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Characteristic Plasma Hormone Changes in Alzheimer's Disease

J. E. CHRISTIE, L. J. WHALLEY, J. BENNIE, H. DICK, I. M. BLACKBURN, D. H. R. BLACKWOOD and G. FINK

A systematic endocrine investigation in dementia, depression and control subjects showed that plasma growth hormone (GH) was higher in the morning and plasma TSH concentrations were higher throughout the day in Alzheimer-type dementia (ATD) than in age-matched depressed patients (MDD), and plasma TSH concentrations were also higher throughout the day in female ATD compared with age-matched female control subjects. The increased plasma TSH concentrations could not be due to reduced negative feedback because plasma T_3, T_4 and rT_3 were in the normal range. Plasma concentrations of oestrogen-stimulated neurophysin (ESN) were lower throughout the day in ATD compared with MDD and controls and lower in the morning compared with other dementias. The high plasma GH and TSH concentrations in ATD may reflect the reduced hypothalamic content of somatostatin in ATD, and the reduced concentrations of ESN may reflect reduced cholinergic activity in ATD brain. These selective hormonal changes provide a useful diagnostic test for Alzheimer's disease.

The neuropathological (Ishii, 1965) and some of the neurochemical features of Alzheimer-type dementia (ATD) affect not only the cerebral cortex but also subcortical structures, including the hypothalamus, in which there is a reduction of choline acetyltransferase (Davies, 1979), noradrenaline (Yates *et al*, 1981) and of somatostatin concentrations (Davies *et al*, 1982). Somatostatin is also reduced in CSF in patients with ATD (Wood *et al*, 1982). Acetylcholine, noradrenaline and somatostatin are involved in the control of the secretion of pituitary hormones (Reichlin, 1985), and the aim of the present study was to determine whether in ATD the central changes in these neurotransmitters are reflected in the basal secretion of pituitary hormones.

There have been few previous neuroendocrine studies in ATD. The majority of the studies have focused on the dexamethasone suppression test (DST), and a high incidence of early escape from dexamethasone suppression has been reported in patients with presenile (Raskind *et al*, 1982; Balldin *et al*, 1983) and senile ATD (Spar & Gerner, 1982; Coppen *et al*, 1983). Samorajski *et al* (1982) reported raised plasma prolactin concentrations in patients in hospital with senile dementia, but this finding was not confirmed in presenile ATD (Balldin *et al*, 1983); and in a study of a small number of patients, Hyyppa *et al* (1980) found the CSF prolactin concentrations were lower in patients with cerebral atrophy. Reduced sleep-related secretion of growth hormone (GH) was described in three ATD patients as compared with three age-matched control subjects (Davis *et al*, 1982).

The present study was designed to test hypotheses that plasma concentrations of pituitary hormones would (a) reflect changes in central neurotransmitters that occur in ATD and (b) prove useful in the differential diagnosis of ATD from other causes of dementia and depression, which is sometimes difficult, especially in elderly patients. The study compared hormone profiles in patients with presenile onset of ATD with those of major depressive disorders (MDD), other types of dementia and control subjects. ATD of presenile onset was studied because although the reduction in choline acetyltransferase is similar in older compared with younger patients with ATD (Yates *et al*, 1983*b*), younger patients with ATD have a more extensive loss of noradrenaline (Yates *et al*, 1983*b*; Rossor *et al*, 1984) and somatostatin (Pierotti *et al*, 1986).

Method

Alzheimer's type dementia

Patients who had developed symptoms suggestive of dementia before the age of 65 were admitted to hospital for investigation. The diagnosis of ATD was based on:

(a) onset of symptoms under the age of 65 with dysmnesia as the initial feature and with steadily progressing dementia
(b) absence of a history suggestive of another type of dementia or focal neurological signs or hypertension
(c) CT scan within normal limits or showing cerebral atrophy and showing no additional pathology
(d) EEG showing no focal abnormalities
(e) normal ECG, haematological, biochemical and CSF clinical investigations.

The 18 patients who met these criteria for ATD and were admitted to the study were all free of psychotropic drugs for at least 6 months before and throughout the duration of the study. They were assessed using the following psychological tests:

(a) orientation (Wechsler, 1955)
(b) short-term memory, forward and backward digit-span (Wechsler, 1955)
(c) long-term memory, Logical Memory (Wechsler, 1955) and Paired Associates Learning (Isaacs & Walky, 1964)
(d) agnosia - common objects; pictures; colours; auditory agnosia; tactile agnosia; naming of body parts (Eisenson, 1954)
(e) apraxia - hand position; finger flexion; use of objects; intrasensitive gestures (Kimura & Archibald, 1974).

