sequence T1-weighted sagittal and axial MRIs (TR = 600 ms; TE = 20 ms, matrix size 256 × 256, scan thickness 5 mm) obtained from a GE 1.5 Tesla super conductive magnet (Signa[®]) were non-specific and the tumour was not visualised, as the signal intensity of the mass was nearly isointense with the surrounding CSF (fig a).

The T2-weighted images (TR = 2500 ms; TE = 80 ms), however, revealed an intraspinal lesion which was outlined by the different signal intensities of the CSF above and below the tumour (fig b). The CSF caudal to the tumour appeared brighter compared with the CSF superior to the tumour. There were no discernible signal differences between tumour and CSF, cephalad to the tumour. Thus the entire margin of the tumour was not well delineated (fig b). Following the injection of IV Gd-DTPA, at the dose of 0.2 ml/kg (0.1 mmol/kg) the T1-weighted MRI showed marked enhancement of the tumour with its margins well delineated from the surrounding CSF (fig c). The tumour extended from the middle of L2 caudal to the upper border of L3 and measured 14 mm in the AP dimension and 32 mm in height. It was an intradural extramedullary lesion. Ependymoma and neurofibroma were the major differential diagnoses.

An L1 through L4 lumbar laminectomy was performed exposing the dark-bluish dura. The dura was opened and the encapsulated 5 × 1.5 cm bluish-brown tumour was easily identified. The CSF caudal to the tumour was xanthochromic and proteinaceous, and clear cephalad to the tumour. It arose from the filum terminale and invaded the conus medullaris. Sharp microscopic techniques were employed to resect the tumour completely. The filum terminale was amputated and a 1 mm ventrally located tumour feeding the artery was divided. The dura was closed in a watertight fashion. The patient made an uneventful recovery. His neurological examination remained intact.

Light microscopic examination of the tumour using hematoxylin and eosin revealed papillary areas consisting of low columnar cells surrounding a central core of acellular hyaline and connective tissue containing small blood vessels (fig d). The architecture of the cells was orderly without mitoses and was consistent with the pathological diagnosis of myxopapillary ependymoma.

Gadolinium DTPA is a paramagnetic contrast medium that decreases the relaxation time of T1 and T2 nuclei in tissues where it accumulates. T1 shortening increases the signal intensity of tissues, whereas T2 shortening decreases the signal. Fortunately, at lower concentrations, the T1 effect predominates. Like iodinated agents used for CT, Gd-DTPA serves as an indicator of blood-CSF barrier disruption for MRI. If this barrier is disrupted, the contrast molecules diffuse into the interstitial compartment, producing T1 shortening and enhancement of T1-weighted images. Spin-echo pulse sequence T1-weighted images were not helpful in this case as the tumour and the surrounding CSF had nearly similar signal intensities. Differences of signal intensity between the tumour and CSF on T2-weighted images allowed the visualisation of the intradural lesion. Brighter signals were observed from the CSF below the tumour secondary to its decreased flow, and increased protein content. Following Gd-DTPA injection the tumour enhanced and its margins were well delineated from the surrounding CSF and from the conus medullaris. Although its enhancing characteristic was not

specific for either a neurofibroma or ependymoma, the true extent and location of the lesion was readily identifiable.

This case confirms a previous study⁶ documenting the superior imaging capacity of Gd-DTPA MRI compared with unenhanced T1 and T2 MRI in diagnosing spinal cord ependymomas⁶ and other hitherto radiographically elusive spinal cord lesions.

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- 1 Barone BM, Elvidge AR. Ependymomas: A clinical survey. *J Neurosurg* 1970;33:428-38.
- 2 Fokes EC Jr, Earles KM. Ependymomas: clinical and pathological aspects. *J Neurosurg* 1969;30:585-94.
- 3 Monajati A, Waynes WS, Rausching W, Ekholm E. MR of the cauda equina. *Amer J Neuroradiology* 1987;8:893-900.
- 4 Sonneland PRL, Scheithauer BW, Onofrio BM. Myxopapillary ependymoma: A clinicopathologic and immunocytochemical study of 77 cases. *Cancer* 1987;56:883-93.
- 5 Specht CS, Smith TW, DeGirolami U, Price JM. Myxopapillary ependymoma of the filum terminale: A light and electron microscopic study. *Cancer* 1986;58:310-17.
- 6 Valk J. GD-DTPA in MR of spinal lesions. *Amer J Neurorad* 1988;9:345-50.
- 7 Williams AL, Haughton VM, Poonas KW, Daniels DL, Kilgore DP. Differentiation of intramedullary neoplasms and cysts by MR. *Amer J Neurorad* 1987;8:527-32.

