

PART XXXIII

URAEMIA

Chairmen: C Giordano
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GLUCAGON-MEDIATED MODIFICATIONS OF GLOMERULAR FILTRATION RATE INDUCED BY ESSENTIAL AMINOACIDS AND KETOANALOGUES

P Cappelli, G Del Rosso, B Di Paolo, M Evangelista, M T Nisi,
A Albertazzi

Institute of Nephrology, University of Chieti, Italy

Summary

Glucagon, secreted after both protein ingestion and aminoacid infusion, increases renal plasma flow and glomerular filtration rate (GFR). In eight normal subjects we examined the effects of the oral intake of essential aminoacids and ketoanalogues on insulin and glucagon secretion and on GFR. While the essential aminoacids stimulated insulin and glucagon increasing GFR, the ketoanalogues did not produce any significant modification when compared to basal values. The substitution of essential aminoacids with corresponding ketoanalogues subtracts the glucagon stimulating activity responsible for the increase in GFR.

Introduction

Glomerular hyperfiltration in surviving nephrons of the diseased kidneys may contribute to their ultimate destruction, particularly following ad libitum protein feeding [1].

One possible factor responsible for the increased glomerular perfusion and filtration may be glucagon. This hormone, secreted by the pancreas after both protein ingestion and aminoacid infusion, increases the renal plasma flow and GFR probably by dilating pre-glomerular vessels [1,2]. It is known that in uraemia hyperglucagonaemia is present, together with an enhanced sensitivity to glucagon [3]. Moreover hyperglucagonaemia may contribute to the high GFR in poorly controlled diabetic patients [4]. There is evidence that a low protein diet, early in the course of kidney disease, slows the progression of chronic renal failure [5]. Promising results have been obtained also in advanced stages with very low protein diets supplemented with essential aminoacids and ketoanalogues [6].

We undertook this study to investigate the effects of oral intake of these supplements on glucagon and insulin secretion and on GFR in normal subjects.

Materials and methods

Eight healthy young subjects participated in the following protocol: day 1, after an overnight fast, we evaluated the basal GFR by inulin clearance within three hours; day 2, again after an overnight fast, all subjects ingested orally one tablet/5kg body weight of the following mixture of essential aminoacids and ketoanalogues (Alfa-Kappa Farma-Biagini): L-lysine acetate 105mg, L-threonine 53mg, L-histidine 38mg, L-tyrosine 30mg, L-tryptophan 23mg, Ca-ketovalline 86mg, Ca-ketoleucine 101mg, Ca-ketoisoleucine 67mg, Ca-ketophenylalanine 68mg, Ca-D-L-hydroxymethionine 59mg/tablet; this amount is the same generally used as supplement in the very low protein diet for uraemic patients. In basal conditions and 15', 30', 60', 90', 120', 150', 180' after ingestion we obtained blood for glucagon, insulin and glucose; during the three hours inulin clearance was evaluated. On the third day, after an overnight fast, all the subjects took one tablet/5kg body weight of a corresponding mixture composed entirely of essential aminoacids (Essentielle Aminosäuren Fresenius): L-lysine acetate 105mg, L-threonine 53mg, L-histidine 38mg, L-tyrosine 30mg, L-tryptophan 23mg, L-valine 75mg, L-leucine 89mg, L-isoleucine 59mg, L-phenylalanine 61mg, L-methionine 52mg. Serum values and inulin clearance were recorded as on the second day. Glucagon (n.v. 50–125pg/ml) and insulin (n.v. 4–25uU/ml) were determined by the standard RIA Kits (Radioassay Systems Laboratories Glucagon Kit; Sclavo Liso-phase Insulin Kit).

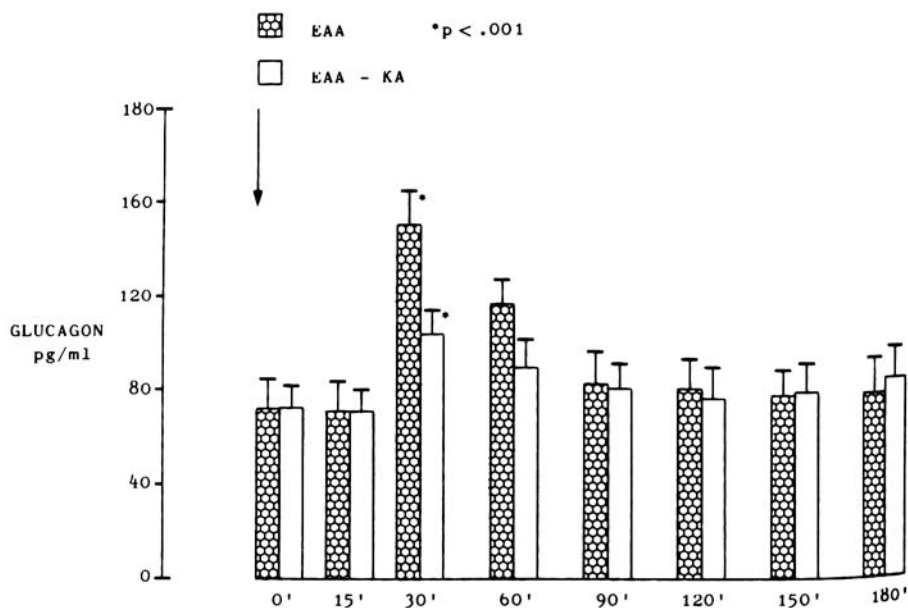


Figure 1. Values of serum glucagon after ingestion of essential amino acids (EAA) and of essential amino acids and ketoanalogues (EAA-KA)

Results

Glucagon (Figure 1) Essential aminoacids produced a progressive increase of glucagon with a peak at 30' (basal $72.37 \pm 12.19 \mu\text{g/ml}$, 30' $150.53 \pm 13.75 \mu\text{g/ml}$, $p < 0.001$) and a subsequent reduction towards basal values (180' $78.53 \pm 14.86 \mu\text{g/ml}$). A similar pattern was induced by essential aminoacids and ketoanalogues but with a significantly lower peak ($103.36 \pm 10.40 \mu\text{g/ml}$, $p < 0.001$).

