HYPERGLUCAGONAEMIA AND RENAL FAILURE

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The heterogeneity of circulating glucagon is now well documented.

In order to study the contribution of the different glucagon immunoreac-
itive components in the hyperglucagonaemia present in renal failure, plasma
from long-term haemodialysis patients, normal subjects and dogs either
nephrectomised or sham-operated was filtered on Bio Gel P-30 columns and
assayed by a specific pancreatic glucagon radioimmunoassay (Antiserum 30K,
kindly donated by Dr RH Unger, Dallas, Texas).

Figure 1. Basal plasma glucagon immunoreactive (30K antiserum) components (mean ± SD)
in long-term haemodialysis patients (HD) compared with those in normal subjects in
basal state. Bio Gel P-30. Differences between values were tested for significance by the
Student’s test.
Total plasma glucagon in haemodialysed patients (n=32) ranged from 180 to 1080 pg/ml; the mean values were significantly high compared to normals (450 ± 209 pg/ml vs 166 ± 73 pg/ml, n=33, mean ± SD, p < 0.001). In these patients total plasma glucagon levels were not affected by residual renal function or by the presence of kidneys and they were not correlated with the plasma creatinine levels.

Plasma gel filtration from nine haemodialysed patients yielded (Figure 1), as did plasma from normals, four glucagon immunoreactive fractions (GIR) which measured: ‘Big Plasma Glucagon’ (BPG) 119 ± 85 pg/ml of plasma (normals 73 ± 22 pg/ml), 9000 mol wt GIR 242 ± 165 pg/ml (normals 27 ± 14 pg/ml, p < 0.001), 3500 mol wt GIR 84 ± 65 pg/ml (normals 23 ± 22 pg/ml, p < 0.02) and 2000 mol wt GIR 13 ± 13 pg/ml (normals 11 ± 8 pg/ml).

In one-day anephric dogs total plasma glucagon immunoreactivity was remarkably high compared with sham-operated dogs (1887 ± 1028 pg/ml, n=7 vs 198 ± 115 pg/ml, n=6, p<0.005) and this hyperglucagonaemia was similarly distributed by gel filtration as in haemodialysed patients, with high levels of the 3500 mol wt GIR (364 ± 188 pg/ml, p < 0.002 vs controls) and even higher of the 9000 mol wt GIR (777 ± 394 pg/ml, p < 0.002 vs controls).

Intravenous somatostatin (kindly donated by Dr R Guillemin, The Salk Institute, La Jolla, California) (3.3 μg/min during 60 min) in nephrectomised dogs (n=4) reduced the levels of both raised GIR components. In Figure 2 are represented the half disappearance time of the 3500 mol wt GIR and of the 9000 mol wt GIR during somatostatin infusion in one nephrectomised dog. The t½ values obtained are approximately 2-fold greater for the 3500 mol wt GIR and

![Figure 2. Disappearance rates of the 3500 and 9000 mol wt GIR during somatostatin infusion in a nephrectomised dog. Linear regression analysis of the drop in log glucagon immunoreactive (GIR) concentration against time was done by the method of least squares using the value at 0 minutes as a 100%](image-url)
3-fold greater for the 9000 mol wt GIR than those reported in hyperglucagonaemic intact dogs\(^1\).

The hyperglucagonaemia found in clinical and experimental renal failure is due to an increase of the 3500 mol wt GIR or ‘true glucagon’ and of the 9000 mol wt GIR — possible glucagon precursor — the levels of the latter being always higher than those of ‘true glucagon’. These findings confirm the results recently reported by Kuku et al\(^2\).

The prolonged half-time of disappearance of the two raised GIR components during somatostatin infusion in nephrectomised dogs, when compared with intact animals, suggests that the kidney is the major degradation site of not only ‘true glucagon’, as has been indicated by several reports\(^3\), but also, and maybe to a greater extent, of the ‘proglucagon’ component.

The main cause of total hyperglucagonaemia in haemodialysed patients seems to be the result of impaired catabolism of these two GIR components, whose pathological implications remain to be elucidated.

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References

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