

## Glucose absorption, hormonal release and hepatic metabolism after guar gum ingestion

C Simões Nunes <sup>1\*</sup>, <sup>\*\*</sup>, K Malmjöf <sup>2\*\*\*</sup>

<sup>1</sup> INRA-CRJ, NASA Department, 78350 Jouy-en-Josas, France;

<sup>2</sup> Swedish University of Agricultural Sciences, Department of Animal Nutrition and Management,  
S-750 07 Uppsala, Sweden

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**Summary** — Six non-anaesthetized Large White pigs (mean body weight  $59 \pm 1.7$  kg) were fitted with permanent catheters in the portal vein, the brachiocephalic artery and the right hepatic vein and with electromagnetic flow probes around the portal vein and the hepatic artery. The animals were provided a basal none-fibre diet (diet A) alone or together with 6% guar gum (diet B) or 15% purified cellulose (diet C). The diets were given for 1 week and according to a replicated 3 x 3 latin-square design. On the last day of each adaptation period test meals of 800 g were given prior to blood sampling. The sampling was continued for 8 h. Guar gum strongly reduced the glucose absorption as well as the insulin, gastric inhibitory polypeptide (GIP) and insulin-like growth factor-1 (IGF-1) production. However, the reduction in peripheral blood insulin levels caused by guar gum was not associated with a change in hepatic insulin extraction. IGF-1 appeared to be strongly produced by the gut. The liver had a net uptake of the peptide. Ingestion of guar gum increased the hepatic extraction coefficient of gut produced IGF-1. Guar gum ingestion also appeared to decrease pancreatic glucagon secretion. Cellulose at the level consumed had very little effect on the parameters considered. It is suggested that the modulation of intestinal mechanisms by guar gum was sufficient to mediate the latter internal metabolic effects.

**guar gum / glucose / liver / insulin / IGF-1 / pig**

**Résumé** — Absorption de glucose, production hormonale et métabolisme hépatique après l'ingestion de gomme de guar. Six porcs de race Large White (poids vif moyen  $59 \pm 1.7$  kg) ont été munis de cathéters permanents respectivement dans la veine porte, le tronc brachiocéphalique et la veine hépatique droite ainsi que de sondes débitométriques électromagnétiques respectivement autour de la veine porte et autour de l'artère hépatique. Les animaux ont reçu un régime dépourvu de fibres (régime A) seul ou supplémenté par 6% de gomme de guar (régime B) ou 15% de cellulose purifiée (régime C). Ces régimes ont été alloués pendant une semaine et selon un dispositif expérimental en double carré latin 3 x 3. Un repas test de 800 g a été distribué pendant le dernier jour de chaque période d'adaptation et des prises de sang ont été réalisées à intervalles réguliers pendant 8 heures postprandiales. La gomme de guar a fortement réduit l'absorption de glucose, la production d'insuline, du polypeptide inhibiteur gastrique (GIP) et de glucagon sans modifier profondé-

\* Correspondence : C Simões Nunes, Société Chimique Roche, BP 170, 68305 Saint-Louis Cedex, France

\*\* Present address: Société Chimique Roche, BP 170, 68305 Saint-Louis Cedex, France

\*\*\* Present address: Kabi Pharmacia, Experimental Biology, S-11287 Stockholm, Sweden

*ment le profil de leur captation hépatique. La somatomedine-C (IGF-1) a été fortement produite par le tractus gastro-intestinal et le foie a montré une extraction nette du peptide libéré par les tissus gastro-intestinaux. L'ingestion de cellulose au taux utilisé n'a eu que très peu d'effets sur les paramètres considérés. La modulation des mécanismes intestinaux par la gomme de guar apparaît comme étant suffisante pour être le médiateur des effets métaboliques internes observés.*

**gomme de guar / glucose / foie / insuline / IGF-1 / porc**

## INTRODUCTION

Dietary fibre influences events at all levels of the alimentary tract. There is considerable interest in the knowledge of nutritional physiological effects of dietary fibre (Laplace and Lebas, 1981; Heaton, 1983; Johnson, 1990). The possible mechanisms by which dietary fibre acts on and also improves some pathological states such as diabetes, hyperlipaemia and hyperuraemia are increasingly becoming the subject of experimental work (Hagander *et al*, 1984; Gulliford *et al*, 1988; Rémésy and Demigné, 1989).

