should alert the clinician to use fludrocortisone with caution and the plasma albumin level should be carefully monitored—since any fall in the latter will potentiate the effect of the mineralocorticoid. The development of the nephrotic syndrome or of congestive cardiac failure, by producing fluid retention and secondary aldosteronism, has a “protective effect” in relieving the postural hypotension in autonomic neuropathy, although vascular reflexes such as the Valsalva manoeuvre and blood pressure response to sustained handgrip will still be abnormal.¹⁴ Fludrocortisone may therefore have to be balanced with a diuretic to avoid serious postural hypotension or excessive fluid retention. Provided fludrocortisone is used with caution in these conditions, it is most useful for treating diabetics with troublesome postural hypotension.

Request for reprints should be addressed to Dr I W Campbell.

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Role of the kidney in regulating plasma immunoreactive beta-melanocyte-stimulating hormone

A G SMITH, SAM SHUSTER, A J THODY, F ALVAREZ-UDE, D N S KERR

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Summary

An analysis of the factors that influence the increase in plasma immunoreactive β -melanocyte-stimulating hormone (β -MSH) concentrations in chronic renal failure showed that: (a) the increase correlated with the increase in serum creatinine concentrations; (b) β -MSH was not cleared from the plasma by haemodialysis; (c) β -MSH concentrations increased with length of time on dialysis and increased further after bilateral nephrectomy but there was no further increase with time; (d) β -MSH levels decreased to normal after renal transplantation; and (e) β -MSH was excreted in urine only when plasma levels rose to well above those of chronic renal failure (in Nelson's syndrome). These findings suggest that the kidney regulates plasma β -MSH by a non-excretory mechanism and is the major site of β -MSH metabolism.

Introduction

We,¹ and others,² have recently found increased plasma concentrations of immunoreactive β -melanocyte-stimulating hormone (β -MSH) in patients with chronic renal failure. By relating the changes in β -MSH levels to severity of renal failure and by studying the effect of various treatments on the plasma concentration of the hormone, we were able to find evidence for the mechanisms of this abnormality.

University Department of Dermatology, Newcastle upon Tyne NE1 4LP

A G SMITH, MB, MRCP, Wellcome research fellow
SAM SHUSTER, PHD, FRCP, professor of dermatology
A J THODY, PHD, lecturer

University Department of Medicine, Newcastle upon Tyne NE1 4LP
F ALVAREZ-UDE, LMS, research registrar
D N S KERR, MSc, FRCP, professor of medicine

Patients and methods

Forty-five patients with chronic renal failure (CRF) were studied. Fourteen patients were treated conservatively (group 1) and others with more advanced CRF were treated as follows: 15 patients who had not undergone nephrectomy were on haemodialysis (group 2); eight patients who had undergone bilateral nephrectomy were on haemodialysis (group 3); and eight patients who had undergone renal transplantation from two to 31 months previously and in whom the serum creatinine was below $177 \mu\text{mol/l}$ (2 mg/100 ml) were taking prednisone 10-40 mg/day and azathioprine 150 mg/day (group 4).

Blood was taken from each patient (immediately before dialysis in those so treated) and plasma immunoreactive β -MSH was measured by a modification of the method of Thody and Plummer.³ In one patient blood was taken on two occasions from the arterial line at the start of haemodialysis, from the arterial and venous lines after three hours of dialysis, and from the arterial line at the end of dialysis. On the first occasion an Ultraflo 2 coil with Cuprophane was used and on the second a Rhone Poulenc RP6 dialyser with high permeability acrylonitrile membrane linked to a closed circuit monitor. In a second patient blood was taken before haemodialysis (using the Ultraflo 2 coil), during dialysis, and after dialysis.

Urinary immunoreactive β -MSH was measured in one normal subject and in four patients with Nelson's syndrome. A 100-ml sample of freshly passed urine was first concentrated by freeze drying. The residue was dissolved in 10 ml of diluent buffer, which was acidified to pH 4 and the β -MSH extracted by adsorption on to the silicate Spherosil. The β -MSH was eluted from the Spherosil by a solution of equal parts of ammonia and ethanol; this solution was evaporated off and the β -MSH assayed as for the plasma. With this method the recovery of added synthetic human β -MSH to 100 ml urine was up to 40%.

