Somatostatin inhibits the ventilatory response to hypoxia in humans

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MAXWELL, D. L., P. CHAHAL, K. B. NOLOP, AND J. M. B. HUGHES. *Somatostatin inhibits the ventilatory response to hypoxia in humans.* J. Appl. Physiol. 60(3): 997–1002, 1986.—The effects of a 90-min infusion of somatostatin (1 mg/h) on ventilation and the ventilatory responses to hypoxia and hypercapnia were studied in six normal adult males. Minute ventilation ($\dot{V}E$) was measured with inductance plethysmography, arterial O_2 saturation (Sa_{O_2}) was measured with ear oximetry, and arterial P_{CO_2} (Pa_{CO_2}) was estimated with a transcutaneous CO_2 electrode. The steady-state ventilatory response to hypoxia ($\Delta\dot{V}E/\Delta Sa_{O_2}$) was measured in subjects breathing 10.5% O_2 in an open circuit while isocapnia was maintained by the addition of CO_2. The hypercapnic response ($\Delta\dot{V}E/\Delta Pa_{CO_2}$) was measured in subjects breathing first 5% and then 7.5% CO_2 (in 52–55% O_2). Somatostatin greatly attenuated the hypoxic response (control mean -790 ml·min^{-1}·%$Sa_{O_2}^{-1}$; somatostatin mean -120 ml·min^{-1}·%$Sa_{O_2}^{-1}$; $P < 0.01$), caused a small fall in resting ventilation (mean % fall -11%), but did not affect the hypercapnic response. In three of the subjects progressive ventilatory responses (using rebreathing techniques, dry gas meter, and end-tidal P_{CO_2} analysis) and overall metabolism were measured. Somatostatin caused similar changes (mean fall in hypoxic response -73%; no change in hypercapnic response) and did not alter overall O_2 consumption nor CO_2 production. These results show an hitherto-unsuspected inhibitory potential of this neuropeptide on the control of breathing; the sparing of the hypercapnic response is suggestive of an action on the carotid body but does not exclude a central effect.

chemoreceptors; ventilatory control; hypercapnia; inductance plethysmography

THE TETRADECAPEPTIDE HORMONE somatostatin was first discovered because of its ability to inhibit growth hormone release (2), but its inhibitory effect extends to other hormones in the pituitary gland and the pancreas and to a wide range of gastrointestinal functions (1). These properties have been investigated extensively and have led to its use as a therapeutic agent (4, 10, 12). During another study in our department, it became apparent that an infusion of somatostatin was in some way interfering with ventilation during hypoxia. We report the previously unsuspected ability of somatostatin to inhibit selectively the ventilatory response to hypoxia.

METHODS

Subjects. Six healthy male volunteers aged 25–48 yr (mean 30 yr) working at the Medical School were studied. All had normal lung function, and all but one were nonsmokers. Studies were carried out with the subjects in the supine position at least 3 h after food or caffeinated beverage. Approval was obtained from the Research Ethics Committee of the Royal Postgraduate Medical School Hammersmith Hospital, and all subjects gave their informed consent.

Infusions. Somatostatin-14 (1.5 mg, Peninsula Labs) was dissolved in 45 ml Haemaccel (Hoechst UK), a 3% colloid solution used clinically as a plasma substitute. The effects of this infusion (given over 90 min) were compared with those of a similar volume of Haemaccel alone as a control in a randomized double-blind sequential fashion. Indwelling cannulas were inserted into a vein in each arm for venous blood collection and infusion. Each infusion lasted 90 min, one following immediately after the other. Somatostatin-14 (mol wt 1,638) was therefore infused at a rate of ~10 nmol/min. One of the investigators prepared and infused the solutions but took no part in ventilatory measurements nor their analysis. The subjects and the other investigators did not know in which order the infusions were given.

