Short report

Cerebrospinal fluid adenosine 3',5'-monophosphate, 5-hydroxyindoleacetic acid and homovanillic acid in patients with sleep apnoea syndrome

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SUMMARY Adenosine 3',5'-monophosphate (cyclic AMP), 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) were determined in the cerebrospinal fluid of patients with respiratory disorder and hypersomnia and in control patients. Patients with the sleep apnoea syndrome confirmed polygraphically showed elevated levels of cyclic AMP and 5-HIAA. Cyclic AMP levels were inversely correlated with arterial PO₂, measured under resting conditions. The level of HVA also was raised, but the change was not statistically significant.

Catecholamine and indoleamine neurotransmitters play a key role in the central regulation of sleep and vigilance. While serotonergic pathways have been implicated in the appearance mainly of slow wave sleep, other evidence suggests an association of dopamine metabolism with REM-sleep.¹ Hypersomnia with periodic sleep apnoea (Pickwick-syndrome, sleep apnoea syndrome) is a disorder of unknown aetiology, characterised by episodes of respiratory arrest during sleep and obstructive or central hypercapnia associated with day-time somnolence in obese subjects.²⁻⁴ Recently, elevated levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA)⁵ and the dopamine metabolite homovanillic acid (HVA)⁶ in the cerebrospinal fluid (CSF) have been reported in this condition. It has been suggested that such metabolic changes might be caused by the obstructive apnoea and might be linked to the day-time sleepiness, which then could be viewed as a secondary disturbance.⁶

Other evidence indicates that the neurotransmitters serotonin and dopamine control the synthesis of adenosine 3',5'-monophosphate (cyclic AMP) in the brain,^{7,8} and cerebral glucogenolysis in response

to these hormones and to anoxia appears to be mediated by this cyclic nucleotide.^{9,10} Indirect evidence for an involvement of cyclic AMP in the regulation of sleep in the brain stem has been reviewed elsewhere.¹¹ In this paper we report the results of a study of cerebrospinal fluid levels of cyclic AMP and of the monoamine metabolites HVA and 5-HIAA in patients with the sleep apnoea syndrome and respiratory disorders.

Patients and methods

Eight patients (seven males, one female, mean age 53.6 years) were studied for suspicion of the sleep apnoea syndrome. All presented with obesity and complaints of diurnal somnolence (table 1). The patients were subjected to complete tests of cardiorespiratory functions including blood gas analysis in the resting condition, all-night polygraphic recording of EEG, EMG, eye movements and respiration, and lumbar puncture with analysis of CSF, in addition to thorough neurological examination, radiography of the skull and routine laboratory examinations.

Seven patients (five males, two females, mean age 39.4 ± 5.2 years) who consulted for lumbago and suspicion of vertebral disc herniation served as controls. All patients were free of central nervous system disease. Routine CSF values (protein content, cell count) were normal. Lumbar punctures were performed in the decubitus position. Eight ml of CSF were removed, aliquots were immediately frozen and stored at -40°C until analysis. Cyclic

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Table 1 Clinical data and results of blood cell count and gas analysis in patients with respiratory disturbances and hypersomnia

Patient age (yr) sex	Diagnosis	Diurnal somnolence	Polygraphic recording	Other symptoms	Body weight (kg)	Erythrocyte count (million/mm ³)	Arterial pH	Art blood gas analysis			Drug treatment
								PO ₂	PCO ₂	Oxygen saturation (%)	
RE 51 M	sleep apnoea syndrome	+	frequent episodes of sleep apnoea	chronic bronchitis	102	4.3	7.43	47	57	85%	none
RO 45 M	sleep apnoea syndrome	+	episodes of sleep apnoea	chronic bronchitis	113	6.0	7.45	38.5	49.5	75%	none
RS 52 M	sleep apnoea syndrome	+	episodes of sleep apnoea	none	91	4.5	7.41	65	35	93%	none
BR 70 M	sleep apnoea syndrome	+	episodes of sleep apnoea	none	100	4.4	7.45	55	39.5	90%	none
GI 59 M	sleep apnoea syndrome	+	episodes of sleep apnoea	light diabetes	101	4.4	7.39	70	35.5	90%	oral antidiabetic
GA 44 M	chronic respiratory insufficiency	+	normal	none	79	5.8	7.39	55	39	90%	none
LA 46 M	chronic bronchitis	+	normal	none	107	4.8	7.39	51.5	38.2	90%	none
FA 62 F	chronic bronchitis	+	normal	none	100	4.2	7.54	56	28	90%	none

AMP was determined by radioimmunoassay with equilibrium analysis according to Cailla *et al* (1973) in triplicate samples. HVA was determined fluorimetrically according to Renaud *et al*.¹² 5-HIAA was measured by the method of Korf and Valckenburgh-Sikkema.¹³ For statistical analysis the test of Cochrane and Student's *t* test were applied.

