Hypothalamic-pituitary dysfunction in respiratory hypoxia

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ABSTRACT Eight hypoxic male patients with stable chronic obstructive airways disease were submitted for combined anterior pituitary function testing. All subjects showed normal growth hormone and essentially normal cortisol responses to adequate hypoglycaemia, two subjects showed delayed responses of thyroid stimulating hormone to administered thyrotrophin releasing hormone and all had basal prolactin levels within normal limits. Basal levels of luteinising hormone were significantly lower than in the group of age-matched controls ($p < 0.02$) but there was a normal increment after the injection of gonadotrophin releasing hormone. Basal levels of follicle stimulating hormone were significantly lower than in the controls ($p < 0.01$), and there was also a reduced response from the pituitary after injection of gonadotrophin releasing hormone ($p < 0.01$). Resting levels of the thyroid hormones thyroxine and tri-iodothyronine were normal while the expected subnormal testosterone level was observed ($p < 0.05$). These results show that hypoxia can produce abnormalities of hypothalamic-pituitary function and that these are primarily located in the hypothalamic-pituitary-testicular axis.

While studying metabolic aspects of chronic obstructive airways disease (COAD), we have recently found reduced serum testosterone values in affected men,¹ and have been able to demonstrate an association between severity of hypoxia and degree of testosterone suppression.² Theoretical consequences of endocrine abnormalities have been discussed in these communications with particular reference to the difference in body habitus between overweight chronic bronchitic "blue bloaters" and thin emphysematous "pink puffers." Though such hormonal changes had not previously been described in patients with COAD, reduced urinary 17-ketosteroid production had already been noted at high altitude³ and in emphysema.⁴ We have postulated that hypoxia produces low androgen output by suppressing hypothalamic-pituitary function. However, decreased response of testosterone secretion after testicular stimulation by injection of human chorionic gonadotrophin (HCG) has been described at high altitude,⁵ suggesting that hypoxia in that situation might have affected the testicular production of testosterone directly. In order to

clarify this apparent discrepancy and to gain a greater understanding of the effect of hypoxia on hypothalamic-pituitary function we have performed combined anterior pituitary stimulation tests in eight men with COAD.

Methods

Approval for the project was granted by the hospital ethical committee and informed written consent was obtained from all patients. Eight stable male chest clinic patients were chosen. All had chronic bronchitis as defined by the Medical Research Council and grade 3 or 4 dyspnoea.⁶ By spirometry (Vitalograph, sitting) forced expiratory volume in one second (FEV₁) was always less than 70% of predicted value and forced expiratory volume/forced vital capacity ratio (FEV₁/FVC) was always less than 70%, indicating airways obstruction. Arterial blood samples were taken from the radial artery with the patient rested for 15 minutes and breathing room air and only hypoxic patients were admitted to the study.

Within two weeks of the above baseline investigations patients attended the chest clinic having

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Table 1 Subjects studied, indices of chronic obstructive airways disease, and drug histories

Subject	Age (yr)	FEV ₁ (% predicted)	FEV ₁ /FVC (%)	PaO ₂ (kPa)	PaCO ₂ (kPa)	Drugs prescribed
1	36	27	57	7.7	7.7	Spironolactone, frusemide, theophylline
2	47	61	52	10.0	5.4	Salbutamol
3	50	27	60	5.7	6.6	Spironolactone, frusemide
4	50	16	50	6.4	7.8	Spironolactone
5	52	53	59	8.4	6.5	Frusemide K, theophylline, allopurinol
6	53	26	37	9.3	6.6	Spironolactone, frusemide, theophylline
7	57	25	62	5.3	8.1	Frusemide K
8	60	36	47	6.5	5.7	Salbutamol, frusemide K, allopurinol, digoxin
Normal values		100	70-90	10.7-13.3	4.7-6.0	

FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; PaO₂ and PaCO₂ = partial pressure in arterial blood of oxygen and carbon dioxide.

fasted overnight. Each then had a combined pituitary stimulation test involving the injection of soluble insulin (0.2 u/kg), thyrotrophin releasing hormone, TRH (200 µg) and gonadotrophin releasing hormone, GnRH (100 µg) (Relefact LH-RH/TRH, Hoechst). Blood samples were taken at standard time intervals and serum was stored at -20°C before assay.