Severely demented hospitalised patients were excluded but a wide range of severity of dementia was represented within the ATD population. Two patients were still in regular employment, three others were living alone while the remainder required the close support of relatives to remain in the community. The patients were reassessed 12 months later and only if the diagnosis remained unchanged were they included in the study.

Other dementias

Demented patients who after full investigation, failed to meet the criteria for ATD were included in the study and formed a dementia group who were unlikely to have ATD. Five of the nine patients had focal changes on the CT scan suggestive of vascular disease and were given a diagnosis of multi-infarct dementia. Two patients presented with personality and behavioural changes which were more pronounced than memory impairment. Both showed frontal lobe patterns of response in psychological tests and the provisional diagnosis was Pick's disease. One patient had the typical features of Huntington's chorea and a positive family history, while another patient had dementia associated with bilateral spasticity in the lower limbs, with a diagnosis thought to be disseminated sclerosis. All nine patients were free of psychotropic drugs for at least 6 months before the study.

Depressed patients

Patients with symptoms of a depressive illness, who had been free of antidepressant and neuroleptic drugs for at least 6 months, were selected from routine admissions to the Royal Edinburgh Hospital. The 16 patients admitted to the study remained free of antidepressant and neuroleptic drugs for the duration of the study. Eight patients were totally drug-free, seven patients received night sedation in the form of a benzodiazepine or chloral hydrate and one patient had received a recent course of ampicillin.

The depressed patients were all interviewed using the Present State Examination (PSE) Wing *et al*, 1974) within a few days of admission to hospital and were also assessed using the Hamilton Depression Rating Scale (Hamilton, 1960). The data from the PSE and clinical case records were assessed independently by two psychiatrists, and patients were classified according to the Research Diagnostic Criteria (RDC) (Spitzer *et al*, 1978). All 16 patients met the criteria for major depressive disorder (MDD), 14 endogenous and two probable endogenous subtype. Depressive delusions or hallucinations were present in ten patients, who therefore met criteria for MDD psychotic subtype.

Control subjects

The 37 control subjects - hospital staff and non-hospital-associated volunteers - were in good health and had not been taking any medication, including oral contraceptives, for at least 6 months.

Age and sex

Table I shows the mean age, age range and male/female composition of the patient groups and control subjects. Seven depressed patients and 11 control subjects were of similar age to the ATD patients. In the instances when plasma concentrations of a hormone showed a significant correlation with age within the total control population, only the age-related groups were used in statistical comparisons. Comparisons of plasma concentrations of luteinising hormone (LH) between ATD and control subjects were made only in post-menopausal women.

TABLE I
Patient and control populations

	n	*Male*	*Female*	*Age (years) Mean ± s.d.*	*Range*
Alzheimer's disease (ATD)	18	5	13	61.0± 5.4	53-70
Major depressive disorder (MDD)	16	8	8	45.5±12.6	25-72
MDD patients of similar age to ATD patients	7	3	4	56.6± 7.7	49-72
Other dementias	9	4	5	64.6± 8.7	44-72
Control subjects	37	14	23	39.9±13.4	18-63
Control subjects of similar age to ATD patients	11	2	9	56.6± 5.6	48-63

Informed consent

All patients and control subjects consented to the study procedures, which they understood were undertaken only for research purposes. In cases where there was any doubt about a patient's understanding, the agreement of a close relative was sought before the patient was included.

Blood sampling

An in-dwelling cannula was inserted at approximately 06:40, kept patent by heparinised saline and left in place until 24:00. Blood samples were taken at 07:00, 07:30 and 08:00 (morning), 15:00, 15:30 and 16:00 (afternoon), and 23:00, 23:30 and 24:00 (evening). This blood sampling technique, designed to take account of the diurnal and pulsatile pattern

of hormone secretion, allowed calculation of mean values for morning, afternoon and evening periods. In 15 ATD, 13 MDD and 9 other dementia patients a dexamethasone suppression test was carried out after the initial sampling day. Dexamethasone, 1 mg in a syrup, was given at 24:00 and blood samples were taken the following day at 08:00, 16:00 and 23:00. Blood samples were collected in lithium heparin-coated tubes containing 100 k IU Trasylol, and kept at 4°C before and during centrifugation. Plasma was stored at −40°C until assay.

