MECHANISMS OF THE INHIBITORY ACTION OF SOMATOSTATIN ON THE HYPOXIC VENTILATORY RESPONSE

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We have recently shown that a somatostatin (SOM) infusion in man inhibits the steady state hypoxic ventilatory response with sparing of the hypercapnic response (Am.Rev.Resp.Dis (Abst) 1986). This effect is probably due to an action on the carotid body, which contains both dopamine and enkephalins each of which can inhibit its activity. We have now measured the effects of SOM on the progressive hypoxic and hypercapnic ventilatory responses and have assessed whether the dopamine antagonist prochlorperazine (PRO) or the opiate antagonist naloxone (NAL) can alter the inhibitory effect of SOM. Five normal subjects (1 female, age 27-35) were studied in a randomised double blind placebo controlled fashion on three separate days. Each day commenced with a bolus i-v dose of N-saline (SAL), NAL (0.1 mg/kg) or PRO (10 mg). Subjects were then given sequential 45 min infusions of either SOM (1 mg/hr) or its diluent alone in a random order. Hypercapnic and hypoxic responses were measured in the semi-recumbent position using the rebreathe techniques of Reubck and Read. SOM consistently inhibited the hypoxic response following SAL (mean decrease 57% SD 43; p<0.05) and following PRO (mean decrease 47% SD 30; p<0.025) when compared to the control response with H. NAL had no overall effect on the control hypoxic response but the decrease in this with SOM infusion was smaller (mean decrease 36% SD 50; p=NS). PRO increased the hypoxic response during both the control (mean +152% SD 130) and SOM infusions (mean +152% SD 126) as well as the control hypercapnic response (+93% SD 130). Neither NAL nor SOM had any effect on the hypercapnic response. This study demonstrates the inhibitory effect of SOM on the progressive hypoxic ventilatory response with sparing of the hypercapnic response. The failure of PRO to prevent the inhibition of the hypoxic responses caused by SOM is not consistent with an action of SOM on dopamine receptors. The weaker action of SOM following NAL is suggestive of an opioid mechanism. Supported by the Wellcome Trust and the Medical Research Council.

FORCE-LENGTH RELATIONSHIP OF HUMAN DIAPHRAGM

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The in vivo force-length characteristic of the human diaphragm has been studied by measuring transdiaphragmatic pressure (Pdi) at different lung volumes by a variety of techniques, more recently during maximal static inspiratory efforts (Pdi PI max) (Braun et al JAP 52: 405-412, 1982). As diaphragm length increased, Pdi initially increased but plateaued at an early stage, and a peak of Pdi was absent. This differed from the force-length characteristic of other muscles and of the diaphragm in animals (Kim et al JAP 41: 369-382, 1976). Braun et al postulated that Pdi PI max, a voluntary manoeuvre, failed to achieve maximum Pdi. To avoid this problem we studied the force-length relationship by measuring Pdi during phrenic nerve twitches. The right and left phrenic nerves were stimulated simultaneously at 1 Hz using square wave impulses of 0.1 msec duration, with surface electrodes in four normal supine subjects. Electromyograms of both hemidiaphragms were obtained with surface electrodes. Oesophageal (PoE) and gastric (Pg) pressures were recorded with balloon catheters and Pdi was obtained as a subtraction of Pg - PoE. Lung volume was measured with an inductance plethysmography. Following a 30 min control infusion (n-saline), SP was infused at a concentration of 0.3 ng/kg/min and, at 5 min intervals, increasing concentrations of 0.6, 1.25, 2.5 and 5 ng/kg/min. The infusion at the highest concentration was continued for 30 min, followed by a further 30 min control period. Vf was measured during each of these periods. During each 30 min steady state periods, a transient hypoxic response (THR) was obtained as follows. The subjects rebreathed into a 4 litre anaesthetic bag containing either 100% oxygen or 100% nitrogen for 30 s. The rebreath was repeated 4 min later with the other gas, the order being randomised. The slope of SaO2 against Vf during the first four breaths in hypoxia for each THR was used as the index of transient hypoxic sensitivity. There was a trend for resting Vf to increase with increasing concentrations of SP but the changes did not achieve significance. Each step increase in SP caused a corresponding increase in Vf which then diminished slightly. Rebreathing the hyperoxic bag did not affect Vf. THR with SP (0.79 ± SD 0.3 l/min/%SaO2) was significantly greater than during the preceding control run (0.56 ± SD 0.2, p<0.01) and the subsequent control run (0.58 ± SD 0.3, p<0.01). The increase in THR with SP infusion in man is indicative of an effect on the carotid body and provides evidence that this neuropeptide may play a role in peripheral chemoreception in man. Supported by the Wellcome Trust and the Medical Research Council.