Ventilatory monitoring. Throughout the studies arterial O_2 saturation (Sa_{O_2}) was monitored with ear oximetry (Hewlett-Packard) and arterial P_{CO_2} (Pa_{CO_2}) was estimated from a transcutaneous CO_2 electrode (Radiometer, Copenhagen) placed on abraded skin on a forearm. Calculations were made by use of a regression formula obtained in a previous study, which showed that it predicted Pa_{CO_2} with 95% confidence limits of ±6.7 Torr and that it followed step changes more accurately (24). The electrode could detect changes in transcutaneous CO_2 within 30–40 s of the onset of voluntary hyperventilation. Ventilation and its subdivisions were measured noninvasively using inductance plethysmography (Respitrace, Ambulatory Monitoring Systems) calibrated with a single-posture technique (14). Accuracy of the inductance plethysmograph was confirmed at the beginning and end of each set of ventilatory measurements by the comparison of tidal volumes over 20 breaths with simultaneous spirometry. Each breath provided a ratio of the tidal volume estimated from inductance plethysmography (VT_{RIP}) to that from the spirometer (VT_{SP}). Each validation provided a mean tidal volume ratio (VT_{RIP}/VT_{SP}). Blood pressure and pulse rate were measured at 15-min intervals. Venous blood samples, taken through a cannula in the other forearm at the beginning and end of

each infusion, were prepared and stored for later analysis. Analysis of plasma somatostatin was carried out by radioimmunoassay with antiserum raised in rabbits using synthetic somatostatin-14 coupled to bovine serum albumin. Characterization of the antiserum, using a range of somatostatin analogues, suggested that recognition was dependent on the tertiary structure of the peptide (19).

Measurements of ventilation were started 35 min after the start of each infusion and were made in subjects breathing gas mixtures in the following order: *a*) air (5 min), *b*) 5% CO_2-55% O_2-40% N_2 (7 min), *c*) 7.5% CO_2-52% O_2-40.5% N_2 (8 min), *d*) 60% O_2-40% N_2 (15 min), and *e*) 10.5% O_2-89.5% N_2 (15 min). During *periods b–e*, gas mixtures of O_2, CO_2, and N_2 were supplied to the subjects through a Venturi mask (Ventimask type II, entraining air in a 1:1 ratio) to create the different inspired gas concentrations at a flow of 40 l/min. During *period e* N_2 was added to the inspirate to lower inspired O_2, and CO_2 was added (at ~0.8–1.5 l/min) to maintain isocapnia as recorded by the transcutaneous CO_2 electrode. O_2 was added where necessary to maintain Sa_{O_2} at >80%. Previous studies of resting ventilation in normal subjects in this department have shown that supplying air through a Venturi mask does not itself affect the pattern of breathing (15). Figure 1 plots minute-by-minute values for Sa_{O_2}, estimated Pa_{CO_2}, and minute ventilation ($\dot{V}E$) for one subject during the ventilatory measurements of one infusion. Changes in $\dot{V}E$ between the hypercapnic *periods b* and *c* represent the hyperoxic hypercapnic response, and changes between breathing 60% O_2 (*period d*) and breathing the hypoxic mixture (*period e*) represent the isocapnic hypoxic response.

Progressive ventilatory responses. On a separate day the progressive isocapnic hypoxic and hypercapnic ventilatory responses were also measured in three of these subjects while they were in the semirecumbent position and were fasting by use of the methods of Rebuck, and Campbell (23) and Read (22). On these occasions 45-min infusions of somatostatin and its diluent were given consecutively and in random order. Rebreathing measurements were made at 15 and 35 min of each infusion. The order of the hypoxic and hypercapnic tests was randomized between subjects. Ventilation was measured by dry gas meter, end-tidal P_{CO_2} was measured by infrared analysis, and Sa_{O_2} with ear oximetry. The isocapnic hypoxic rebreathes were carried out at an end-tidal P_{CO_2} of 44 Torr. Because ventilatory control may alter with changes in overall metabolism (5), Douglas bag collections of expired air were made from the 10th to the 15th min of each infusion for calculation of O_2 consumption and CO_2 production. Gas concentrations were measured by mass spectrometry.