Hormonal assays

Plasma hormone concentrations of GH, TSH, prolactin (PRL), LH and oestrogen-stimulated neurophysin (ESN) were determined using the NIADDK radioimmunoassay kits. The reference preparations were as follows: for GH, HS2243E; for TSH, WHO 1st IRP 68/38; for PRL, NIAMDD-HPRL-RP-1 (AFP-2312C); and for LH, LER-907. The reference preparation for ESN was that given to NIADDK by Dr A. Robinson, University of Pittsburg. Anti-rabbit gamma globulin (Scottish Antibody Production Unit (SAPU), Carluke, Scotland) at a final dilution of 1/100 was used as a second antibody. All samples were measured in duplicate. The sensitivity of the assays (90% B/Bo) were 1.6 mU/litre for GH (100 μl sample); 0.8 mU/litre for TSH (200 μl sample); 70 mU/litre for PRL (50 μl sample); 0.60 U/litre for LH (100 μl sample); and 85 pmol/litre for ESN (100 μl sample). The intra-assay coefficients of variation (COV) were 7.1% (low pool - 5.3 mU/litre and 7.4% (high pool - 40.0 mU/litre) for GH; 6.2% (low pool - 4.1 mU/litre) and 6.0% (high pool - 13.8 mU/litre) for TSH; 6.6% (low pool - 182 mU/litre) and 5.4% (high pool - 1.31 U/litre) for PRL; 7.4% (low pool - 1.34 U/litre) and 3.4% (high pool - 3.35 U/litre for LH; and 5.8% (low pool - 332 pmol/litre) and 4.9% (high pool - 672 pmol/litre) for ESN. The inter-assay COV were 8.4% (low pool) and 7.4% (high pool) for GH; 7.0% (low pool) and 9.1% (high pool) for TSH; 9.9% (low pool) and 8.4% (high pool) forPRL; 10.3% (low pool) and 8.9% (high pool) for LH; and 8.4% (low pool) and 7.8% (high pool) for ESN.

Total cortisol concentrations were determined by radio-immunoassay using a modification of the method of Seth & Brown (1978) with an antiserum (SAPU), raised in sheep against cortisol-3-0-carboxymethyloxime-bovine serum albumin. Anti-sheep/goat serum (SAPU) at a final tube dilution of 1/83 was used as the second antibody. The sensitivity of the assay (90% B/Bo) was 11.6 nmol/litre cortisol. The intra-assay COV were 2.2% (low pool - 153 nmol/litre), 2.8% (middle pool - 310 nmol/litre) and 3.2% (high pool - 560 nmol/litre). The interassay COV were 4.6% (low pool). 2.68% (middle pool) and 6.34% (high pool).

Statistical analysis

The distributions of the mean morning (07:00, 07:30 and 08:00), afternoon (15:00, 15:30 and 16:00) and evening (23:00, 23:30 and 24:00) plasma concentrations of cortisol, GH, TSH, PRL, LH and ESN in patients and control subjects were significantly skewed. The cortisol data were log-transformed to approximate normality, and the significance of the differences in the mean plasma cortisol concentrations between ATD, MDD, other dementias and control subjects was determined by one-way analysis of variance and the multiple range test of Duncan (1961). The distributions of the other hormones, however, remained skewed despite transformation, and the Mann–Whitney U test was used to determine the significance of differences between the values. In all 96 comparisons were made between the groups; thus by chance alone up to five significant differences would be expected (four at $P<0.05$ and one at $P<0.02$). In the ATD group, correlations between the mean morning, afternoon and evening plasma GH, TSH, cortisol, PRL and ESN concentrations were made using Spearman's Rank Correlation coefficient (30 comparisons). Also, within the ATD group, mean morning, afternoon and evening concentrations of GH, TSH, cortisol and ESN were correlated with psychological test scores (60 comparisons).