Somatostatin receptors and the modulation of adenylyl cyclase activity in Alzheimer's disease

The most consistently reported neuropeptide dysfunction in Alzheimer's disease is that affecting somatostatin neurotransmission, as characterised by a loss of somatostatin-like immunoreactivity and decreased numbers of somatostatin receptor recognition sites.¹ Such changes in the number of receptor recognition sites, however, give no information as to the functional integrity of the receptor in the disease state.² A recent study on rat brain established that somatostatin modulation of neural function involves the inhibition of adenylyl cyclase activity by the occupation of receptor sites negatively coupled, via GTP-binding ("G") proteins, to this enzyme.³ As a result, in our study, we

have assessed the integrity of somatostatin receptor function in Alzheimer's disease by assaying both the levels of receptor recognition sites and the ability of somatostatin to inhibit adenylyl cyclase activity.

Brains from a series of eight clinically diagnosed and histopathologically confirmed Alzheimer's disease cases [mean (SEM) age 81 (2) years, mean (SEM) post mortem delay 21 (4) hours] and eight control subjects [mean age 75 (2) years, mean post mortem delay 23 (3) hours] were collected at necropsy. Tissue from the superior temporal cortex (Brodmann area 22) was dissected, slowly frozen and stored at -70 °C until used for the preparation of synaptic membranes. Adenylyl cyclase assays were performed on washed synaptic membrane fractions (10-15 µg protein) which were incubated for 10 minutes at 30 °C in assay buffer consisting of 80 mM Tris acetate (pH 7.4), 0.5 mM ATP, 10 µM GTP 1 mM theophylline, 0.3% BSA, 0.5mM EGTA, 5 mM phosphocreatine, 50 units/ml creatine phosphokinase, 2 mM MgSO₄, with and without 100 µM somatostatin-14. Assays were terminated by boiling for 3 minutes and the cyclic AMP produced assayed using a commercial kit (TRK 432, Amersham). The concentration of somatostatin-14 used (100 µM) was the same as that reported necessary to achieve inhibition of rat cortical membrane adenylyl cyclase.³

Somatostatin receptor levels were determined using extensively washed and lysed membrane preparations (ca. 70 µg protein/assay) which were incubated for 60 minutes at 37 °C in 50 mM Tris HCl (pH 7.4) buffer containing 10 mM MnCl₂, 1 mg/ml BSA and 60 µg/ml bacitracin, with two different concentrations of [¹²⁵I]-Tyr¹¹-somatostatin-14 (30 and 110 pM). Non-specific binding was defined using 1 µM unlabelled somatostatin-14. Incubations were terminated by centrifugation and tissue bound radioactivity determined following washing of the pellet.

In addition to these experiments, the effects of 10 µM neuropeptide Y-36 (NPY) on adenylyl cyclase activity were determined, since this neuropeptide has also been shown to mediate inhibition of the enzyme.⁴ Such experiments were also considered important in view of the known co-localisation of somatostatin and NPY in some cortical neuronal sub-populations and the reported loss of NPY immunoreactive neurons in Alzheimer's disease temporal cortex.⁵

Basal adenylyl cyclase enzyme activities in the control and Alzheimer's disease groups were not significantly different from each other (table). The large apparent difference (20%) between the control and Alzheimer's disease group basal activities was due to a single control case showing high activity (138.2 pmol cAMP/min/mg protein).

Table Somatostatin receptor function in Alzheimer's disease

Adenylyl cyclase activity	Control	Alzheimer's disease
Basal activity ¹	60.3 (11.8)	47.4 (6.0)
activity + 100 µM somatostatin ¹	48.6 (8.8)	43.0 (6.3)
difference from basal ¹	11.7 (3.2)	4.4 (1.2)**
% somatostatin inhibition of basal activity	18.3 (1.9)	10.1 (2.5)*
activity + 10 µM NPY ¹	39.5 (9.2)	32.2 (5.8)
difference from basal ¹	20.8 (3.0)	15.2 (2.0)
% NPY inhibition of basal activity	36.2 (2.5)	33.7 (4.9)
[¹²⁵ I] Tyr Somatostatin binding		
110 pM [¹²⁵ I] somatostatin ²	19.9 (4.2)	14.7 (2.6)
30 pM [¹²⁵ I] somatostatin ²	6.2 (1.3)	5.2 (0.9)

**p < 0.02 two-tailed Mann-Whitney U-test, with respect to corresponding control values.

*p < 0.05 two-tailed Mann-Whitney U-test, with respect to corresponding control values.