Collection and analysis of data. Analysis of data from the inductance plethysmograph was carried out by a computer and used to display a breath-by-breath update

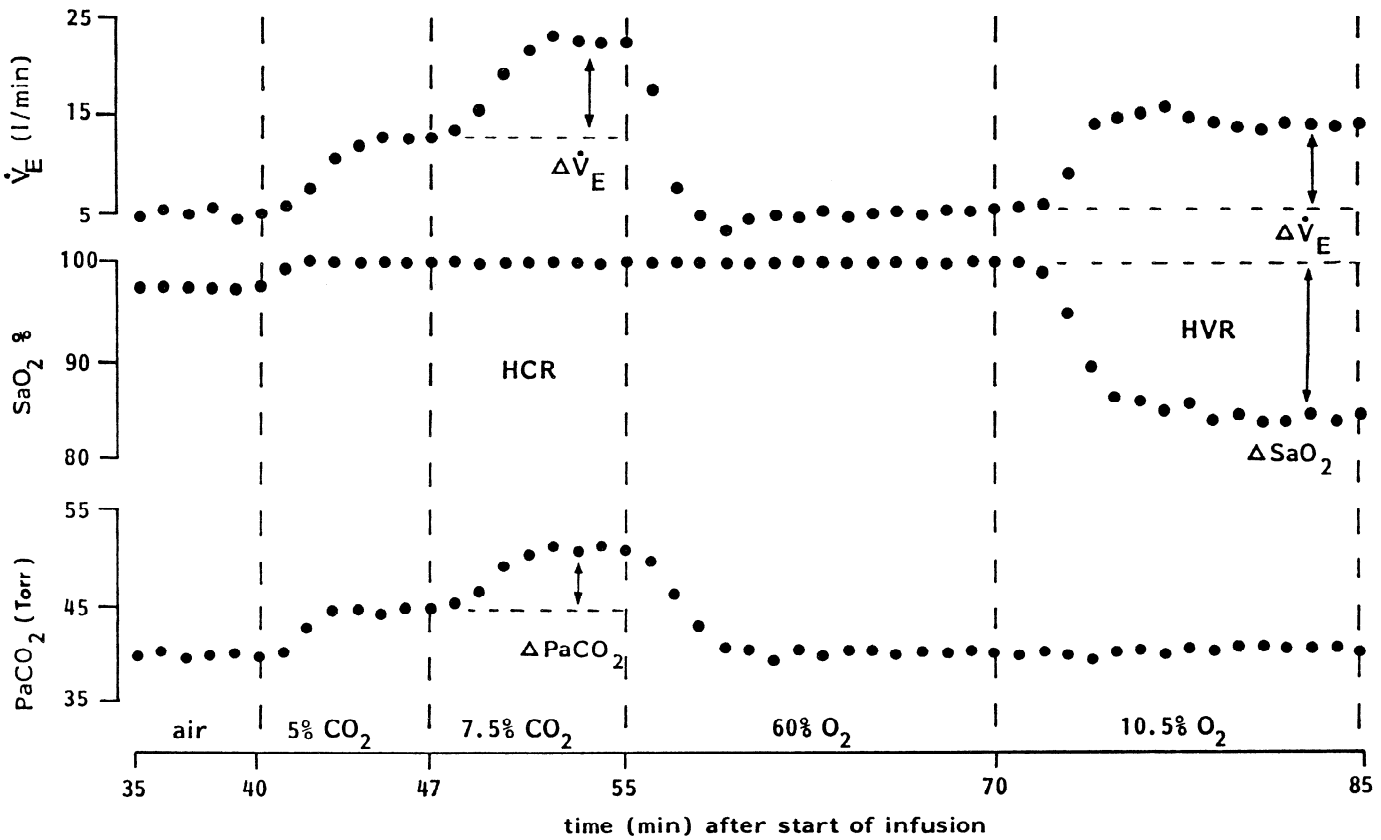

FIG. 1. One-minute means of arterial P_{CO_2} (Pa_{CO_2}, estimated by transcutaneous CO_2 electrode), arterial O_2 saturation (Sa_{O_2}), and minute ventilation ($\dot{V}E$) during ventilatory measurements of one subject during one infusion. *Horizontal axis* represents time from start of infusion, separates out different test periods (*a–e*, see text) and indicates gas mixtures being used during these periods. HCR, hypercapnic ventilatory response; HVR, hypoxic ventilatory response.

