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Review

Abraham Guz memorial: Still unresolved hypotheses: Lung reflexes and perceptions of breathing

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ABSTRACT

This article constitutes a review of the studies performed by the group of the late A. Guz and other authors on the subjects of lung reflexes and perceptions of respiration. The experimental data suggest that the lung inflation and deflation reflexes are present in man, mediated by large myelinated afferent nerve fibres in the vagus nerves, but that the inflation reflex is weaker than in animals, possibly due to central neuronal inhibition. The authors of animal results on the deflation reflex differ as to the afferent fibres involved in the vagi, but it is argued, on the basis of the data, that the preferred hypothesis is that increased activity of the large myelinated mediates the inflation reflex, and decreased activity in these same fibres mediates the deflation reflex. Smaller myelinated fibres are thought to mediate cough and increased breathing in response to airway irritation, while small non-myelinated C fibres mediate hyperpnoea in response to parenchymal congestion and various disease states. The unpleasant sensation at the break point of breath-holding is not chemically mediated but may depend on a complex response involving vagal afferent, phrenic efferent and phrenic afferent pathways. Other experiments in humans on perception of various unpleasant respiratory sensations are discussed with unclear conclusions.

1. Introduction

The death in the Spring of 2014 of Prof Abraham Guz was followed by a memorial meeting at Hodgkin Huxley House, under the kind auspices of the Physiological Society, on the fifth November 2014. Very little was said at the meeting of the early work on lung reflexes of Prof Guz, performed in London between 1960 and 1974. These studies deserve to be better known. His papers in the Journal of Physiology can be accessed electronically, but not the publications in other journals, e.g., Clinical Science. In the present article I review these early studies of two aspects of the work: lung reflexes and perceptions of breathing. In addition, I review the participation of these studies in the development of the two subjects since that time.

Guz was a respiratory physician who frequently observed the great distress in patients with dyspnoea – breathlessness – gasping for breath. He wanted to understand the mechanisms which mediated this very unpleasant sensation. As the lungs are innervated by the vagus nerves, i.e., the Xth cranial nerve, it was natural to be interested in what afferent fibres in these nerves enter the brain stem and in the central connections giving rise to reflex effects and cerebral perceptions.

2. Lung reflexes involving the vagus nerves in the afferent limb

2.1. The inflation and lung CO_2 reflexes

The most studied afferent pathways in the vagus nerves arise from three main receptors. There are (1) lung stretch receptors connected to large diameter myelinated nerve fibres (2) cough and irritant receptors in the airways connected to small myelinated fibres, and (3) receptors near the lung capillaries (juxtamedullary or J receptors) connected to small non-myelinated fibres.

In 1960, it was well known, from the work of Hering (1868) and Breuer (1868, 1970) in animals, that lung inflation i.e., stimulation of lung stretch receptors, inhibited breathing, while deflation of the lungs produced increased breathing. Also Head (1889a,b) described a paradoxical reflex in which some inflations stimulated gasping rather than apnoea. These results were confirmed (Larrabee

Abbreviations: PCO_2, the partial pressure of carbon dioxide (CO_2); $P_{ET}CO_2$, the PCO_2 in the expired air at the end of a breath out; $PaCO_2$, the PCO_2 in an arterial blood sample; DC, direct current, a steady non-oscillating electric current; Douglas, bags, large bags used by respiratory physiologist for delivering or collecting gas mixtures; Douglas tap, large bore metal taps used in external breathing cuicuits; Curare, induces total muscle paralysis; Gallamine, induces total muscle paralysis; Bupivocaine, a long acting local anaesthetic; Vagus nerve, the Xth cranial nerve innervating thoracic viscera and connected to the hind brain; Phrenic nerve, arises from the cervical segments 3, 4, and 5 of the spinal cord innervates the diaphragm; Intercostal, nerves from the thoracic segments of the spinal cord innervate intercostal muscles.

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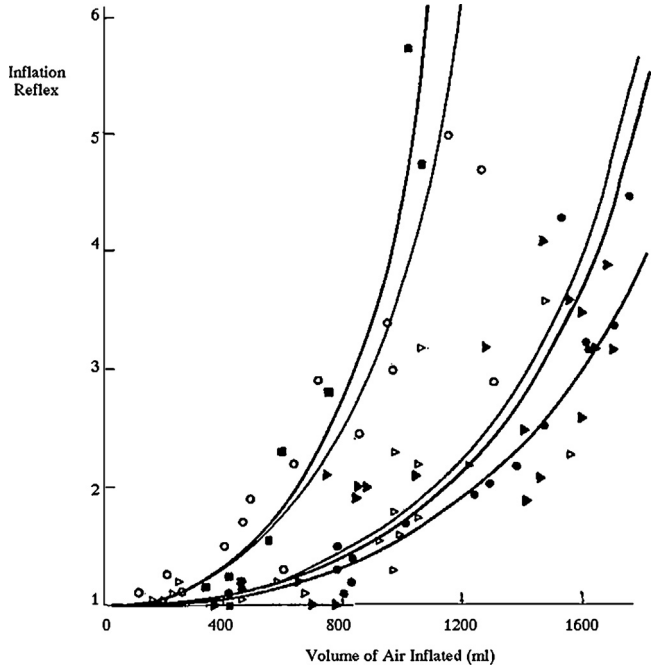

Fig. 1. The effect of lung inflation in five anaesthetised patients undergoing surgical procedures; each patient has been alloted a different symbol. The inflation reflex was quantified by dividing the duration of the apnoeic response by the control breath interval. The data has been replotted from Guz et al. (1964) with the dependent variable transfered to the ordinate. Inflation volumes above the normal tidal volume of 300–400 ml were required to affect breathing.

and Knowlton, 1946) and stimulated much study of breathing responses in animals dependent on afferent nerve activity in the vagus nerves, i.e., abolished by vagotomy. Detailed study of the afferent fibres that make up the vagus nerve established that the inflation reflex was mediated by the slowly adapting stretch receptors (Einthoven, 1908; Adrian, 1933; Paintal, 1953; Widdicombe, 1954a; Schelegle and Green, 2001) while the fibres mediating the deflation and paradoxical reflexes remained uncertain. Paintal (1955) claimed to have found "specific deflation receptors" but these responded to many other stimuli and were later re-classified (see below).

