NORMALISATION OF GROWTH HORMONE HYPERSECRETION IN URAEMIC DIABETICS AND NON–DIABETICS. STUDIES WITH ARTIFICIAL PANCREAS AND ARTIFICIAL KIDNEY

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Introduction

Haemodialysis of diabetic patients is often complicated by serious electrolyte and metabolic abnormalities occurring during as well as after dialysis. The aim of the present investigation was to study the occurrence and dynamics of these abnormalities.

The problems encountered are often especially difficult when dialysis against glucose-free dialysate is performed, as is the case in many centres. While non-diabetic uraemic patients are easily able to withstand the loss of 20–30 grammes of glucose occurring during 5–7 hour dialysis and maintain their blood sugar at normal values, insulin treated diabetics often reach quite hypoglycaemic values during rather prolonged periods. It is interesting that such diabetics who have neuropathy of diabetic as well as uraemic aetiology as a rule exhibit no signs or symptoms of hypoglycaemia. Neither are they able to respond with the well-known counter-regulatory secretion of growth hormone and glucagon during hypoglycaemia, as it will be demonstrated in the present report.

The behaviour of relevant hormones and metabolites during haemodialysis performed at normoglycaemia maintained by the use of an artificial beta cell (Biostator R) will also be illustrated.

Material and Methods

Four young non-obese uraemic juvenile-onset insulin-treated diabetics and five non-diabetics matched for age, sex and bodyweight all on long-term treatment with haemodialysis were studied with half-hourly blood samples during a 24 hour period involving 5–7 hour haemodialysis using 1.3m² Cordis artificial kidney. The dialysate was glucose free, buffered with acetate 33mMol/L pH 7.2. Two experiments (morning and evening dialysis) were performed in each diabetic and one experiment (morning dialysis) in each of the non-diabetics. The diabetics were further studied twice (morning and evening dialysis) with an
artificial beta cell (Biostator R) operative during the periods of haemodialysis.

Plasma growth hormone, pancreatic glucagon and insulin were measured by wick chromatography [1]. Lactate, pyruvate, alanine, glycerol and β-hydroxybutyrate were measured by fluorimetric assays [2], and FFA by a modification of the method of Ho and Meng [3].

Results and Discussion

Figure 1 shows the patterns of plasma glucose, growth hormone, glucagon, FFA, glycerol, beta-hydroxybutyrate, lactate and alanine during a 24 hour period in one diabetic patient. Haemodialysis was performed from 08.00 to 13.00 hr. A reduced insulin dose was given in the morning and the usual dose in the evening and the next morning. Meals were eaten as indicated and the patient was asleep during night. Initially the blood sugar was in the low normal range. Despite breakfast, blood glucose dropped to around 20mg% and stayed there until 20 grammes intravenous glucose was given after which it again decreased. After dialysis and the meals indicated blood glucose rose to acceptable levels of between 100 and 200mg%. The patient was totally unaware of the two prolonged hypoglycaemic episodes.

The initial decrease in plasma growth hormone from a very high peak continues during the early part of the haemodialysis and plasma growth hormone then remains perfectly stable at low normal levels throughout dialysis and during the following 5 hours, whereafter it regains the high and fluctuating pattern characteristic of diabetic and uraemic patients [4,5]. It is also seen that the two hypoglycaemic episodes induce no trace of growth hormone secretion or any increase in the pancreatic glucagon level.

The behaviour of the other parameters i.e. the free fatty acids, glycerol, beta-hydroxybutyrate, lactate and alanine is unremarkable. The increase in free fatty acids is due to the loading dose and boluses of heparin necessary to prevent clotting in the artificial kidney.

This immediate suppression of growth hormone secretion during haemodialysis and the succeeding few hours has now been observed in most of the 25 cases studied so far regardless of the circumstances of dialysis i.e. whether it was performed during hypoglycaemia or constant normoglycaemia maintained by glucose infusions or by the artificial pancreas.

The same pattern of suppression of plasma growth hormone during dialysis often continuing for some hours afterwards has been observed in uraemic non-diabetic patients, who are also characterised by having high and fluctuating growth hormone [6]. The notable difference between non-diabetic and diabetic uraemics is that the former are able to remain normoglycaemic during dialysis against glucose-free medium. This must be due to the ability of non-diabetic uraemics to adjust their insulin output in accordance with the losses of glucose during dialysis (20–30g) and with the decrease in insulin resistance occurring during the rapid amelioration of their azotaemic state. The diabetic patients suffer from hypoglycaemia because of the continuing release of insulin from subcutaneous depots and from their antibody-bound insulin in plasma.

The nature of this dialysis-induced suppression of growth hormone hyper-
secretion is unknown. We have tried further to study its efficiency and how it operates by administering well-known growth hormone stimuli like arginine infusion, oral L-dopa and insulin hypoglycaemia during and immediately after dialysis. None of these were able to penetrate the suppressive effect of dialysis.

We have found that the disappearance of growth hormone in serum is not just caused by adhesion to or penetration through the dialysis membrane. This is also borne out by the fact that the suppression often continues for some hours after cessation of dialysis. Neither is it due to the rise in FFA induced by heparinisation during dialysis. Obviously it is tempting to speculate that some unknown growth hormone stimulating factor is operative in uraemia and dia-
betes which rapidly disappears during dialysis and reappears at a variable point of time after dialysis. We have looked for such a factor in the ultrafiltrate after lyophilisation and fractionation, so far without success.

Theoretically, the observed growth hormone suppression might also be due to increased secretion of a growth hormone inhibitor during dialysis. So far we can say that no increase occurs in plasma somatostatin during dialysis.

In conclusion, it seems as if the growth hormone hypersecretion of diabetes and uraemia is caused by metabolic substances small enough to be rapidly dialysable, so that plasma growth hormone is suppressed to very low values usually within an hour after commencement of haemodialysis. Further, that renewed formation of plasma concentrations of the substances adequate enough to re-induce abnormal growth hormone secretion often requires some hours after discontinuation of haemodialysis.

References