on a monitor as well as a chart recorder. Means of $\dot{V}E$ and its subdivisions over intervals of 15 s while the subjects were breathing air (*period a*), during the last 2 min of each level of hypercapnia (*periods b* and *c*), and during the last 5 min of breathing 60% O_2 (*period d*) and the last 5 min of isocapnic hypoxia (*period e*) were collected and stored for later analysis. The means of ventilatory variables while the subjects breathing air (*period a*) and during hypoxia (*period e*) and the values for hypercapnic and hypoxic responses for each infusion were compared by paired *t* tests. The values for hypercapnic responses were normalized with a logarithmic transformation. *P* values of > 0.05 were taken as not significant.

RESULTS

Accuracy of ventilatory measurements. For all the subjects the $V_{T_{RIP}}/V_{T_{SP}}$ was 1.013 ± 0.03 (SE). The mean of absolute changes in this ratio between the beginning and end of each infusion for all the subjects was 0.05 ± 0.02. Thus the mean error of estimates of tidal volume and ventilation was ±2.5%.

Ventilation during air breathing and in isocapnic hypoxia. The means of ventilatory variables during air breathing (*period a*) and in isocapnic hypoxia (*period e*) with each infusion are given in Table 1. When the significance of changes in so many variables is analyzed, the possibility of the occurrence of type I errors must be considered. Compared with the control infusion, infusion of somatostatin during this period caused a small drop in $\dot{V}E$ [mean % fall −11 ± 4% (SE); $P = 0.05$] in all six subjects. This was due to small reductions in mean inspiratory flow (V_T/T_I) and increases in the timing components of the respiratory cycle [inspiratory (T_I) and expiratory (T_E) times] with no change in the duty inspiratory cycle (T_I/T_T, where $T_T = T_I + T_E$). There were no changes in estimated Pa_{CO_2} or in Sa_{O_2} with somatostatin during this period. The ventilatory variables in hypoxia show how the normal response to hypoxia is a large increase in V_T/T_I with small reductions in T_I and T_E and no change in T_I/T_T. The major effect of somatostatin in hypoxia was a reduction in V_T/T_I despite the substantially lower Sa_{O_2} and slightly higher estimated Pa_{CO_2}. The ventilatory variables were also normalized by expressing them as a percentage of their corresponding base-line values during the control infusion. No new significant changes were revealed, and *P* values for those changes already found to be significant became marginally smaller.

TABLE 1. *Ventilatory data breathing air and in hypoxia*

	On Air (*Period a*)		In Hypoxia (*Period e*)	
	Control	Somatostatin	Control	Somatostatin
$\dot{V}E$, l/min	5.92±0.5	5.11±0.3*	14.5±1.6	7.78±1.0†
f, min^{-1}	13.7±0.7	12.1±1.0	15.8±1.1	14.2±1.1
V_T, liter	0.43±0.04	0.44±0.06	0.92±0.10	0.57±0.10†
V_T/T_I, l/min	14.2±1.5	12.4±1.1	33.7±3.4	20.0±3.0†
T_I/T_T	0.41±0.01	0.41±0.02	0.42±0.02	0.39±0.01‡
T_I, s	1.80±0.1	2.13±0.2	1.63±0.1	1.78±0.2
T_E, s	2.61±0.1	2.99±0.3	2.25±0.2	2.65±0.3
Pa_{CO_2}, Torr	40.5±1.1	40.6±1.3	40.6±1.1	41.4±1.4
Sa_{O_2}, %	97.1±0.3	97.4±0.3	88.1±1.7	82.2±0.6‡

Values are means ± SE; $n = 6$. $\dot{V}E$, minute ventilation; f, breathing frequency; V_T, tidal volume; V_T/T_I, mean inspiratory flow; T_I/T_T, duty inspiratory cycle; T_I, inspiratory time; T_E, expiratory time; Pa_{CO_2}, arterial P_{CO_2} estimated by the transcutaneous electrode; Sa_{O_2}, arterial O_2 saturation. Somatostatin different from control: * $P = 0.05$; † $P < 0.01$; ‡ $P < 0.05$.

