behavioral aspect. What does an increase in respiratoy frequency during anxiety mean, and is this tendency determined by individual trait? These respiratory timing changes were dominantly affected by anxiety more than by metabolism regulation. As we mentioned, the amygdala has a role for fear conditioning. The amygdala immediately evaluates the outer stimulation and produces various physiological changes to protect ourselves. In respiration, conditioning was observed in ventilatory responses to auditory stimuli after pairing with hypoxic stimulus[11] and in an anticipatory of physical exercise[12], and these responses involved respiratory feed forward mechanism. However, it is unknown whether the conditioning process is determined by individual trait or whether the personality trait dominantly affect respiratory frequency before conditioning.

Second, if activity of the amygdala elicits frequency changes in respiration, what is the relationship between the amygdala and other respiratory related areas? One study found that the central nucleus of the amygdala (ACE) contributes to excitation of the inspiratory cycle, possibly through the projection to the parabrachial nucleus; this study also demonstrated that the respiratory entrainment to ACE stimulation occurs during the alert state[13]. The lateral part of the ACE projects to the medial part of the central nucleus, restricted parts of the bed nucleus of the stria terminals, and the parabrachial nucleus in the pons[14]. From these studies it is reasonable to assume that the respiratory outputs modulated by either direct electrical stimulation or emotional stimulation of the amygdala is conducted through the route of the amygdala-parabrachial nucleus.

In this chapter, we report the results from only one case of amygdala stimulation on respiration; however, emotional breathing mediated from the amygdala might be related to the movement of the chest rather than the abdomen which would explain the tightness of the chest when one feels anxiety.

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Immediate Effects of Bilateral Carotid Body Resection on Total Respiratory Resistance and Compliance in Humans

Benjamin Winter and Brian J. Whipp

1. Introduction

In 1962, Nadel and Widdicombe[1] conclusively demonstrated a reflex increase in airways resistance (Raw) in response to carotid body stimulation in the dog. This effect could be eliminated by blocking either the glossopharyngeal or vagus nerves, i.e. the afferent or efferent limbs of the reflex respectively. That the peripheral chemoreceptors not only act reflexly on respiration but also cause reflex bronchoconstriction was also stressed by Widdicombe[2] in his review of "Chemoreceptor Control of the Airways." This is among the reasons often cited as a basis for potential benefits that might accrue from bilateral carotid body resection (BCBR) in patients with severe chronic obstructive pulmonary disease (COPD).[3]

However, there is no convincing evidence that this reflex is actually operative in humans and, even were it to be so, whether it is sufficiently potent to change Raw in the face of the numerous other factors which lead to airflow impairment in such patients. What evidence is available, however, suggests that this might be the case. For example, Vermeire et al.[4] have demonstrated that Raw (determined plethysmographically) was reduced significantly in a group of COPD patients following BCBR (although this was not apparent in their flow-volume analysis). In addition, Whipp and Ward[5] reported a small but significant increase in forced expiratory volume in 1 second (FEV_1) after BCBR, without an increase in total lung capacity (TLC), in a group of 146 patients with severe COPD, confirming the previous report of Winter.[6] Although such results are suggestive of improved Raw as a result of BCBR, they are not conclusive evidence because of other secondary factors that could influence Raw, such as altered blood and alveolar gas tensions[7] and increased mucus expectoration.[6]

Benjamin Winter • (deceased), Garfield Hospital, Monterey Park, California, 91754. **Brian J. Whipp** • Department of Physiology, St George's Hospital Medical School, London SW17 0RE, U.K.

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