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The Effect of Short-Term Glucagon Infusion on Kidney Function in Normal Man

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Summary. Kidney function was studied in six normal males before and during a 2 h glucagon (10 ng/kg/min) infusion. The following variables were determined during each 20 min clearance period; glomerular filtration rate (GFR), renal plasma-flow (RPF), filtration fraction (FF), urinary albumin and β_2-microglobulin-excretion rates. Glucagon infusion resulted in a fourfold increase in plasma glucagon concentration. The infusion induced a significant increase in GFR (+9%), FF (+ 9%) and urinary β_2-microglobulin excretion rate (+ 32%), ($p < 0.01$). RPF and urinary albumin excretion rates were not significantly changed. We suggest that glucagon may contribute to the reversible kidney function alterations typically found in poorly regulated juvenile diabetes, a state with relative or absolute hyperglucagonaemia.

Key words: Diabetes, functional diabetic microangiopathy, glucagon, kidney function.

It is well documented that functional alterations occur in the microcirculation all over the body in poorly controlled juvenile diabetics [9, 12]. The changes are particularly well documented in the kidneys, viz. increased glomerular filtration rate, GFR [9]. The trigger mechanism of these alterations is not known, but several factors have been suggested e. g. growth hormone [9], hypoxia, due to increased oxygen affinity of the red cells [2], and hyperosmolality [13]. In a recent investigation, however, we found no evidence for the involvement of the above mentioned mechanisms [12].

Hyperglucagonaemia is present in poorly controlled diabetes [10]. Enhanced GFR has been demonstrated in animals and man during glucagon infusion in pharmacological doses [1, 3, 7]. Therefore, glucagon might be involved in the pathogenesis of the kidney function alterations in diabetes.

In order to evaluate this hypothesis, we determined glomerular filtration rate (GFR), renal plasma flow (RPF), filtration fraction (FF), urinary albumin and β_2-microglobulin-excretion rates before and during glucagon infusion in normal man. The glucagon infusion induced moderately elevated plasma levels, as typically found in poorly controlled juvenile diabetics.

Material and Methods

Six healthy non-obese male medical students, aged 22–28 years, all of whom had been fully informed of the nature of the study before giving their consent, were investigated. None of the subjects was taking drugs.

The investigations were performed early in the morning in the fasting state. The subjects were supine during the investigation, standing up only during voiding. To promote diuresis 250 ml of tap water was given every 20 min, starting one hour before the experiment and continuing throughout the clearance procedure. All the below mentioned variables were measured in each 20 min clearance period.

GFR and RPF were measured using the classical steady state infusion technique with ^{125}I-iothalamate and ^{131}I-iodohippurate, respectively [9]. Urinary albumin and β_2-microglobulin were measured with radioimmunoassays [4, 8]. Plasma concentrations of glucagon and growth hormone were measured by radioimmunoassay [5, 6]. Plasma glucose was measured by a glucose-oxidase method on an auto-

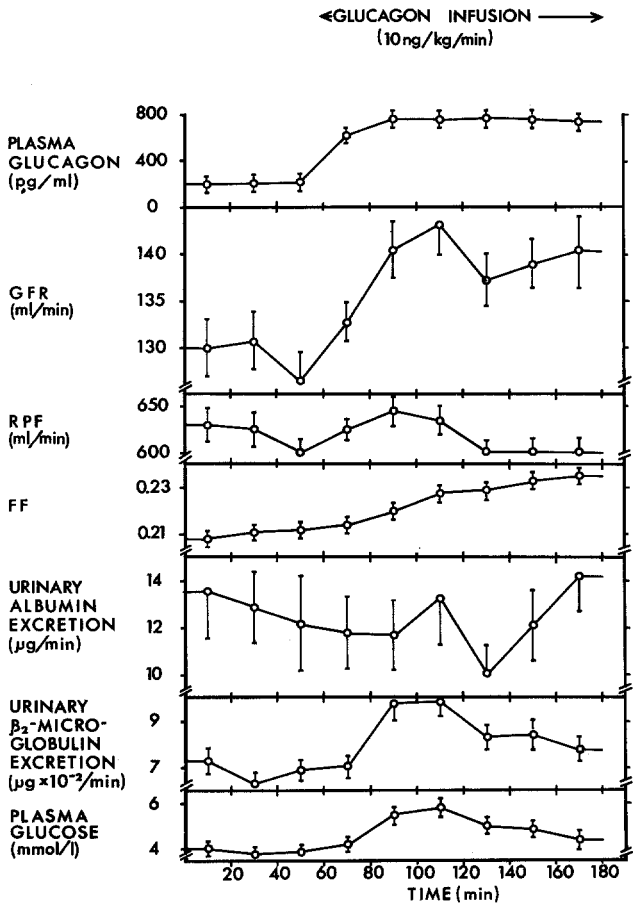

Fig. 1. Influence of physiological increments in plasma glucagon on kidney function in normal males (mean ± S.E.M.). Glomerular filtration rate (GFR), filtration fraction (FF) and urinary β_2-microglobulin excretion rate increased significantly, ($p < 0.01$). Renal plasma flow (RPF) and urinary albumin excretion remained unchanged

analyzer. Blood pressure and pulse rate were determined at least 6 times during the investigation.