Guar gum has been shown to reduce glucose, insulin and gastric inhibitory polypeptide (GIP) plasma concentrations in man (Morgan *et al*, 1979; Gulliford *et al*, 1988) and to have no effect on glucagon plasma concentrations (Gulliford *et al*, 1988). Nothing is known about the effects of guar gum ingestion on the insulin-like growth factor-1 (IGF-1) level of secretion, which is dependent on nutritional status (Buonomo and Baile, 1991). We have recently studied the effects of wheat straw meal and guar gum on pig porto-arterial differences in amino-nitrogen, urea, glucose and insulin levels (Malmjöf *et al*, 1988, 1989). The aim of the present work was to study the quantitative absorption and hepatic metabolism of glucose as well as the production of insulin, pancreatic glucagon, GIP and IGF-1 in the growing pig after the ingestion of diets containing purified cellulose or guar gum.

The most reliable data on metabolite production and utilization in the splanchnic bed are obtained when measurements are made *in vivo*. Splanchnic metabolism *in vivo* can be studied if blood flow rate through the liver (arterial and portal supplies) is recorded continuously and if the metabolite concentrations can be measured in blood samples taken from one of the hepatic veins, the portal vein and one artery. In the present study we used such an experimental model (Simões Nunes *et al*, 1989).

## MATERIALS AND METHODS

### *Animals and diets*

Six castrated male Large White pigs ( $59 \pm 1.7$  kg initial body weight) were used. Each animal was fitted with 3 catheters placed respectively in the portal vein, the brachiocephalic artery and the right hepatic vein as well as with electromagnetic flow probes around the portal vein and the hepatic artery as described by Simões Nunes *et al* (1989). The animals were given a basal non-fibre diet (diet A) alone or together with 6% guar gum (diet B) or 15% purified cellulose (diet C). The diets were given for 1 week and according to a replicate 3 x 3 latin square design. On the last day of each such adaptation period 800-g test meals were given prior to blood sampling. All the meals were distributed immediately after wetting them and mixing with 1.200 ml water. Blood sampling was continued for 8 h. Diet composition is given in table I. Throughout the experimental period the animals were kept in individual cages which permitted easy access to the

**Table 1.** Composition of experimental diets (%).

Diet composition	Experimental diets		
	A (%)	B (%)	C (%)
Hydrochloric casein (UCCP)	17.3	17.3	17.3
Peanut oil	4	4	4
Maize starch	60.1	60.1	60.1
Guar gum	—	6	—
Purified cellulose	—	—	15
Mica powder	15	9	—
Mineral mixture <sup>a</sup>	2.5	2.5	2.5
Vitamin mixture <sup>b</sup>	1	1	1
Antioxidant	0.1	0.1	0.1

<sup>a, b</sup> According to Simões Nunes *et al* (1989).

cannulae and probes. To prevent obstruction by blood clots, the cannulae were rinsed daily with heparinized 0.9% NaCl solution (100 IU/ml).

### Measurements

Each test meal started at 09 h 00 after a fasting period of 24 h. On the day of each test meal, portal vein and hepatic artery blood flow-rates were recorded continuously. Blood was sampled simultaneously from the hepatic vein, brachiocephalic artery and portal vein (3 ml/route) from time 0 until 8 h after the beginning of the meal every 10 min during the first 40 min, at 1 h, every 30 min during the 2nd h and once every hour afterwards. One ml of each blood sample was collected in ice-chilled tubes containing 10 µl heparin (50 IU) and immediately analyzed for its glucose (Hill and Kessler, 1961) and L-lactic acid concentrations (Minaire *et al*, 1965). The other 2 ml of each blood sample were collected for plasma immunoreactive insulin, glucagon, GIP and IGF-1 measurements in ice-chilled tubes containing 20 µl heparin and 1 000 KIU Trasylol (apronitin)/ml blood. Plasma samples were rapidly prepared after centrifugation (1 600 g, 4 °C, 15 min) and stored at -80 °C until an assay performed within 2 months of the experi-