All serum hormone measurements were made using radioimmunoassay methods. Serum follicle stimulating hormone (FSH), luteinising hormone (LH) and growth hormone (HGH) concentrations were obtained using procedures recommended by the Supraregional Assay Service, prolactin was measured as described by Cowden *et al*⁷ and thyroid stimulating hormone (TSH) by a modification of the method of Hall *et al*⁸ using a rabbit anti-human TSH serum kindly donated by Professor WR Butt. The reference standards for FSH, LH, HGH, prolactin, and TSH assays were MRC 69/104, 68/40, 66/217, 75/504, and 68/38 respectively. Thyroxine and T3 were measured with semi-automated radioimmunoassays⁹ using second antibody separation. Serum cortisol levels were obtained from an assay that employs a solid-phase linked antibody (Corning Medical) and testosterone was measured in diethyl

ether extracts of serum using an antibody that had approximately 20% cross-reactivity with dihydrotestosterone.

Our laboratory normal data for all these methods have been obtained from appropriate volunteer and hospital inpatient populations. For this study in particular the FSH and LH levels observed in hypoxic men after the administration of GnRH were compared with data obtained from eight age matched control male subjects. Statistical comparisons were made using Wilcoxon's Rank test.

Results

Objective evidence of COAD in all subjects is presented in table 1 together with a record of the drugs prescribed at the time of study. The basal prolactin and thyroid function test results are recorded in table 2 together with data relating to the TSH response to TRH and the HGH and cortisol responses to insulin-induced hypoglycaemia. All subjects had normal prolactin levels and were biochemically euthyroid at the time of study. An adequate increment of serum TSH occurred in all cases but in subjects 5 and 8 the peak TSH level was observed at 60 minutes rather than 30 minutes after

Table 2 Anterior pituitary function in men with chronic obstructive airways disease. Basal prolactin status and thyroid function and responses of TSH to TRH and HGH and cortisol to insulin-induced hypoglycaemia

Subject	Basal serum prolactin (mu/l)	Basal serum T4 (nmol/l)	Basal serum T3 (nmol/l)	Serum TSH (mu/l)			Minimum plasma glucose (mmol/l)	Serum HGH (mu/l) peak level	Serum cortisol (nmol/l) maximum increment
				0'	30'	60'			
1	272	84	1.9	3.0	9.8	6.8	0.8	42	75
2	168	99	0.9	1.9	10.0	9.1	1.1	37	450
3	200	116	2.5	2.2	7.7	7.0	1.1	57	200
4	187	75	1.5	1.8	6.6	6.4	0.9	33	215
5	130	76	2.4	4.3	6.1	7.9	1.8	21	340
6	256	110	2.2	4.7	11.0	8.1	0.9	40	525
7	124	96	2.4	2.7	6.6	4.4	1.1	32	570
8	271	63	1.8	3.7	5.7	6.5	0.5	21	200
Normal values	60-360	55-144	0.9-2.8	UD-8.0	Increment > 3.6	< 2.2	> 15	> 200	

TSH = thyroid stimulating hormone; TRH = thyrotrophin releasing hormone; HGH = human growth hormone; T4 = thyroxine; T3 = tri-iodothyronine; UD = undetectable.