Results

Relationship between age, sex and plasma hormone concentrations in control subjects

Plasma cortisol and plasma ESN concentrations were not significantly correlated with age. Afternoon plasma GH concentrations decreased with age (morning, $r=-0.24$, NS: afternoon, $r=-0.30$, $P<0.05$; evening, $r=-0.23$, NS). Morning and afternoon plasma TSH concentrations (morning, $r=0.36$, $P<0.02$; afternoon, $r=0.31$, $P<0.02$; evening, $r=0.24$, NS) increased with age, and afternoon plasma prolactin concentrations (morning, $r=-0.02$; afternoon, $r=0.35$, $P<0.02$; evening, $r=0.16$) also increased with age. We concluded that plasma GH, TSH and prolactin concentrations correlated with age and that comparisons between ATD and other groups would require age-matching.

Plasma concentrations of TSH, cortisol and ESN were similar in male and female control subjects at all three time periods. Plasma GH concentrations were higher in female as compared with male control subjects in the evening only ($P<0.01$) and plasma prolactin concentrations were higher in female compared with male control subjects in the afternoon ($P<0.02$). When the female control population was divided into pre- and post-menopausal groups, the post-menopausal women, as expected, had higher plasma LH concentrations at all three times of day ($P<0.02$) than the pre-menopausal women.

Growth hormone

Table II shows that plasma GH concentrations in the morning were significantly higher in ATD as compared with age-related control subjects ($P<0.02$) but not different from age-related MDD. Female ATD patients had higher morning ($P<0.02$) and afternoon ($P<0.05$) plasma GH concentrations than age-related female control subjects. The other dementia group had GH concentrations similar to those in control subjects.

TABLE II

Plasma GH and TSH concentrations in Alzheimer presenile dementia, other dementias and age-matched control subjects

	Growth hormone (mU/l) (mean ± s.e.)				TSH (mU/l) (mean ± s.e.)			
	n	*Morning*	*Afternoon*	*Evening*	*n*	*Morning*	*Afternoon*	*Evening*
Alzheimer	17	7.7 ± 1.0*	7.4 ± 1.3	5.2 ± 0.7	18	12.2 ± 6.6†††	7.5 ± 3.0††	12.2 ± 6.1†
Depression	7	9.3 ± 2.8	7.5 ± 1.5	4.8 ± 0.7	7	3.3 ± 0.2	3.1 ± 0.2	3.7 ± 0.5
Other dementias	9	5.1 ± 0.9	4.5 ± 0.8	6.0 ± 1.1	9	4.7 ± 0.6	4.0 ± 0.4	5.1 ± 0.5
Controls	11	4.1 ± 0.5	3.9 ± 0.3	6.9 ± 2.3	11	4.4 ± 0.2	3.9 ± 0.2	4.9 ± 0.5
Alzheimer (female)	12	8.8 ± 1.1**	8.6 ± 1.6*	5.6 ± 0.8	13	15.4 ± 9.0*	8.9 ± 4.1*	15.3 ± 8.4**
Controls (female)	9	4.1 ± 0.5	4.0 ± 0.4	7.7 ± 2.8	9	4.2 ± 0.1	3.8 ± 0.2	4.5 ± 0.2

ATD *v.* controls: $^{*}P<0.05$; $^{**}P<0.02$.
ATD *v.* MDD: $^{\dagger}P<0.05$; $^{\dagger\dagger}P<0.02$; $^{\dagger\dagger\dagger}P<0.002$.

Thyroid-stimulating hormone

Table II shows that the plasma TSH concentrations were higher at all three time periods in ATD compared with age-related MDD (morning, $P<0.002$; afternoon, $P<0.02$; evening, $P<0.05$). Female ATD patients had significantly higher plasma TSH concentrations throughout the day compared with age-related female control subjects (morning, $P<0.05$; afternoon, $P<0.05$; evening, $P<0.02$), and morning TSH concentrations were greater than 6 mU/litre in seven of 13 (54%) ATD women but only in one female other dementia patient and no female MDD patients or control subjects. The other dementia patients had plasma TSH concentrations similar to those in control subjects. Plasma triiodothyronine (T_3) and thyroxine (T_4) and reverse triiodothyronine (rT_3) concentrations were similar in ATD and age-related control subjects (ATD, mean ± s.e., $T_4 = 96.4 \pm 5.7$ nmol/litre, $T_3 = 1.58 \pm 0.09$ nmol/litre, $rT_3 = 0.30 \pm 0.05$ nmol/litre; control subjects, mean ± s.e., $T_4 = 99.5 \pm 4.5$ nmol/litre, $T_3 = 1.73 \pm 0.07$ nmol/litre, $rT_3 = 0.22 \pm 0.01$ nmol/litre). All subjects had T_3 and T_4 concentrations within the normal laboratory range. One ATD patient had very high plasma TSH concentrations (mean for the day 98.5 mU/litre) but normal T_3, T_4 and rT_3 concentrations and no clinical features of hypothyroidism. This patient's thyroid status was reassessed over a 4-year period, during which she developed no features of hypothyroidism, her T_3 and T_4 remained within the normal range and her plasma TSH concentrations gradually declined to a value of 10.9 mU/litre.