Figure 2*A* gives, for each infusion, the mean values for $\dot{V}E$ and Sa_{O_2} obtained during the last 5 min while subjects were breathing 60% O_2 (*period d*) and for the last 5 min of isocapnic hypoxia (*period e*), during which ventilatory variables were all steady. The individual values for the hypoxic ventilatory response ($\Delta\dot{V}E/\Delta Sa_{O_2}$) were calculated from individual means of $\dot{V}E$ and Sa_{O_2} during these periods and are plotted in Fig. 2*B*. The $\Delta\dot{V}E/\Delta Sa_{O_2}$ during somatostatin infusion [mean −120 ± 56 (SE) $ml \cdot min^{-1} \cdot \%Sa_{O_2}^{-1}$] was significantly less than during control (−790 ± 170 $ml \cdot min^{-1} \cdot \%Sa_{O_2}^{-1}$; $P < 0.01$) and amounted to only 15% of the control value. This conclusion was not altered by normalizing the data before the hypoxic responses were calculated. During the last 5 min of hypoxia the transcutaneous P_{CO_2} was maintained steady despite the 30- to 40-s response lag; readings taken at 15-s intervals showed a maximum deviation averaging 0.83 Torr (range 0.3–2.3 Torr) without any trend to increase or decrease systematically. Although isocapnia was preserved during the control infusion, the mean estimated Pa_{CO_2} in hypoxia during somatostatin infusion (41.4 Torr) was slightly higher than during the preceding hyperoxic period (40.1 Torr), because in two subjects estimated Pa_{CO_2} actually increased during hypoxia without added CO_2. During the somatostatin infusion one of these subjects had no hypoxic response and in the other ventilation actually decreased during hypoxia.

Ventilation in hyperoxic hypercapnia. During the periods of data collection in conditions of hyperoxia with 5% CO_2 (*period b*), with 7.5% CO_2 (*period c*), and without added CO_2 (*period d*), ventilatory variables were steady. The means of $\dot{V}E$ and estimated Pa_{CO_2} at the end of each of these periods for each infusion are plotted in Fig. 3*A*. The slope of the line at higher levels of estimated Pa_{CO_2} is greater than that at lower levels. This was a feature of 11 of the 12 hypercapnic runs and may be a reflection of the nonlinearity of the hypercapnic response at alveolar P_{CO_2} close to the normal range (9). In our protocol the normocapnic hyperoxic point (*period d*) was obtained after CO_2 breathing and might in some way have been affected by this. However $\dot{V}E$ during *period d* [control 6.1 ± 0.3 (SE) l/min; somatostatin 5.6 ± 0.4) was not different from that obtained during the control period air breathing (Table 1).

We have therefore taken individual slopes ($\Delta\dot{V}E/\Delta Pa_{CO_2}$) in the higher Pa_{CO_2} range to represent steady-state hypercapnic ventilatory responses (Fig. 3*B*). The mean value was slightly less with somatostatin (3.7 $l \cdot min^{-1} \cdot Torr^{-1}$; range 1.5–7.8) than with the control (4.1 $l \cdot min^{-1} \cdot Torr^{-1}$; range 1.8–7.8). The difference between these was not significant and was mostly due to a large change in the sensitivity of one subject. This conclusion was not altered by using the mean of slopes obtained in the lower CO_2 range or the mean of slopes of regression