Results

In patients with chronic renal failure not yet requiring treatment by dialysis there was a correlation between the degree of renal impairment as measured by serum creatinine levels and the plasma levels of β -MSH (fig 1).

Of the patients maintained on haemodialysis those who had undergone bilateral nephrectomy had significantly higher levels of β -MSH than those who had not (fig 2). The mean value ($\pm$ SE) for patients with kidneys was $249 \pm 46 \text{ ng/l}$, which was significantly less than the mean value of $558 \pm 69 \text{ ng/l}$ after nephrectomy ($P < 0.001$). This difference did not relate to the duration of dialysis, as the mean

length of time on haemodialysis was 22 months in the bilateral nephrectomy group and 27 months in those who still had their kidneys. This suggested the possibility that the diseased kidneys maintained a function in MSH metabolism. This possibility was tested by relating plasma β -MSH levels to duration of terminal renal failure since progressive deterioration of renal function would be likely to occur with time. A significant correlation ($r = 0.61$; $P < 0.02$) was indeed found between the plasma β -MSH levels and the number of months on dialysis in the patients who had kidneys but not in those who had had a bilateral nephrectomy (fig 3). After restoration of renal

FIG 1—Correlation between plasma immunoreactive β -MSH and serum creatinine concentrations.
Conversion: SI to traditional units: Creatinine: $1 \mu\text{mol/l} \approx 0.0113 \text{ mg/100 ml}$.

FIG 2—Plasma immunoreactive β -MSH during haemodialysis treatment in patients who retained their kidneys and those who underwent bilateral nephrectomy. Open circles and bars indicate means $\pm$ SE.

FIG 3—Difference in effect of total duration of dialysis on plasma β -MSH levels in patients treated by bilateral nephrectomy and those not.

FIG 4—Effect of transplantation on plasma β -MSH levels. Open circle and bar indicate mean $\pm$ SE.

function by transplantation the plasma β -MSH levels returned to normal (fig 4).

The possibility that plasma is cleared of β -MSH by renal excretion was studied in one normal subject and four patients with raised plasma β -MSH levels due to Nelson's syndrome. Urinary excretion was negligible until plasma levels rose to well above those found in chronic renal failure (table I).

The lack of effect of dialysis on plasma β -MSH levels during dialysis is shown in table II.

TABLE I—Plasma and urinary levels of immunoreactive β -MSH in four patients with Nelson's syndrome and one normal subject

Case No:	1	2	3	4	Normal subject
Plasma immunoreactive β -MSH (ng/l)	30 000	4000	2000	100	20
Urinary immunoreactive β -MSH (ng/l)	100	2	20	1	0

TABLE II—Plasma immunoreactive β -MSH levels (ng/l) during dialysis in two patients

	Ultraflo 2 coil (patient A)	RP6 Highly permeable membrane (patient A)	Ultraflo 2 coil (patient B)
Before dialysis	466	400	250
Arterial line during dialysis	426	466	250
Venous line during dialysis	426	505	200
After dialysis	490	465	300

Discussion

In our previous study of patients with chronic renal failure¹ we found a great increase in plasma immunoreactive β -MSH concentrations. Our present study confirms this observation and that Gilkes *et al.*² We could relate the magnitude of the increase in β -MSH levels to the severity of renal failure, as measured by the serum creatinine concentration. In our earlier study, in which we included patients on dialysis, we could not show this correlation, presumably because of the effect of dialysis on serum creatinine and the fact that the patients were near or at the end-stage of renal failure.

Dialysis does not remove β -MSH from the plasma and this correlation suggests that the change in plasma β -MSH is causally related to the severity of renal damage. This is supported by (a) the higher levels of β -MSH found in patients on haemodialysis who also had had a bilateral nephrectomy, (b) the direct relationship of plasma β -MSH to the progression of intrinsic renal damage as indicated by the total duration of dialysis in patients who retain their kidneys, and (c) the observation that transplantation of a healthy kidney restores plasma β -MSH

levels to normal, although we cannot exclude the possibility that prednisone, administered for immunosuppression, may have contributed to the decrease in plasma β -MSH concentration.

The way that the kidney influences β -MSH metabolism is uncertain. Since the patients on haemodialysis who retain their kidneys pass little urine the difference in plasma β -MSH levels between those with kidneys and those without suggests that the kidney regulates β -MSH metabolism by a non-excretory mechanism. This is supported by our studies of urinary β -MSH, which showed that significant amounts of β -MSH were excreted in the urine only when plasma levels rose to well above the levels of chronic renal failure.