Cortisol

At all three time periods, MDD had higher plasma cortisol concentrations than control subjects ($P<0.05$) but not significantly greater than ATD (Table III). In the evening, ATD patients and also the other dementia patients had significantly higher plasma cortisol concentrations than control subjects ($P<0.05$).

After the administration of dexamethasone, three of 15 ATD patients (20%) had a 16:00 cortisol concentration greater than 138 nmol/litre and the 23:00 post-dexamethasone cortisol was also raised in these three patients. In patients with MDD, six of 13 (46%) had 16:00 cortisol concentrations greater than 138 nmol/litre. In the other dementia group three of 9 patients (two Picks and one Huntington's) had 16:00 cortisol concentrations greater than 138 nmol/litre. The ATD patients had a lower ($P<0.05$) 16:00 post-dexamethasone cortisol concentration (115 ± 57 nmol/litre) than the depressed patients (167 ± 36 nmol/litre).

Oestrogen-stimulated neurophysin

Plasma ESN concentrations (Table III) were significantly lower at all three time periods in ATD compared with MDD patients (morning, $P<0.01$; afternoon, $P<0.01$; evening, $P<0.05$) and with control subjects (morning, $P<0.001$; afternoon, $P<0.01$; evening, $P<0.001$). They were also lower in the morning ($P<0.05$) in ATD as compared with other dementia patients. The nine values for each patient or control subject were averaged and the plasma ESN concentration for the day was significantly lower in ATD compared with MDD ($P<0.001$), other dementias ($P<0.05$) and control subjects ($P<0.001$) (Fig. 1). All ATD patients had a mean plasma ESN concentration < 170 pmol/litre. The averages of the nine plasma ESN concentrations for the day for the ATD patients were also compared with the average ESN concentrations of 37 patients with psychosis, who were within the age range 50–72 years but not all of whom met the drug-free criteria. The elderly psychotic group had higher plasma ESN concentrations – 161 ± 18 pmol/litre – compared with the ATD patients – 105 ± 6 pmol/litre ($P<0.001$).

Prolactin and luteinising hormone concentrations

Plasma prolactin concentrations (mean ± s.e.) were similar in ATD (morning 493 ± 123 mU/litre, afternoon 355 ± 27 mU/litre, evening 360 ± 26 mU/litre), age-related MDD (morning 687 ± 304 mU/litre, afternoon 678 ± 313 mU/litre, evening 527 ± 158 mU/litre), other dementias (morning 403 ± 57 mU/litre, afternoon 318 ± 30 mU/litre, evening 425 ± 36 mU/litre) and control subjects (morning 344 ± 36 mU/litre, afternoon 291 ± 20 mU/litre, evening 335 ± 28 mU/litre).

Plasma LH concentrations (mean ± s.e.) did not differ significantly in post-menopausal women with ATD ($n = 11$; morning 16.4 ± 1.6 U/litre, afternoon 14.3 ± 1.1 U/litre, evening 15.0 ± 1.4 U/litre) compared with female patients with other dementia ($n = 5$; morning 11.9 ± 2.3 U/litre, afternoon 12.0 ± 1.6 U/litre, evening 12.7 ± 1.6 U/litre) and post-menopausal female control subjects ($n = 9$; morning

TABLE III
Plasma cortisol and oestrogen-stimulated neurophysin concentrations

	Cortisol (nmol/l)[1] (mean ± s.e.)				Oestrogen-stimulated neurophysin (pmol/l)[2] (mean ± s.e.)			
	n	*Morning*	*Afternoon*	*Evening*	*n*	*Morning*	*Afternoon*	*Evening*
Alzheimer	17	469 ± 23	244 ± 22	210 ± 25*	16	105 ± 6***	102 ± 6**	107 ± 9***
Depression	16	511 ± 31*	301 ± 39*	214 ± 24*	14	230 ± 41††	239 ± 45††	202 ± 37†
Other dementias	9	530 ± 41*	274 ± 41	249 ± 34*	9	192 ± 44§	173 ± 36	163 ± 34
Controls	37	436 ± 25	230 ± 13	154 ± 16	36	191 ± 24	185 ± 25	239 ± 38