Table 3 Anterior pituitary function in men with chronic obstructive airways disease. Basal testosterone levels and gonadotrophin concentrations before and after GnRH in affected subjects and age-matched controls

Subjects	Age (yr)	Serum 17 OHA (nmol/l) 0'	Serum LH (u/l)			Serum FSH (u/l)		
			0'	30'	60'	0'	30'	60'
1	36	21	4.8	15	23	0.6	1.6	1.4
2	47	13	3.6	50	50	2.0	4.6	4.6
3	50	18	4.5	50	42	0.7	2.5	2.5
4	50	11	1.8	41	16	1.8	3.9	4.3
5	52	10	2.8	19	21	1.7	3.7	3.8
6	53	8	4.5	40	47	1.6	3.2	3.7
7	57	10	7.7	42	49	0.9	8.2	8.2
8	60	14	1.7	18	27	1.5	2.5	3.1
Mean	51	13.1	3.95	34	34	1.35	3.71	3.95
<i>Controls</i>								
1	35	19	6.7	20	20	1.9	4.9	5.2
2	42	23	5.9	38	38	2.8	5.4	6.5
3	48	17	7.7	42	31	5.1	7.1	7.3
4	51	17	9.2	21	20	4.8	7.7	8.2
5	52	21	4.2	25	33	3.9	8.3	9.7
6	55	11	6.9	33	36	8.3	18	21
7	59	27	8.6	22	20	4.1	5.6	5.7
8	60	27	5.1	39	34	2.3	4.0	4.5
Mean	50	20.2	6.8	30	29	4.1	7.6	8.5
Significance of difference*	NS	$p \leq 0.05$	$p \leq 0.02$	NS	NS	$p \leq 0.01$	$p \leq 0.01$	$p \leq 0.01$
Normal range		11-36	UD-9.0			UD-7.0		

*Statistics using Wilcoxon's Rank Test.

GnRH = gonadotrophin releasing hormone; 17 OHA = 17-hydroxyandrogens (testosterone); LH = luteinising hormone; FSH = follicle stimulating hormone; UD = undetectable.

TRH. All subjects achieved adequate hypoglycaemia after 0.2 units/kg of insulin, and in all cases the peak serum GHG level exceeded the lower limit of normal. Four of the eight subjects had adequate cortisol responses to hypoglycaemia, three had equivocal responses (subjects 3, 4, and 8), and one (subject 1) had a clearly subnormal response.

Basal levels of serum testosterone ($p < 0.05$), LH ($p < 0.02$), and FSH ($p < 0.01$) were significantly lower in patients than in age-matched controls (table 3). A normal pituitary response of LH was noted after GnRH administration to patients but the FSH response was significantly lower than in the control group both at 30 minutes and 60 minutes after stimulation.

Discussion

We have confirmed our previous finding that serum testosterone levels are lower in hypoxic men with chronic obstructive airways disease than in age- and sex-matched controls. We have shown that hormone binding globulin capacity is not reduced in these hypoxic subjects (unpublished data) and therefore these subnormal testosterone levels are real and will be accompanied by a fall in the circulating level of free androgen. Low levels of testosterone have also been reported in chronic liver disease¹⁰ but we are confident that liver disease was not a causative factor in our study since none of our cases had liver

congestion from cor pulmonale and all had normal biochemical indices of liver function. The strong correlation between the degree of testosterone reduction and severity of hypoxia supports hypoxia as the primary cause.² The extent of testosterone deficiency is less marked in this study than in our previous series of COAD subjects who were in relapse and more hypoxic when tested. This agrees with our recent finding that the serum testosterone level returns towards normal as the degree of hypoxia improves in patients recovering from cor pulmonale (unpublished data). The anterior pituitary stimulation tests were performed to determine the aetiology of this subnormal serum androgen and to look for other endocrine abnormalities.

Basal thyroid hormone levels were normal in the subjects studied confirming our previous results,¹ and as expected there was a normal increment of TSH in all subjects after a bolus injection of TRH. The delayed response of TSH in two subjects is of interest since this pattern has been linked with hypothalamic dysfunction.¹¹ However, our two isolated observations indicate that at most hypoxia causes a very minor change in the hypothalamic-pituitary-thyroid axis.