Results

Of the eight patients with diurnal somnolence and obesity five were diagnosed as having the sleep apnoea syndrome (table 1). The other three patients had normal polygraphic recordings with no apnoeic episodes. Polycythaemia was present in two patients, one with the sleep apnoea syndrome and one with chronic respiratory insufficiency. All patients had

some degree of hypoxia as evidenced by a decrease of PO₂. Hypercapnia not corrected by hyperventilation existed only in the first two patients with sleep apnoea syndrome (table 1). Oxygen saturation was least in these patients.

As shown in table 2 the mean level of cyclic AMP was markedly elevated ($p < 0.005$) in the group of patients with the sleep apnoea syndrome in comparison to the control group of patients. The levels of HVA showed large variations and the mean level was not statistically significantly increased in sleep apnoea patients. The levels of 5-HIAA were increased ($p < 0.001$) in sleep apnoea patients as compared to other obese patients with respiratory disease and diurnal somnolence, as well as with the control group of patients free of central nervous

Table 2 Cerebrospinal fluid cyclic AMP, HVA and 5-HIAA in patients with sleep apnoea syndrome, respiratory disease with diurnal somnolence and in control patients

Patients	Cyclic AMP (pmol/ml)	Homovanillic acid (ng/ml)	5-hydroxyindoleacetic acid (ng/ml)
Sleep apnoea syndrome			
RE	42	21	56
RO	45	80	74
RS	29	9	34
BR	20	136	63
GI	14	63	44
	total: 30.0 ± 6.0*	61.8 ± 22.7	54.2 ± 7.0†
Respiratory disease			
GA	33	11	21
LA	6	6	22
FA	20	39	17
	total: 19.7 ± 7.8	18.7 ± 10.2	20.0 ± 1.5
Control patients			
	total: 15.5 ± 2.9	29.8 ± 7.5	20.7 ± 2.2

* $p < 0.005$ vs control patient group.

† $p < 0.001$ vs control patient group.

system disease. Within the group of sleep apnoea patients there was a correlation between the levels of cyclic AMP and Po_2 ($r = -0.86$, $p < 0.05$). Further, a correlation was found between 5-HIAA and Po_2 ($r = -0.86$, $p < 0.05$). No correlation was apparent between HVA and the values of blood gas analysis.

Discussion

Cyclic AMP levels in CSF are elevated in patients with sleep apnoea syndrome. Moreover, the cyclic AMP levels are positively correlated to the degree of hypoxia and of hypercapnia in our patients. This finding is not specific for the sleep apnoea syndrome, but is a reflection of the metabolic disturbance induced by hypoxia, for we also found an increased level of cyclic AMP in a patient with polycythaemia, as a result of chronic hypoxia due to primary respiratory disease. Increased cyclic AMP levels in the CSF appear to be a useful indicator of central hypoxia, as has been shown also in animal experiments.¹⁴ Evidence for locally increased cyclic AMP metabolism was also reported in patients with cerebral infarction.¹⁵

The observation of increased levels of 5-HIAA in the sleep apnoea syndrome confirms earlier preliminary reports.^{5,6} Normal levels of 5-HIAA were found in the small group of patients with respiratory disease and diurnal somnolence but undisturbed sleep. In contrast to Baruzzi's observation⁶ in only two cases, our patients showed a statistically insignificant elevated mean level of HVA; marked increases in some patients were not correlated with any of the other metabolic parameters tested.

Our findings suggest that serotonergic systems and cyclic AMP as a second messenger are involved in the sleep apnoea syndrome. Apparently, neither the serotonin metabolite nor cyclic AMP is altered in other syndromes with hypersomnia such as narcolepsy and the subwakefulness syndrome (Cramer *et al.*, unpublished observation). While cyclic AMP levels may reflect cerebral hypoxia, the disturbance of serotonin metabolism may be more specifically connected to the sleep disorder in the sleep apnoea syndrome. Under severe cerebral ischaemia, brain levels of serotonin were decreased.¹⁶ This would be in accordance with the role of serotonin in sleep suggested by Jouvet.¹⁷ Baruzzi *et al.*⁶ have shown that 5-HIAA and HVA levels in the CSF decreased in one patient after tracheostomy, concomitant with the clinical disappearance of the sleep disorder. It would be interesting to correlate cyclic nucleotide levels with the course of the disease in individual patients with sleep apnoea, in order to clarify their role in the disease process.

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