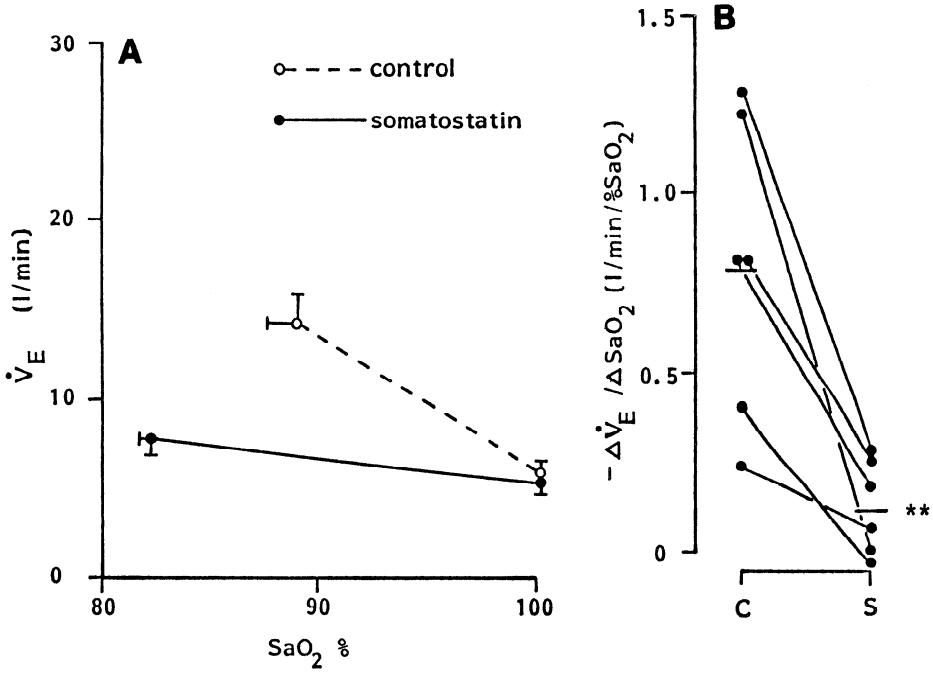

FIG. 2. *A*: means (±SE) of minute ventilation ($\dot{V}E$) plotted against arterial O_2 saturation (Sa_{O_2}) during hyperoxic run (*period d*) and hypoxic run (*period e*) during control and somatostatin infusions (see text for details) ($n = 6$). *B*: individual values for hypoxic ventilatory response ($-\Delta\dot{V}E/\Delta Sa_{O_2}$) during control (C) and somatostatin (S) infusions ($n = 6$). *Horizontal bars* represent mean values. ** Somatostatin mean different from control mean, $P < 0.01$.