ment. Insulin was measured with a commercial assay system (CEA, France; Sorin Biomedica, Spa, Italy). The antibody specificity was: insulin, 100%; porcine glucagon, 0.03%; porcine C peptide, < 0.07%; pig proinsulin, 21.4%. The sensitivity (ID<sub>50</sub>) was 5 µU/ml of plasma and the within- and between-assay variations 8 and 9%, respectively. Pancreatic glucagon was measured with a commercial assay system (Novopharmaceutic, Copenhagen, Denmark). The antibody specificity was: pancreatic glucagon, 100%; gut glucagon, < 0.1%; secretin, < 0.02%; cholecystokinin, < 0.02%; vasoactive intestinal peptide, < 0.02%; GIP, < 0.02%. The sensitivity (ID<sub>50</sub>) was 25 pg/ml of plasma and the within- and between-assay variations 17% and 19% respectively. IGF-1 was also measured with a commercial assay system (Amersham, Les Ulis, France). The antibody specificity was: IGF-1, 100% and IGF-2, 0.05%. The sensitivity (ID<sub>50</sub>) was 100 pg/ml of plasma and the within- and between-assay variations 11 and 13%, respectively. GIP was measured according to Rérat *et al* (1985). The sensitivity (ID<sub>50</sub>) was 90 pg/ml of plasma and the within- and between-assay variations 9 and 16%, respectively. Blood concentration values of all these hormones and hormonal peptides were calculated taking into account the hematocrit measurements which were made throughout the 8 h of observation.

### Calculations

The determination of absorbed quantities (AQ) or produced intestinal or pancreatic hormone quantities (HQ), splanchnic input (SI), hepatic input (HI), hepatic output (HO), hepatic balance (HB), hepatic extraction coefficient (HEC) and splanchnic balance or non-hepatic tissue balance (SB) were calculated by the following formulae (Simões Nunes *et al*, 1989):

$$AQ \text{ or } HQ = (Pc - Ac) \times Pf;$$

$$SI = Ac \times (Pf + Haf);$$

$$HI = (Pc \times Pf) + (Ac \times Haf);$$

$$HO = Hc \times (Pf + Haf);$$

$$HB = HI - HO;$$

$$HEC = (HI - HO/HI) \times 100;$$

$$SB = (Hc - Ac) \times (Pf + Haf)$$

where *Pc* is the portal concentration, *Pf* the portal flow, *Ac* the arterial concentration, *Haf* the hepatic artery flow and *Hc* the hepatic vein concentration.

Statistical analysis (Snedecor and Cochran, 1967) involved calculation of the mean and standard error of the mean as well as an analysis of variance followed by Duncan's multiple range test. These calculations were performed with the Statistical Analysis System (SAS Institute, Cary, NC).

### RESULTS

#### Blood flow rates and hepatic and gut movements of glucose and lactic acid

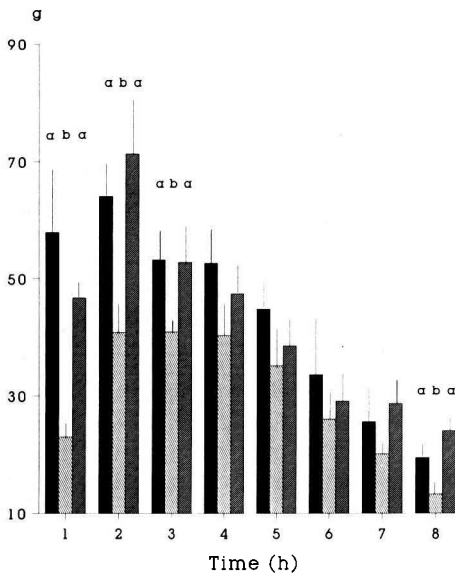
The nature of the test meal did not affect the blood flow-rate patterns. However, the ingestion of the meal was accompanied by an increase in the total hepatic blood flow. This increase appeared to be due to an increase in the portal flow. For all the animals and all the experiments the mean total hepatic blood flow rate was  $3\,242 \pm 48$  ml/min ( $55 \pm 0.8$  ml/kg/min) and the arterial supply constituted on average 20% of the total blood received by the organ.

The absorbed quantities of glucose were the highest for diet A and the lowest for guar gum diet (table II). The pattern of absorption was almost the same for the 3 diets with the largest absorption rates from the 2nd to the 5th h after the beginning of the meal (fig 1). The hepatic uptake of glucose was the highest after A and the lowest and equal for both B and C. The glucose hepatic uptake pattern followed that

**Table II.** Means (g/8 h) of absorbed quantities (AQ), hepatic balance (HB) and hepatic extraction coefficient (HEC) of glucose and lactic acid in the pig after ingestion of diets A, B and C.

Parameters	A	B	C
Glucose AQ	352 ± 40 <sup>1a</sup>	240 ± 32 <sup>b</sup>	336 ± 24 <sup>a</sup>
HB	144 ± 40	104 ± 16	104 ± 40
HEC	10 ± 3	8 ± 1	7 ± 3
Lactic acid AQ	15.1 ± 1.44	16.2 ± 0.64	17.3 ± 1.76
HB	12.3 ± 5.12	17.0 ± 3.84	8.2 ± 5.94
HEC	7 ± 5	16 ± 4	12 ± 5

<sup>1</sup> Mean ± standard deviation of the mean of 6 determinations. In the same row values with different superscript letters are significantly different (<sup>a, b</sup> *P* < 0.05).