Protocol

After 40 min of constant infusion, 3 control clearance periods of 20 min each were performed. Then a glucagon (Novo, Copenhagen) infusion (10 ng/kg/min) was started and continued for 6 experimental clearance periods. Thyroid uptake of radioactive iodide was blocked by daily administration of 100 mg of potassium iodide.

Wilcoxon's non-parametric test for paired comparison was used for statistical analysis, excluding the values for the transitional clearance period starting when the hormone infusion was initiated.

Results

Figure 1 demonstrates the changes in plasma glucagon and kidney function produced by the infusion of glucagon (10 ng/kg/min) in normal man. Plasma glucagon concentration increased rapidly, reaching a steady level of about 800 pg/ml within 30 min. The mean basal glucagon concentration was about 200 pg/ml. GFR increased in all subjects shortly after the start of the infusion and remained elevated during the whole infusion period, averaging 140 ml/min during infusion compared to a control mean of 129 ml/min ($p < 0.01$). RPF remained nearly unchanged; mean 617 ml/min during glucagon infusion compared to a control mean of 619 ml/min. The calculated filtration fraction increased gradually in all subjects during infusion; mean 0.23 compared to a control mean of 0.21, ($p < 0.01$).

Glucagon had no influence on urinary albumin excretion; mean 12.9 μg/min before and 11.8 μg/min, during infusion. Urinary β_2-microglobulin increased significantly in all subjects during infusion, mean 9.0 μg × 10^{-2}/min compared to an average control value of 6.8 μg × 10^{-2}/min, ($p < 0.01$).

There was a small (1–2 mmol/l) transient increase in plasma glucose maximal at 40–60 min. Blood pressure and pulse rate were not significantly changed. Plasma growth hormone remained unchanged in 5 of the subjects, while a 4 fold increase was observed in one subject during the glucagon infusion. There were no qualitative or quantitative differences in the renal variables between this subject and the remaining 5 subjects, except for a more pronounced increase in GFR (+ 20%).

Discussion

Elrick et al. [3] showed that glucagon (0.9–7.5 mg) administered as a single dose intramuscularly or intravenously, or as a continuous intravenous infusion, increased GFR and RPF by approximately 10–15 per cent in normal man. Butturini et al. [1] found an increase of about 10 per cent in GFR and RPF, giving a single intravenous injection of 1 to 3 mg glucagon in normal man. A similar effect on kidney function has been demonstrated in dogs during intravenous infusion of 5 μg glucagon/min [7]. By contrast, we used a much smaller dose of glucagon (10 ng/kg/min) given as a continous intravenous infusion for 2 h. The total amount of glucagon administered in the present study was approximately 0.1 mg. The infusion caused an increase to four fold the normal glucagon concentration, i.e. the levels observed in poorly controlled juvenile diabetes [10]. GFR increased promptly in all subjects and remained elevated throughout the infusion period. This increase can either be due to an increased

transglomerular filtration pressure and/or increased permeability-surface area-product. The significant increase in filtration fraction during infusion is compatible with elevated intraglomerular filtration pressure. This was not due to an increase in the total vascular resistance of the kidney since renal plasma flow and systemic blood pressure remained unchanged during infusion. Therefore, it is suggested that glucagon induces a dilatation of vas afferens and a constriction of vas efferens, keeping the total vascular resistance unchanged. Variations in intrarenal pressure may also play a role in keeping renal plasma flow constant.

Peterson et al. [11] have demonstrated that tubular proteinuria, viz. reduced tubular protein reabsorption, is characterised by a considerably elevated urinary β_2-microglobulin excretion and a normal or slightly elevated urinary albumin excretion. The present finding of a significantly elevated urinary β_2-microglobulin excretion and a normal urinary albumin excretion during the infusion, suggest that glucagon reduces the tubular protein reabsorption.

The small rise in plasma glucose does not contribute to the above mentioned changes, as discussed previously [9].

Kidney function is changed in poorly regulated juvenile diabetics. GFR is elevated, RPF unchanged, FF increased and urinary β_2-microglobulin and albumin excretion enhanced [9, 12]. Qualitatively, the same alterations were demonstrated during glucagon infusion, except for one crucial point, the unchanged urinary albumin excretion. Despite this, we should like to suggest that hyperglucagonaemia may contribute to the functional kidney changes observed in poorly regulated diabetes.

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