1. Conversion, SI to traditional units, cortisol: 1 nmol/litre ≈ 0.36 μg/litre.
2. Conversion, SI to traditional units, ESN: 1 pmol/litre ≈ 0.012 μg/litre.
*v. control subjects $P<0.05$: ATD v. controls: **$P<0.01$, ***$P<0.001$; ATD v. MDD, †$P<0.05$, ††$P<0.01$; ATD v. other dementias, §$P<0.05$.

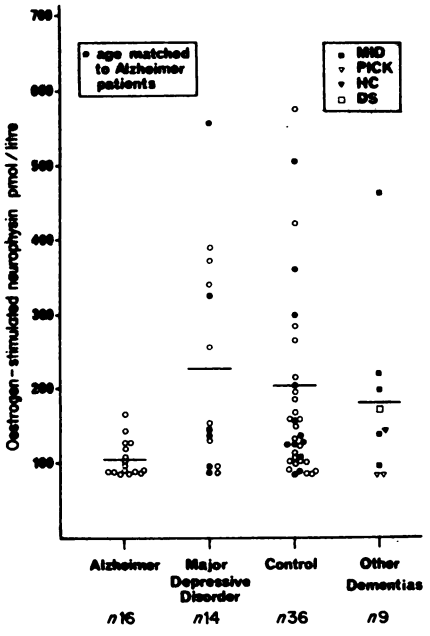

FIG. 1 Mean plasma oestrogen-stimulated neurophysin concentrations based on nine estimations in 'neuroendocrine day' studies carried out in patients with Alzheimer-type dementia (ATD) major depressive disorder (MDD) and other dementias (MID = multi-infarct dementia, Pick = Pick's disease, HC = Huntington's chorea, DS = disseminated sclerosis) and in normal control subjects: ATD v. controls - $P<0.001$; ATD v. MDD - $P<0.001$; ATD v. other dementias - $P<0.05$ (conversion, SI to traditional units, 1 pmol/l ≈ 0.012 μg/l).

14.6 ± 2.2 U/litre, afternoon 14.3 ± 1.9 U/litre, evening 13.9 ± 1.4 U/litre).

Relationship between plasma hormone concentrations and performance in psychological tests

Table IV shows the correlations in ATD patients between the mean plasma hormone concentrations and psychological test scores. Plasma cortisol concentrations, particularly in the evening, were inversely correlated with psychological test scores; that is, the more demented patients had higher plasma cortisol concentrations. Orientation was the only subtest which showed a positive significant correlation with afternoon and evening plasma TSH concentrations. Evening plasma GH concentrations were inversely correlated with psychological test scores. There were no significant correlations between plasma ESN concentrations and psychological test scores.

Intercorrelations between plasma concentrations of TSH, GH, cortisol, prolactin and ESN in ATD and in control subjects

Plasma cortisol concentrations in the evening were inversely related to TSH concentrations in ATD ($r = -0.50$, $P<0.05$) but not in control subjects. Plasma TSH concentrations in the morning positively correlated with PRL concentrations in ATD ($r = 0.50$, $P<0.05$). Afternoon plasma concentrations of GH correlated inversely with ESN concentrations in ATD ($r = -0.52$, $P<0.05$). In the control subjects the only significant correlation was a positive correlation between evening plasma concentrations of GH and PRL ($r = 0.83$, $P<0.001$).

Diagnostic implications

Morning plasma TSH concentrations were useful in discriminating between ATD and age-related MDD patients, with 13 ATD patients (72%) but none of the MDD patients having TSH concentration greater than 4.5 mU/litre. When morning plasma TSH and ESN concentrations (TSH > 4.5 mU/litre; ESN < 170 pmol/litre) were used to discriminate between ATD, MDD, other dementias and control subjects, 75% of the ATD patients were correctly identified, together with one patient with multi-infarct dementia and one control subject, but no MDD patients; a specificity of 86% (Fig. 2).