**Fig 1.** Hourly means of absorbed glucose (g) in the pig after ingestion of diets A (■), B (▨) and C (▩). At each time interval values with different superscript (a, b) are significantly different ( $P < 0.01$ ).

of absorption and represented 41%, 43% and 31% of the absorbed quantities respectively for A, B and C. The mean hepatic extraction rate was  $\approx 8\%$ . Thus, the glucose reaching the peripheral circulation constituted 59% of that absorbed for diet A, 57% for diet B and 69% for diet C.

There were no differences between the diets in lactic acid absorption and hepatic uptake (table II).

### Insulin, GIP, glucagon and IGF-1

The lowest mean production of insulin was observed after ingestion of guar gum diet (table III). This production represented only 70% of that noted after ingestion of the fibre-free diet and 80% of that obtained for the cellulose diet. Moreover, after intake of diet A and C the insulin produced during the first postprandial hour constituted respectively 29 and 35% of the hormone secreted in 8 h whilst after ingestion of guar gum diet the first-hour insulin production only consti-

**Table III.** Means of production (P), hepatic balance (HB) of insulin (U/8 h), GIP ( $\mu\text{g}/8\text{ h}$ ) and glucagon ( $\mu\text{g}/8\text{ h}$ ) and mean hepatic extraction coefficients according to the hormone produced (HEP) or according to the quantity of hormone exposed to the liver (HEC) in the pig after ingestion of diets A, B and C.

Parameters		A	B	C
Insulin	P	21.1 $\pm$ 3 <sup>1a</sup>	14.7 $\pm$ 1.50 <sup>b</sup>	18.6 $\pm$ 2.07 <sup>ab</sup>
	HB	15.3 $\pm$ 2.14 <sup>a</sup>	11.6 $\pm$ 1.36 <sup>b</sup>	10.0 $\pm$ 0.97 <sup>b</sup>
	HEP	72 $\pm$ 10 <sup>a</sup>	79 $\pm$ 9 <sup>a</sup>	54 $\pm$ 5 <sup>b</sup>
	HEC	32 $\pm$ 4 <sup>a</sup>	34 $\pm$ 4 <sup>a</sup>	22 $\pm$ 2 <sup>b</sup>
GIP	P	29.8 $\pm$ 5.20 <sup>a</sup>	13.4 $\pm$ 3.13 <sup>b</sup>	23.7 $\pm$ 3.77 <sup>a</sup>
	HB	9.0 $\pm$ 3.51 <sup>ab</sup>	6.4 $\pm$ 1.58 <sup>b</sup>	9.1 $\pm$ 1.95 <sup>a</sup>
	HEP	30 $\pm$ 12	47 $\pm$ 12	38 $\pm$ 8
	HEC	7 $\pm$ 3 <sup>a</sup>	17 $\pm$ 4 <sup>b</sup>	13 $\pm$ 3 <sup>ab</sup>
Glucagon	P	174 $\pm$ 51 <sup>ab</sup>	104 $\pm$ 28 <sup>b</sup>	223 $\pm$ 54 <sup>a</sup>
	HB	62 $\pm$ 11 <sup>a</sup>	38 $\pm$ 7 <sup>b</sup>	75 $\pm$ 9 <sup>a</sup>
	HEP	35 $\pm$ 6	37 $\pm$ 6	34 $\pm$ 4
	HJEC	10 $\pm$ 2	9 $\pm$ 2	11 $\pm$ 1

<sup>1</sup>; and a, b Cf legend to table II.

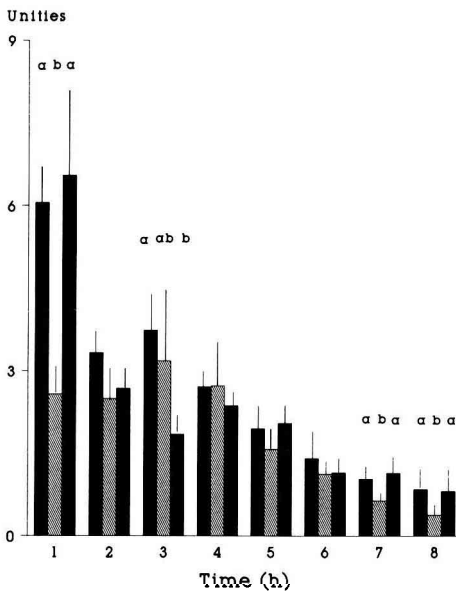
tuted 17% of the total measured hormone (fig 2). The kinetic profiles of hepatic uptake of insulin reflected those of production. The hepatic extraction coefficients of the insulin produced were always > 50%. The lowest hepatic extraction coefficients of insulin were noted for the cellulose diet.