The first attempt to investigate the inflation reflex in humans was made in new born infants who demonstrated the presence of the inflation and paradoxical reflexes (Cross et al., 1960). Widdicombe (1961) and also connected the airway of anaesthetised patients undergoing surgical operations to a pressurised Douglas bag. The volume of inflation was measured by integrating the output of a pneumotachogragh fitted in line with the airway. Airway occlusion, at the end of a breath in, had no effect in humans, and it was necessary to inflate large volumes of air into the lungs of patients in order to elicit a pause in breathing. By contrast, as was already known, the dog inflation reflex was so strong that merely occluding the airway at peak inspiration caused a pause in the breathing rhythm. The results of Guz et al. (1964) in 5 subjects, shown in Fig. 1, demonstrated that the inflation volumes used were way above normal tidal volume. But was this response to large inflation volumes dependent on afferent nerve impulse traffic in the vagus nerves, as in animals?

The first attempt to obtain data on this question was by Guz et al. (1964) in consenting patients. His team had to transport all their recording equipment, Douglas bags, etc., to the Strand in central London where a surgeon performing thyroidectomies was willing to put local anaesthetic on the vagus nerves with the patients' consent. Lignocaine (2%) was applied to the vagus nerves when the neck was dissected; this did not affect breathing or arterial PCO_2 but did

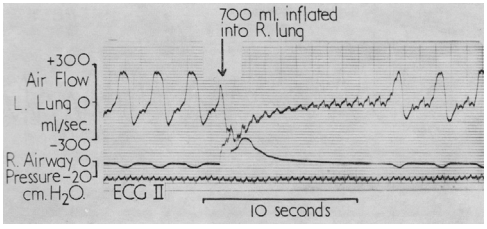

Fig. 2. A tracing from an anaesthetised patient breathing through a double endobronchial tube (Carlens). Breathing of the left lung was recorded by pneumotachograph (Guz et al., 1966a). Upon inflation of the right lung, there was an apnoeic pause. That this was the Hering-Breuer inflation reflex was confirmed by blockade of the right vagus nerve.

abolish the apnoeic pause in reponse to large lung inflations, thus demonstrating that this response was a vagally mediated reflex. A further series of studies on such neck surgery patients who consented (Guz et al., 1966a) utilised a Carlens endobrochial tube that allows separate inflation of each lung, and recording of air flow in and out of the other lung with breathing. It was found that inflation of one lung caused an apnoeic pause on the airflow trace (Fig. 2). This was abolished by application of 2% lignocaine on the ipsilateral nerve, but not when the lignocaine was applied to the contralateral vagus nerve. This result confirmed that the inflation reflex in humans was mediated by the vagus nerve, and added the observation that there was no apparent cross-over of the afferent nerve fibres involved from one lung to the contralateral vagus.

A remaining question was, "What afferent fibres; were they the large myelinated fibres that were thought to mediate the inflation reflex in animals?" Guz and Trenchard (1971a) thought that the antidromic technique first described by Douglas and Ritchie (1957) seemed very suitable for studying the activity in the vagus nerves of humans, because this method involves recording from the whole nerve trunk without damaging the nerve in any way (Douglas and Ritchie, 1957). This was not possible in thyroidectomy patients, but was possible in radical operations to remove cancerous tissue. During stimulation of the intact vagus nerve antidromically in consenting patients, Guz recorded the A wave and measured the fastest conduction velocities which turned out to be compatible with conduction in the large myelinated fibres. These were very simlar to the data obtained in dogs and cats by themselves and previously by others e.g., Paintal (1953). The amount and frequency of discharge from pulmonary stretch receptors in man, dog and cat, were shown to increase with inspiration and decrease with expiration; the larger the tidal volume, the greater the discharge. At the end-expiratory level in man and dog, a tonic stretch receptor discharge was present. It seemed that humans were similar to animals with regard to large fibre characteristics.

The authors therefore suggested that the much weaker inflation reflex in humans was the result of different adaptation in the central nervous system rather than a different afferent nerve sensitivity. Consistent with this interpretation are the findings of Olinsky et al. (1974), that, whereas in premature neonates, airway occlusion caused a 50% apnoeic pause, full term infants showed only a 25% apnoea. This suggests that the central nervous loss of the lung inflation reflex sensitivity in humans compared with animals begins in utero and develops to full insensitivity after birth. The central nervous respiratory centre is sited in the ventrolateral medulla (the nucleus tractus solitarius)(Hall, 1833; Euler von, 1986; Bonham et al., 2006); it is not easy to turn recordings from neurons in this site into a firm description of the central handling of respiratory reflexes (Hayashi et al., 1996). McCrimmon (2006) has more recently reviewed this subject

The question then arises, "How do we know that these fibres mediate the inflation reflex?" Widdicombe and Nadel, 1963