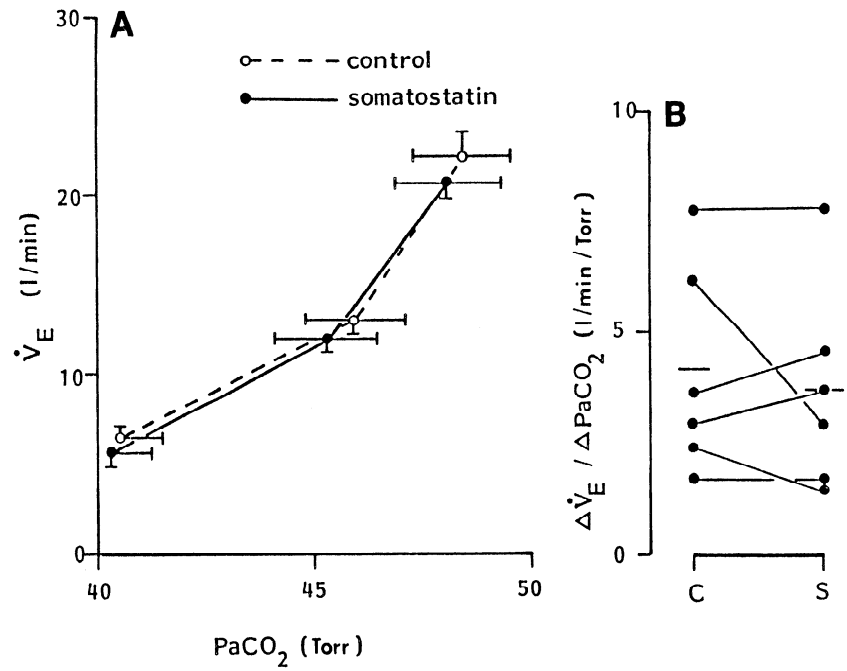

FIG. 3. *A*: means (±SE) of minute ventilation ($\dot{V}E$) plotted against estimated arterial P_{CO_2} (Pa_{CO_2}) during hyperoxic runs (*periods b–d*) during control and somatostatin infusions (see text for details) ($n = 6$). *B*: individual values for hypercapnic ventilatory response ($\Delta\dot{V}E/\Delta Pa_{CO_2}$) during control (C) and somatostatin (S) infusions ($n = 6$). *Horizontal bars* represent mean values.

lines drawn through all three points, nor was it changed by normalizing the data before calculating the hypercapnic responses.

Progressive ventilatory responses. The individual values of the steady-state and progressive hypoxic and hypercapnic responses of the three subjects who underwent both parts of the study are set out in Table 2 with the values of O_2 consumption and CO_2 production. The progressive responses show a mean 73% reduction of the hypoxic response but no change in the hypercapnic response, consistent with the results obtained in the steady state. The changes in overall metabolism were small (<4%). Two of the subjects had their progressive hypoxic responses measured 15 min after the start of each infusion and show that the inhibition of this response is already present at this stage.

Other measurements. At any given stage there were no significant differences in blood pressure or pulse rate between the two infusions. At the start of each study, and at the end of each control infusion, plasma somatostatin levels were within the normal range for our laboratory (<30 pmol/l). At the end of each somatostatin infusion plasma somatostatin levels ranged between 1,040 and 2,380 pmol/l (mean 1,800 pmol/l). There was no significant correlation between plasma somatostatin and the reduction in the hypoxic response. Three of the subjects felt mildly nauseated during somatostatin infusion.

DISCUSSION

Somatostatin infusion (1 mg/h) caused a small reduction in resting ventilation and a profound drop in the

TABLE 2. *Steady-state and progressive ventilatory responses and overall metabolism*

Subj No.	Hypoxic, $l \cdot min^{-1} \cdot \%Sa_{O_2}^{-1}$				Hypercapnic, $l \cdot min^{-1} \cdot Torr^{-1}$				$\dot{V}O_2$, ml/min		$\dot{V}CO_2$, ml/min	
	SS		PRG		SS		PRG					
	C	S	C	S	C	S	C	S	C	S	C	S
1	−0.8	−0.2	−1.5	−0.4	1.8	1.8	1.2	1.7	259	257	216	219
2	−0.2	−0.1	−0.8	+0.2	3.0	3.7	2.1	1.8	201	199	168	161
3	−1.3	−0.3	−4.3	−1.6	3.6	4.6	3.4	3.2	219	195	185	173
Mean	−0.8	−0.2	−2.2	−0.6	2.8	3.4	2.2	2.2	226	217	190	184

Individual and mean values for steady-state (SS) and progressive (PRG) hypoxic and hypercapnic ventilatory responses, O_2 consumption ($\dot{V}O_2$), and CO_2 production ($\dot{V}CO_2$) in 3 subjects during infusions of somatostatin (S) and of its diluent as control (C).

steady-state isocapnic hypoxic ventilatory response. Despite this, there was no overall change in the steady-state hyperoxic hypercapnic response. In three subjects progressive ventilatory responses were also measured with results similar to the steady-state measurements. In these subjects somatostatin caused no significant change in overall metabolism as measured by O_2 consumption and CO_2 production.