The lowest mean production and hepatic balance of glucagon were observed after ingestion of diet B (table III). This production represented only 46% of that measured after ingestion of diet C and 59% of that noted for diet A. No significant difference in kinetic profile of glucagon production and hepatic extraction coefficient appeared between the 3 diets.

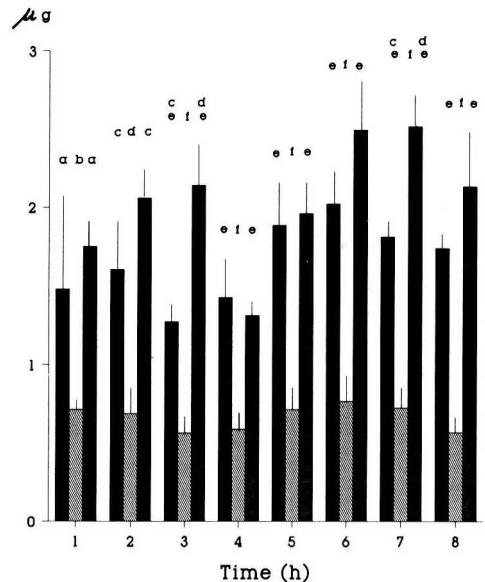
Ingestion of guar gum strongly reduced GIP secretion (table III). GIP produced after guar gum ingestion represented 45% of

that obtained after diet A and 56% of that measured after C feeding. The kinetic profile of the secretion was not the same for all diets. Thus, GIP production after ingestion of diet A was biphasic with maxima during the first and the 6th–7th h after feeding; that noted after diet B was rather small and uniform during the first 6 h after the meal, whilst the secretion observed after diet C was the highest during the 2nd, 3rd and 4th postprandial hours. The hepatic extraction coefficient of GIP was significantly higher after ingestion of guar gum diet than after those of the fibre-free or cellulose diets.

The gut secretion of IGF-1 was lowest after ingestion of guar gum (table IV). Whatever the ingested diet, the hourly IGF-1 gut secretion was quite constant and uniform during the 8 h of observation (fig 3). No influence of the meal intake was



**Fig 2.** Hourly means of insulin secretion (U) in the pig after ingestion of diets A (■), B (▨) and C (▩). At each time interval values with different superscript (a, b) are significantly different ( $P < 0.01$ ).



**Fig 3.** Hourly means of IGF-1 gut production ( $\mu\text{g}$ ) in the pig after ingestion of diets A (■), B (▨) and C (▩). At each time interval values with different superscript (a, b, etc) are significantly different (a, b:  $P < 0.05$ ; c, d:  $P < 0.01$ ; e, f:  $P < 0.001$ ).

**Table IV.** Means of IGF-1 ( $\mu\text{g}/8\text{ h}$ ) gut production (GP), hepatic input (HI), hepatic balance (HB) and hepatic extraction coefficients of gut production (HEGP) and of the peptide exposed to the liver (HEC) in the pig after ingestion of diets A, B and C.

IGF-1	A	B	C
GP	13.2 $\pm$ 1.51 <sup>(1)ac</sup>	5.50 $\pm$ 1.18 <sup>de</sup>	16.8 $\pm$ 1.22 <sup>bf</sup>
HI	61.7 $\pm$ 6.18 <sup>a</sup>	43.9 $\pm$ 3.33 <sup>b</sup>	62.1 $\pm$ 6.92 <sup>a</sup>
HB	5.2 $\pm$ 0.80	4.0 $\pm$ 0.90	5.0 $\pm$ 1.48
HEGP	39 $\pm$ 6 <sup>c</sup>	72 $\pm$ 16 <sup>d</sup>	30 $\pm$ 9 <sup>c</sup>
HEC	8 $\pm$ 1	9 $\pm$ 2	8 $\pm$ 2

1 Cf legend to table II. In the same row values with different superscript letters are significantly different (ab:  $P < 0.05$ ; cd:  $P < 0.01$ ; ef:  $P < 0.001$ ).

thus observed on the level of IGF-1 gut secretion. The liver was responsible for a net uptake of the circulating IGF-1.