Discussion

The present study has identified selective changes in plasma concentrations of TSH, GH and ESN that are specific to ATD and which can be related to the

TABLE IV

Correlations between mean morning, afternoon and evening plasma hormone concentrations and the score achieved in psychological tests in Alzheimer patients

	Morning	*Afternoon*	*Evening*
Growth hormone ($n=17$)			
Total score	0.01	−0.06	−0.58*
Orientation	−0.06	−0.13	−0.40
Paired Associates Learning + Logical Memory	−0.12	−0.08	−0.56*
Apraxia	−0.03	0.03	−0.33
Agnosia	0.10	−0.03	−0.46*
TSH ($n=18$)			
Total score	0.14	0.29	0.30
Orientation	0.37	0.43*	0.40*
Paired Associates Learning + Logical Memory	0.24	0.35	0.38
Apraxia	−0.19	0.17	0.14
Agnosia	0.08	0.17	0.24
Cortisol ($n=18$)			
Total score	−0.31	−0.18	−0.42*
Orientation	−0.41*	−0.16	−0.59**
Paired Associates Learning + Logical Memory	−0.38	−0.10	−0.38
Apraxia	−0.41*	−0.15	−0.27
Agnosia	−0.25	−0.05	−0.54*
Oestrogen-stimulated neurophysin ($n=16$)			
Total score	0.11	0.20	0.19
Orientation	0.26	0.12	0.23
Paired Associates Learning + Logical Memory	0.17	0.17	0.29
Apraxia	−0.06	0.23	0.16
Agnosia	−0.21	−0.14	−0.16

*$P<0.05$; **$P<0.02$.

known neurochemical deficits in ATD. Although raised plasma GH concentrations could be due to increased release of GH-releasing hormone (GHRH), it is more likely in ATD to be due to decreased release of somatostatin, which is known to be deficient in ATD. Since somatostatin also inhibits TSH, a similar mechanism may account for the increased plasma TSH concentrations in ATD. Hypothalamic TSH releasing hormone (TRH) concentrations are normal in post-mortem tissue in ATD (Yates *et al*, 1983*a*) and it is, therefore, unlikely that raised plasma TSH concentrations are due to increased release of TRH.

The increase in plasma GH and TSH concentrations is more marked in the female ATD patients.

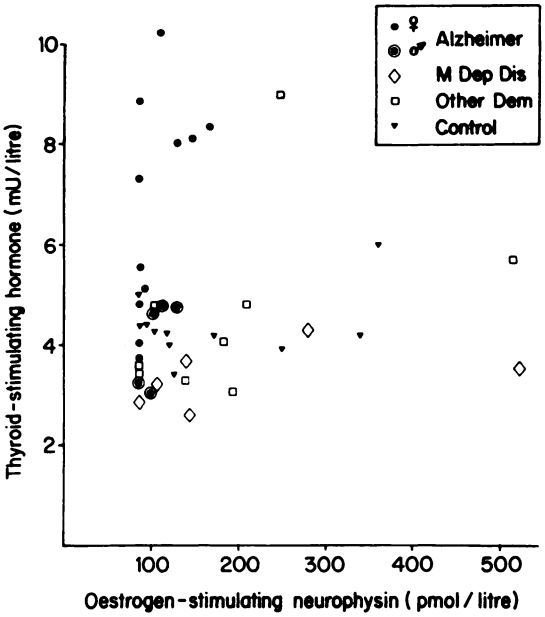

FIG. 2 Morning plasma thyroid-stimulating hormone concentrations plotted with morning oestrogen-stimulated neurophysin concentrations for patients with Alzheimer-type dementia, major depressive disorder, other dementias and control subjects.

Raised morning plasma TSH concentrations are more common in women, particularly those over the age of 45 years. In the Whickham Community Survey (Tunbridge *et al*, 1977), the percentage of morning TSH concentrations greater than 6 mU/litre was 7.5% for females and 2.8% for males for the whole population, irrespective of age. The percentage of raised TSH concentrations in the age range 55–64 years was 10% for females and 1.9% for males, and in the age range 65–74 years was 8% for females and 6.9% for males. In the present study, seven out of the 13 female ATD patients (54%) had morning TSH concentrations greater than 6 mU/litre, far in excess of that expected in the general population. The increase in plasma TSH concentrations in female ATD patients appears to be central, because peripheral indices of thyroid function (T_3, T_4 and rT_3) were within the normal range and similar to those of control subjects. Plasma GH concentrations did not correlate with TSH in either ATD or control subjects, but the control of the secretion of these hormones is complex and somatostatin is only one of many factors involved (Mendelson, 1982; Scanlon *et al*, 1980). Evening plasma TSH concentrations in ATD were inversely correlated with plasma cortisol concentrations, and it is possible that raised cortisol

concentrations in the more severely demented patients inhibit TSH secretion (Re *et al*, 1976).