Measurement of ventilatory response. The use of a transcutaneous P_{CO_2} electrode and respiratory inductance plethysmography to measure these steady-state responses merits comment. This equipment permits ventilatory monitoring without the discomfort of noseclips and mouthpieces; a more detailed description of the method and its application have been published (14). Despite the time lag (30–40 s) for the P_{CO_2} electrode to respond to a sudden change, no difficulty was experienced in this or the previous study (14) in maintaining a steady P_{CO_2} reading during the last 5 min of the 15-min periods of hypoxia. Although the absolute accuracy of the electrode cannot compare with direct measurements of arterial or alveolar P_{CO_2}, its relative accuracy in detecting change is sufficient for the purpose. The inductance plethysmograph values for tidal volume were checked against a spirometer at the beginning and end of each series of measurements, and no appreciable drift in inductance plethysmograph-to-spirometric ratios was observed. In addition, the effects of somatostatin on the responses to progressive hypercapnia and hypoxia, where ventilation (spirometer) and P_{CO_2} (end-tidal gas analysis) were measured directly, were essentially similar in the three subjects in whom steady-state and progressive responses were compared.

Central sites of action. Somatostatin immunoreactivity has been demonstrated in the ventrolateral and ventral subnuclei of the nucleus tractus solitarius in the medulla of the rat, which receive afferents from lung stretch receptors and participate in the respiratory "off-switch" mechanism (11). In the same report application of somatostatin into the cisterna magna of anesthetized rats caused slow deep breathing followed by apnea. Peptides such as somatostatin when given intravenously are thought not to cross the blood-brain barrier except at a few very small areas of brain (20), although this does not exclude the possibility that a breakdown fragment of somatostatin may do so. However, hyperoxia inhibits the peripheral chemoreceptors so that any change in ventilation during the hypercapnic periods would have been due to central chemoreception. The selective sparing of the hypercapnic response makes it more difficult to implicate a central effect.

Peripheral site of action. The carotid body is the principal peripheral chemoreceptor in humans and is responsible for sensitivity to hypoxia and, to a small extent, hypercapnia. Patients, who have had carotid body resection, have no ventilatory response to hypoxia but retain most of their hypercapnic response (13). There are no reports of somatostatin localized in the carotid body, but somatostatin immunoreactivity has been found in association with catecholamines in many sympathetic ganglia including the superior cervical ganglion from which the sympathetic supply to the carotid body derives (8).

The carotid body contains neurotransmitters and neuropeptides (7, 25), some of which inhibit or modulate its activity [such as dopamine (7) and Leu- and Met-enkephalin (18)], others of which stimulate it [such as acetylcholine (7), substance P (16), and vasoactive intestinal peptide (17)]. The precise mechanism of chemoreception in the carotid body has not been fully elucidated (7), but somatostatin may be acting directly on carotid body receptor cells or may be inhibiting or modulating the release or action of these neurotransmitters or peptides as it does in other tissues (1).

Physiological implications. The plasma levels of somatostatin in this study that were 100-fold greater than basal levels were clearly pharmacological, although up to 50-fold increases have been found in some patients with somatostatinoma (21). In normal humans there is a diurnal variation of plasma somatostatin with levels ranging between 15 and 45 pmol/l (3). Somatostatin levels are raised for 1–2 h after meals and then decline (3). Although Zwillich et al. (26) showed that chemoreceptor responses are increased postprandially, their measurements were made between 2 and 3 h after ingestion. Postprandial somatostatin levels remain raised for much longer after an evening meal (3), suggesting the possibility that somatostatin might play a part in the reduction in hypoxic response in sleep (6). It remains to be established whether relatively small changes in plasma levels are accompanied by changes in hypoxic sensitivity.

In conclusion, high levels of plama somatostatin in humans cause a profound inhibition of the hypoxic ventilatory response with sparing of the hypercapnic response. This effect is probably mediated peripherally at the carotid body rather than centrally. Future work with this peptide may shed further light on the mechanisms of chemoreception. Inhibition of hypoxic sensitivity may put certain patients at risk when this peptide or its analogues are being used clinically (4, 10, 12).

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