SUBSTANCE P ENHANCES THE TRANSIENT VENTILATORY HYPOXIC RESPONSE IN MAN

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Substance P (SP) is found in the carotid body and increases carotid body activity in the cat (McQueen; J.Phys:1980:302:31). Its respiratory effects in man have not been reported. 5 healthy male subjects (age 28-38) were studied in the supine position. Oxygen saturation was measured by ear oximetry and ventilation by
Ohio spirometer. The phrenic nerves were twitched during relaxation of at least 5 seconds at resting end expiration (FRC) and then at different lung volumes between total lung capacity (TLC) and residual volume (RV).

Twitch Pdi increased as lung volume decreased from TLC to RV. We conclude that the active force-length characteristic of the human diaphragm is reflected in twitch height and that the shape of this relationship resembles the force-length curve of the diaphragm obtained in animals.

**164 THE EFFECT ON RESPIRATORY WATER LOSS OF PROLONGED VENTILATION OF COLD AIR IN ASTHMATICS**

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Eucapnic hyperventilation of cold air was developed as a test for asthma from the observation that exercise induced asthma (EIA) depended upon increased respiratory heat exchange (RHE) (Chandler Deal et al J Appl Physiol 1979;49:476).

Evaporation of water from the airway surface liquid contributes significantly to RHE. We have previously reported (abstract 124 Oct 84) the effects on water loss (Wce) and RHE of prolonged ventilation of cold air in normal subjects. In order to demonstrate whether water handling by the airways is substantially different in asthma we have used the same procedure to assess individuals with reversible airflow obstruction.

Eleven stable asthmatic subjects under eucapnic conditions inhaled cold (−14°C) dry air at a frequency of 24 breaths/min initially at resting tidal volume (Vt) for 10 minutes, then at maximum Vt for 5 minutes and again at resting Vt for 5 minutes. During this procedure there was no break from breathing cold air. Expired air temperature (Te) (Cu/CuNi thermocouple), expired Vt (Heated Fliesch pneumotachograph and integrator) and end expiratory dewpoint (Michell dewpoint hygrometer) were continuously monitored at the mouth. From these values Wce and RHE were calculated.

Two factor analysis of variance was used to compute the effect of two subjects on Wce and RHE.

<table>
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<th>Time (min)</th>
<th>Wce (mg/l)</th>
<th>RHE (cal/l)</th>
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As previously noted for normal subjects the water loss and RHE per liter of expired air fell with time at both high and low Vt. After hyperventilation both parameters fell towards the basal levels at 10 minutes. The dip below basal levels in normal subjects was absent. This may result from bronchoconstriction, though spirometry changed little, or drugs the subjects being on inhaled B2 agonists or steroids though none had used these within 4 hours of the experiment. We are investigating this further.

**165 IS ALVEOLAR CARBON MONOXIDE A RELIABLE INDEX OF TOBACCO SMOKE UPTAKE?**

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Carboxyhaemoglobin (COHb) levels can be inferred in smokers using non-invasive measurements of alveolar carbon monoxide (CO), but these methods may be inadequate to record the acute effects of smoking a single cigarette.

Accordingly, we compared alveolar CO (after a 20 s breath hold, BH2O) with direct COHb both before and after one cigarette on 100 studies in 42 volunteers. % COHb was measured spectrophotometrically from whole venous blood, (Radiometer OSM2 Hemoximeter) and CO by infra red analyser (ADC, 1–100 ppm). We have shown the 20 or 25 s breath holding manoeuvre is comparable to the rigorous 3 minute rebreathing test at normal oxygen levels (Kirkham et al, Clinical Science 1985; 68 113P).

The pre-smoking BH2O and % COHb relationship was linear and highly significant: % COHb = −0.158 + 0.176 x BHCO (ppm), r = 0.951. However, there was a marked difference in the magnitude of the change in CO, or "CO boost" between the techniques. The mean BHCO boost was 2.76 ppm, SD 2.93, (9.0% of the mean of 30.75 ppm for all readings combined) while the % COHb values were 1.17%, SD 0.49 (21.0% of the mean of 5.57%).

In 15 studies, the BHCO boost was negative, but % COHb always rose. While the two boost values were significantly correlated, r = 0.715, this only explains half the variability of the two sets of readings. With neither method was there a significant correlation with the mean level of CO and the corresponding boost, while the variability of the two techniques was similar (correlation of pre and post values gave an r value of 0.971 for BHCO and 0.977 for % COHb). These results suggest that alveolar and blood CO levels follow different time courses during and immediately after smoking.

We conclude that alveolar CO measurements provide a satisfactory alternative to direct carboxyhaemoglobin values at rest. However, they do not provide a reliable indicator of the acute changes during smoking.

**166 BLOCKING NOCTURNAL VAGAL ACTIVITY DOES NOT ABOLISH "MORNING DIP" IN ASTHMATICS**

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The cause of nocturnal wheeze and "morning dip" in peak expiratory flow rate (PEFR) in asthmatics is unknown. Vagal tone increases at night (Bast; Exp Brain Res 1979; 7: 169) and could result in airway narrowing. To determine whether blocking overnight vagal activity