1. pmol cAMP/min/mg protein, mean (SEM).

2. fmol/mg protein, mean (SEM).

In both the control and Alzheimer's groups, significant inhibitions of adenylyl cyclase activity were produced by somatostatin ($2P = 0.012$, Wilcoxon's matched-pairs signed ranks test) and NPY ($2P = 0.012$). In the Alzheimer's group, however, the degree of somatostatin enzyme inhibition was significantly lower than that for the control group. This difference was seen when both the absolute decreases in cAMP produced and the percentage decreases in basal activity were compared (table). Furthermore, there was a larger spread in the observed somatostatin inhibitions for the Alzheimer's group (compare the SEM values to the mean values in the table). In three of the Alzheimer's cases, essentially no somatostatin inhibition of adenylyl cyclase activity was found, whereas the lowest percentage inhibition seen in the control cases was 12%. For the control group, there were found to be no correlations (Spearman's rank) between either basal activity, somatostatin or NPY inhibitions of basal activity and age or postmortem delay.

The levels of $^{125}\text{Tyr}^{11}$ -somatostatin-14 binding in the control and Alzheimer's disease groups were not significantly different (table), a finding in accordance with some⁶ but not all¹ previous reports. These data suggest that the lower degree of somatostatin inhibition of adenylyl cyclase activity in the Alzheimer's group was not due simply to a lower receptor number in this group. Important also to note, was that the degree of NPY enzyme inhibition was similar in both groups, indicating that the observed deficit was specific to the somatostatin system and was unlikely to be a result of such factors as agonal status or drug treatment of the disease cases.

This study showing a reduced somatostatin modulation of adenylyl cyclase activity in Alzheimer's disease is the first to our knowledge demonstrating a functional deficit of somatostatin receptor integrity in this disorder.² Further experiments will be necessary to determine the mechanism underlying this dysfunction, such as for example studying the integrity of somatostatin receptor—"G"-protein—adenylyl cyclase interactions. It will also be interesting to determine whether this dysfunction is found in other brain regions showing different degrees of Alzheimer's disease pathology and whether it is important for the cognitive decline seen in the disorder.

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- 1 Cowburn RF, Roberts PJ, Hardy JA. Transmitter deficits in Alzheimer's disease. In: Davies DC, ed. *Alzheimer's disease: towards an understanding of the aetiology and pathogenesis*. London: John Libbey, 1989:9–32.
- 2 Fowler CJ, O'Neill C, Garlind A, Cowburn RF. Alzheimer's disease: is there a problem beyond recognition? *Trends in Pharmacol Sci* 1990;11:183–4.
- 3 Schettini G, Florio T, Meucci O, Landolfi E, Grimaldi M, Ventra C, Marino A. Somatostatin inhibition of adenylyl cyclase in different brain areas. *Brain Res* 1989;492:65–71.

- 4 Westlind-Danielsson A, Undén A, Abens J, Andell S, Bartfai T. Neuropeptide Y receptors and the inhibition of adenylyl cyclase in the human frontal and temporal cortex. *Neurosci Lett* 1987;74:237–42.
- 5 Davies CA, Morroll DR, Prinja D, Mann DMA, Gibbs A. A quantitative assessment of somatostatin-like and neuropeptide Y-like immunostained cells in the frontal and temporal cortex of patients with Alzheimer's disease. *J Neurol Sci* 1990;96:59–74.
- 6 Whitford C, Candy J, Edwardson JA, Perry R. Cortical somatostatinergic system not affected in Alzheimer's and Parkinson's diseases. *J Neurol Sci* 1988;86:13–18.