Basal serum prolactin values were all normal in this series of patients although we have previously noted high levels in three of 16 COAD subjects.¹ Hyperprolactinaemia is known to accompany low serum testosterone levels in some cases of male

hypogonadism,^{12 13} but this study suggests that elevated prolactin is seen only rarely in COAD and is not closely related to the low testosterone levels.

Insulin-induced hypoglycaemia resulted in a normal HGH response in all subjects, so hypoxia would appear to have no effect on the synthesis and secretion of this hormone. No consistent effect of hypoxia could be shown on the cortisol response to hypoglycaemia there being four normal responses and four equivocal or abnormal. However, with the exception of subject number 8 (equivocal response), the latter group were receiving spironolactone, the metabolites of which are known to cross-react in the assay system used (GH Beastall, unpublished data), so it would be unwise to interpret these results as indicating adrenal insufficiency. Moreover we would not expect the hypothalamic-pituitary-adrenal axis to be suppressed by hypoxia since Davies and Few¹⁴ have shown a stress-induced increase in serum cortisol in volunteers exercising under conditions of hypoxia compared to normoxia.

The only consistent abnormalities of pituitary hormone homeostasis were those observed for the gonadotrophins. Significantly low basal levels of both FSH and LH compared with age-matched controls would seem to exclude primary testicular failure as a cause of the low serum testosterone of COAD and to suggest instead either a hypothalamic or pituitary lesion. The normal LH response demonstrates that the pituitary can be stimulated by exogenous GnRH in these subjects and so provides evidence in favour of a hypothalamic cause of the deficient steroidogenesis.

Theoretical evidence can be advanced in favour of such hypothalamic involvement. It is known that the normal circadian secretion of LH relies upon a precisely timed pulsatile release of GnRH.¹⁵ Thus a loss of this rhythm of GnRH production induced by hypoxia could lead to subnormal LH and testosterone concentrations. Alternatively such a disruption of GnRH rhythm might be brought about by raised intracranial pressure which occurs in hypercapnia even to the extent of causing an eroded pituitary fossa¹⁶ and which has been implicated as the cause of hypothalamic hypopituitarism in patients suffering from "normal-pressure" hydrocephalus.¹⁷

The observation of a reduced FSH response to GnRH in COAD patients in the presence of a normal LH response is of great interest as it would appear to imply a pituitary lesion inconsistent with the theories outlined in the previous paragraph. However, it is well established that the feedback control of LH by testosterone and its metabolites differs appreciably from that of FSH. Indeed androgens appear to have opposite effects on LH and

FSH secretion since pretreatment of pituitary cells with androgen can markedly inhibit the LH response to GnRH while the effect of FSH is stimulatory.¹⁸ If the corollary applies then the pattern of gonadotrophin responses observed in this study might be more easily explained. The observed fall in serum testosterone could affect the pituitary directly and lead to a diminution in FSH response but not the LH response to exogenous GnRH. The theory would gain support should the FSH response to GnRH in affected patients return to normal as the serum testosterone rises after reversal of hypoxia or with testosterone replacement therapy.

There are possible clinical consequences of the fall in basal levels of FSH, LH, and testosterone in patients with COAD. We have shown evidence of sexual impotence in this group of subjects, probably resulting from the low testosterone levels rather than from the general debility of COAD.¹⁹ As yet we do not know if such patients have azoospermia and infertility as a result of reduced FSH secretion. Also the fluctuations in serum testosterone parallel changes in body mass known to occur in COAD, such patients losing lean body mass in right-sided heart failure and regaining it in recovery.²⁰ In view of the known anabolic effects of androgens it is tempting to speculate on a cause and effect relationship.

In conclusion we have demonstrated consistent abnormalities of gonadotrophin status in hypoxic patients with chronic obstructive airways disease as well as isolated instances of delayed TSH responsiveness to TRH. These results, taken in conjunction with the previously demonstrated and now confirmed low testosterone levels, indicate that hypoxia can produce abnormalities of pituitary function and that these are primarily located in the hypothalamic-pituitary-testicular axis. Studies are in hand to test some of the theories advanced.

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