There are two possible non-excretory mechanisms: the kidney may influence β -MSH secretion or control its metabolism. The difference in plasma β -MSH levels between patients with kidneys and those without kidneys excludes the possibility of a pituitary stimulator elaborated by the diseased kidney or a metabolite retained in the blood despite dialysis. It does not exclude, however, the possibility of a retained stimulator that is normally destroyed by the kidney. An alternative hypothesis is that the kidney normally produces a factor that inhibits β -MSH secretion by the pituitary. Production of this factor would progressively decrease in chronic renal failure, resulting in a greater secretion of pituitary β -MSH. This and pituitary stimulation seem unlikely, especially since the increased β -MSH secretion would generally be associated with an increased secretion of ACTH,⁴ and this has not been found in CRF.² Thus the most probable explanation is that the kidney is the major site of β -MSH metabolism, and impairment of this metabolism leads to increased plasma β -MSH levels in CRF.

The exact nature of immunoreactive β -MSH is unknown in CRF although it appears to be lipotrophin in normal people.^{1 2} The RP6 membrane is permeable to molecules with a molecular weight of less than 10 000. Thus substances with a molecular weight of less than 5000 should show an arteriovenous difference during dialysis. The findings in table II suggest that the hormone must have a molecular weight well above 5000 and is therefore unlikely to be the 22-amino-acid synthetic human β -MSH, which has a molecular weight of about 2500. Thus our findings suggest that the immunoreactive β -MSH of chronic renal failure is a lipotrophin. The function of this hormone is not known in man, although lipotrophin and MSH peptides are sebostrophic in the rat.^{5 6} As the present evidence suggests that β -MSH is metabolised by the kidney the possibility that it acts on this organ in health would merit attention.

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SHORT REPORTS

Guanethidine sympathetic blockade: its value in reimplantation surgery

The reimplantation of severed digits is relatively new, the first successful reimplantation being performed by a Chinese surgeon in 1967¹, since then the number of reimplantations has increased dramatically. Sympathetic blockade of the injured arm has two theoretical advantages; firstly, it improves the blood flow to the reanastomosed fingers and, secondly, it decreases the risk of vasospasm. Stellate ganglion blockade has been used on an intermittent basis for up to 18 days.² Complications associated with a stellate ganglion blockade include Horner's syndrome, pneumothorax, and intradural and extradural injection. To avoid these complications Lendvay³ used adrenergic blockade with chlorpromazine. The vasodilation, however, was incomplete and the patients were heavily sedated.

In 1974 Hannington-Kiff⁴ described a new method of sympathetic blockade; the highly tissue-bound drug guanethidine was isolated in a limb by using a tourniquet. Guanethidine displaces the nor-adrenaline from sympathetic nerve endings and produces a continuous sympathetic blockade lasting from several days to three weeks. This method has been used on three occasions and one case is reported here.

Case report

A 42-year-old man suffered a crush injury to his left thumb; he had no relevant medical history and examination was otherwise negative. Examination of the thumb showed a partial amputation with no nerve or vessel continuity; and it was decided to attempt reanastomosis. The time between injury and start of anaesthesia for reimplantation of the thumb was four-and-a-half hours. Immediately after induction of anaesthesia, a 19-gauge butterfly needle was inserted into the dorsum of the left hand and the limb exsanguinated using an Esmarch's bandage. The tourniquet was then inflated. Guanethidine 20 mg diluted in 20 ml of physiological saline together with 500 units of heparin was then injected into the arm.

The tourniquet was inflated for two hours, during which time internal fixation of the fractured proximal phalanx and metacarpus was performed. On tourniquet release there was no change in blood pressure. The efficacy of the block was assessed by comparing the temperature in the reimplanted thumb with that in the fingers and thumb of the opposite hand. This was done with a sensitive thermocouple, care being taken to avoid measuring temperatures after a dressing change. The figure shows a sustained rise in skin temperature of the reimplanted left thumb and also of the left index finger compared with the normal right hand. There was also a consistent $\frac{1}{2}^{\circ}\text{C}$ difference between thumb and fingers in both blocked and unblocked hands. The reimplantation was a success. The patient now has a fully functional thumb with minimal sensory loss.

Temperature in thumbs and index fingers after reimplantation of left thumb.