Plasma dopamine-beta-hydroxylase activity in depressed patients: role of treatment

Dopamine-beta-hydroxylase (DBH) catalyses the hydroxylation of dopamine to noradrenaline and is known to be released with the neurotransmitter from the peripheral sympathetic nerves.^{1,2} It has been suggested that serum DBH could be an index of the activity of the sympathetic nervous system.³ Moreover, several authors have established a relationship between central noradrenergic deficiency and the occurrence of depressive disorders. Plasma DBH measurements in depressive disorders has led to conflicting results although most authors found decreased DBH activity.^{4,5} Large inter-individual variations in plasma DBH activity can explain these discrepancies. Thus the aim of this study was to compare plasma DBH activity in the same depressed inpatients before and after antidepressant treatment.

Seventeen patients [two men and 15 women, mean (SEM) age: 40.5, (15.2) years] were included in this study. They all suffered from major depressive disorders according to DSM 3 R criteria and were treated with tricyclic antidepressants. Patients treated with ECT or drugs acting on the autonomic nervous system (especially cardiovascular drugs or neuroleptics) were excluded. Plasma DBH was measured at rest after an overnight fast before and five weeks after antidepressant treatment using the spectrophotometric method of Nagatsu and Udenfriend⁶ with tyramine as substrate. The assays were performed blind to diagnosis. The changes were evaluated before and after treatment using a Wilcoxon test. The comparisons with a control group of 15 normal healthy volunteers [six men and nine women, mean (SEM) age: 34, (8) years] were performed using a Mann-Whitney test. The level of significance was $p < 0.05$.

All the patients were clinically euthymic at the second DBH measurement (that is, five weeks after the beginning of the treatment). Mean plasma DBH activity (SEM) was 18.39, (2.02) $\mu\text{mol/min/l}$ in controls; 6.43, (1.08) $\mu\text{mol/min/l}$ in depressed patients before treatment ($p < 0.01$ when compared with controls) and 10.82, (2.56) $\mu\text{mol/min/l}$ in euthymic patients (that is, depressed patients treated by antidepressants) ($p < 0.01$ when compared with values obtained in these patients before treatment).

Although plasma DBH activity is a peripheral blood index, it more directly reflects the metabolism of catecholamines than other indices such as the metabolite MHPG or dexamethasone suppression test which, are indirect approaches of central noradrenergic activity. Plasma DBH activity may reflect the state of releasable stores of the enzyme in sympathetic nerve endings.⁷

It may be concluded that plasma DBH activity is decreased in depressed patients when compared with age-matched controls. Whether this decrease is observed in every patient or in a subgroup remains a prospective for future studies.

The most interesting and original result is the increase in plasma DBH activity in euthymic patients, that is, after five weeks of treatment with tricyclic antidepressants. The respective role of antidepressant drugs and thymic improvement remains unclear. However, the level of plasma DBH activity remains significantly ($p < 0.05$) lower in euthymic patients than in controls thus a genetic component in the pathophysiology of depressive states could be suggested since altered plasma levels of DBH may reflect a genetic susceptibility.² Finally, further studies are needed to evaluate the potential interest of serum DBH activity as a marker of depressive states or at least clinical subtypes of depression.

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- 1 Weinshilboum RM. Serum dopamine-beta-hydroxylase. *Pharmacol Res* 1989;30:133–66.
- 2 Kopin IJ. Plasma levels of catecholamines and dopamine-beta-hydroxylase. In: Trendelenburg U, Weiner N, eds. *Catecholamines II: Handbook Exp Pharmacol*. Berlin: Springer Verlag, 1989:211–75.
- 3 Laduron P. Scope and limitation in dopamine-beta-hydroxylase measurements. *Biochem Pharmacol* 1975;24:557–62.
- 4 Sapru MK, Rao BSSR, Channabasavanna SM. Serum dopamine-beta-hydroxylase activity in clinical subtypes of depression. *Acta Psychiatr Scand* 1989;80:474–8.
- 5 Puzynski S, Rode A, Zaluska M. Studies on biogenic amine metabolising enzymes (DBH, COMT, MAO) and pathogenesis of affective illness. *Acta Psychiatr Scand* 1983;67:89–95.
- 6 Nagatsu T, Udenfriend S. Photometric assay of dopamine-beta-hydroxylase activity in human blood. *Clin Chem* 1972;18:980–3.
- 7 Hörtnagl H, Stadler-Wolfersgrün R, Brücke T, et al. Changes of dopamine-beta-hydroxylase activity in human plasma during prolonged overactivity of the sympathetic nervous system in various diseases. *Naunyn-Schmiedeberg's Arch Pharmacol* 1978;303:235–42.