The highly significant reduction of plasma ESN concentrations in ATD may be related to the marked deficiency in ATD brain of acetylcholine which is known to stimulate oxytoxin release (Poulain & Wakerley, 1982) and, therefore, presumably the oxytocin-associated ESN. The decreased ESN concentrations may, however, also be due to decreased synthesis of ESN itself, since in rats the staining intensity for the neurohypophysial hormones decreases progressively with age, especially in the paraventricular nucleus and in oxytocin-containing neurones (Watkins & Choy, 1980), but recent studies of human brain have failed to show any change in the area of oxytocin cells with increasing age (Fliers *et al*, 1985). Scrapie in sheep, which has some neuropathological features in common with those of ATD, causes degeneration of magnocellular neurones, with loss of neurophysin in the posterior pituitary gland (Parry & Livett, 1976).

The majority of studies report that concentrations of dopamine and homovanillic acid are normal in ATD (Yates *et al*, 1979; Mann *et al*, 1980). Consistent with this finding, plasma prolactin concentrations were similar in ATD patients and age-related controls in the present study, as well as in the study of Balldin *et al* (1983). The raised evening plasma cortisol concentrations in ATD compared with control subjects are not useful diagnostically, because the morning and evening plasma cortisol concentrations are increased in other dementias and increased throughout the day in MDD, as has also been shown to be the case in many previous studies of depression (Gibbons, 1964; Carpenter & Bunney, 1971; Sachar *et al*, 1973). Raised plasma cortisol concentrations are found in many psychotic patients, irrespective of the presence of depressed mood (Christie *et al*, 1986). The raised evening plasma cortisol concentrations in the ATD patients appears to be a feature of the more severely demented patients, with an inverse relationship between cortisol concentrations and psychological test scores. Only three of 15 ATD patients (20%) showed early escape from dexamethasone suppression, and the non-suppressors included the two most severely demented patients in the study. Previous studies in demented patients have suggested a 40–50% incidence of early escape from dexamethasone suppression (Raskind *et al*, 1982; Spar & Gerner, 1982; Balldin *et al*, 1983; Coppen *et al*, 1983), similar incidence to that reported in endogenous depression (Carroll *et al*, 1981), but the majority of patients, unlike those in the present study, were hospitalised, severely demented patients.

Plasma TSH and ESN concentrations are useful in discriminating between ATD, other causes of dementia and depression. Morning TSH concentrations greater than 4.5 mU/litre, identified 72% of ATD and no depressed patients, and the additional use of morning ESN concentrations improved the discrimination between ATD, other dementias, MDD and control subjects to a sensitivity of 75% and specificity of 86%.

These results show significant increases in the concentrations of GH, TSH and cortisol and a decrease in concentration of ESN in the plasma of patients with ATD. Increased plasma GH and TSH concentrations in ATD are consistent with reports of reduced somatostatin in post-mortem neurochemical studies, while decreased ESN may be caused by decreased cholinergic activity. The finding of predictable changes in pituitary output based on established neurochemical abnormalities supports the rationale for neuroendocrine studies in psychiatry. These characteristic hormonal changes in ATD provide the basis for psychopharmacological analysis of the central neurochemical abnormalities of ATD and offer important biological markers for discriminating between ATD, other dementias and major depression.

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*J. E. Christie, MPhil, MRCPsych, *Clinical Scientist and Consultant*; L. J. Whalley, MD, MRCPsych, *Clinical Scientist and Consultant*; J. Bennie, MIBiol, *Senior Research Officer*; H. Dick, MIST, *Technical Officer*; I. M. Blackburn, PhD, *Clinical Scientist and Clinical Psychologist*; D. H. R. Blackwood, PhD, MRCPsych, *formerly Clinical Scientist and Senior Registrar; now Senior Lecturer, Department of Psychiatry*; G. Fink, MD, DPhil, *Director, MRC Brain Metabolism Unit*

Correspondence: *MRC Brain Metabolism Unit, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF*

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J E Christie, L J Whalley, J Bennie, H Dick, I M Blackburn, D H Blackwood and G Fink

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