Insulin (Figure 2) Essential aminoacids stimulated the secretion of insulin with a peak at 30' (basal $6.94 \pm 1.29 \mu\text{U/ml}$, 30' $14.29 \pm 2.87 \mu\text{U/ml}$, $p < 0.005$) and a subsequent reduction. Essential aminoacids and ketoanalogues did not cause any insulin change.

We never observed any change in serum glucose.

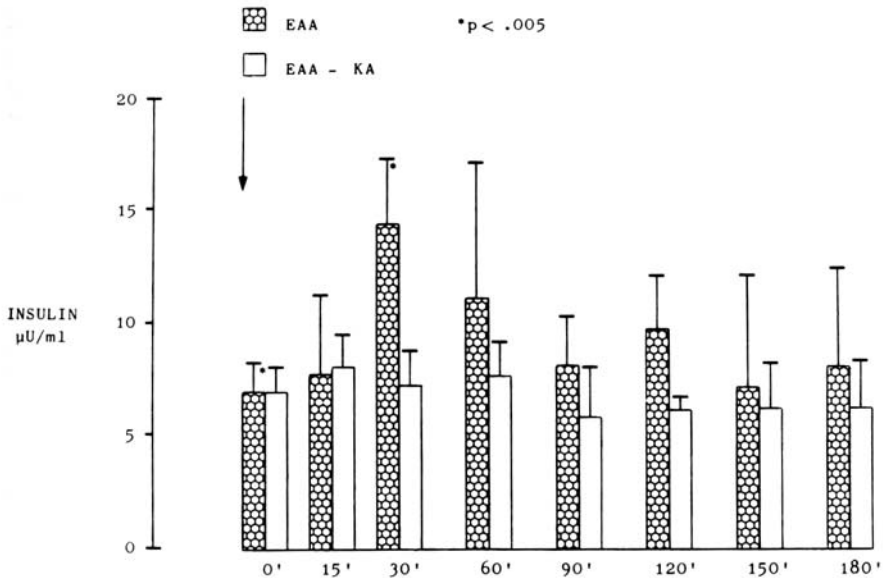


Figure 2. Values of serum insulin after ingestion of essential aminoacids and of essential aminoacids and ketoanalogues

Glomerular filtration rate The inulin clearance after essential aminoacids ($138.2 \pm 16.7 \text{ml/min}/1.73 \text{m}^2$) was higher than in basal conditions ($124.2 \pm 10.8 \text{ml/min}/1.73 \text{m}^2$) and after essential aminoacids and ketoanalogues ($121.7 \pm 14.6 \text{ml/min}/1.73 \text{m}^2$) but this was not significant.

Discussion

The aim of this work was to investigate the effects of essential aminoacids and ketoanalogues on pancreatic secretion of glucagon and insulin and if there exists

some difference between the two types of supplements used to supplement the very low protein diets in chronic uraemia. The results demonstrate that the substitution of five essential aminoacids with the corresponding ketoanalogues removes completely the insulin and partially the glucagon stimulating activity.

Concerning insulin it must be remembered that the aminoacids with the major stimulating activity [7] are the branched chain leucine and isoleucine, which are absent in the essential aminoacids and ketoanalogues mixture. The importance of this effect in regard to the insulin resistance and glucose intolerance of chronic renal failure remains to be elucidated. In uraemic patients fed a low protein diet supplemented with essential aminoacids and ketoanalogues a reduction of fasting levels of serum glucose with a decreased concentration of total immunoreactive insulin was observed [8].

Concerning glucagon the most powerful stimulating aminoacid of those present in the mixture is phenylalanine [7] substituted by the corresponding ketoanalogue; the others, less important (tryptophan, threonine, lysine, histidine) are not. This is the reason why essential aminoacids and ketoanalogues maintain a mild glucagon stimulating activity. It seems possible to exclude a correlation between the insulin stimulation and the increase in glucagon due to a relative hypoglycaemia; indeed we never observed any change in serum glucose after the intake of essential aminoacids or essential aminoacids and ketoanalogues. It is interesting to observe that the ketoanalogues do not modify the GFR while essential aminoacids, on the contrary, do. This happens contemporaneously to the stimulation of glucagon even if the difference in GFR values do not attain significance.

Therefore, if glucagon has a role in glomerular hyperfiltration during the course of renal insufficiency, this can explain the promising results obtained in slowing the progression of chronic renal failure with a very low protein diet supplemented with essential aminoacids and ketoanalogues which should be more effective than the corresponding essential aminoacids supplemented diet [9].

Additional studies need to elucidate the possible importance in uraemic patients of data recorded in subjects with normal renal function. Moreover, we should try to discover if glucagon is an ultimate mediator of renal haemodynamic modifications or an intermediate effector triggering some other hormonal factor such as glomerulopressin [4] which is stimulated mainly by an increased uptake of free aminoacids in the liver.

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