The hepatic extraction coefficients of IGF-1 were the highest after ingestion of guar gum diet, the difference being significant for the hepatic extraction coefficient of circulating peptide.

## DISCUSSION

The effects of fibre on postprandial blood glucose and insulin levels have often been investigated, but little is known about the effects of fibre either on the release of other splanchnic hormones, and on the mechanisms of these effects; or regarding their effects on the hepatic metabolism of nutrients and hormones. The latter were the main aim of the present study.

Ingestion of guar gum strongly reduced glucose absorption. Decreased glucose absorption was also observed in man after ingestion of guar gum (Gulliford *et al*, 1988; Torsdottir *et al*, 1989). Diminished glucose absorption after addition of guar gum to the diet has been attributed to a delayed gastric emptying (Holt *et al*, 1979)

but the correlation between gastric emptying and the postprandial absorption has been found to be controversial (Blackburn *et al*, 1984). Therefore, the slower absorption of glucose induced by guar gum does not seem to be explained by delayed gastric emptying, but rather supports the theory of a slower digestion or absorption (Hagander *et al*, 1984). The importance of viscosity with regard to the physiological effects of guar gum has been reported to be fundamental (Rainbird and Low, 1986; Torsdottir *et al*, 1989; Cherbut *et al*, 1990). Thus, the effect of guar gum on glucose absorption disappeared when the fibre's property of increasing viscosity of the meal was destroyed by hydrolysis or processing of the guar gum (Jenkins *et al*, 1978; Torsdottir *et al*, 1989). Moreover, the decreased starch hydrolysis in the small intestine induced by viscous dietary fibre which limits further steps of carbohydrate digestion and absorption appears to be quite important in the mechanisms of action of viscous fibre such as guar gum (Isaksson *et al*, 1982; Hamberg *et al*, 1989).

The absorbed glucose was primarily extracted by the liver, confirming that there

was a direct uptake of glucose by the liver during postabsorptive hyperglycaemia (Barrett *et al*, 1986; Simões Nunes *et al*, 1989). The hepatic glucose uptake rate was not modified by the ingestion of guar gum or cellulose. This suggested that the influence of guar gum on glucose metabolism took place principally at the luminal level.

Cellulose at the level used in this study did not influence the glucose absorption rate and kinetic profile of absorption. The weak capacity of cellulose in reducing glucose absorption was also demonstrated in man (Jenkins *et al*, 1983), as well as its lack of effect on the digestion and intestinal absorption of lipids in the rat (Borel *et al*, 1989) whilst guar gum also reduced lipidic absorption (Turner *et al*, 1990; Girard-Globa *et al*, unpublished results).

Additionally the insulin (Malmjöf *et al*, 1989) and GIP responses were flattened after guar gum supplemented diet while cellulose failed to change their production. Decreased insulin and GIP secretions were also observed in man after guar gum ingestion (Morgan *et al*, 1979; Gulliford *et al*, 1988). Carbohydrate in the upper gastrointestinal tract stimulates GIP release. Thus, a reduced GIP response to a given meal indicated a reduced concentration of glucose for absorption in the upper part of the gut. The reduced insulin release after guar gum ingestion appeared to be mainly due to the lower glucose and to the low secretion of GIP. Guar gum intake also reduced insulinotropic amino acid absorption (Simões Nunes and Malmjöf, 1991). However, the lower insulin plasma concentrations observed after guar gum diet were not found to be associated with a change in hepatic insulin extraction. Guar gum ingestion appeared to decrease the glucagon secretion. Such an effect was not observed in man by Gulliford *et al* (1988). The present work also confirmed that the

hepatic extraction coefficient of insulin was higher than that of glucagon (Ishida *et al*, 1983; Simões Nunes *et al*, 1991).

From our results it appeared that IGF-1 was largely produced by the gastrointestinal tissues and thus may play important role in gut tissue growth and enterocyte renewal. Another unsuspected finding was that the liver had a net uptake of circulating IGF-1, suggesting that most of the plasma IGF-1 was of non-hepatic origin, yet again raising the question of the autocrine/paracrine or endocrine action of IGF-1 (Daughaday and Rotwein, 1989). Nevertheless, the possible different protein binding capacities of IGF-1 as regards hepatic, arterial and portal blood should also be considered even if every precaution as indicated by Daughaday and Rotwein (1989), has been taken in the sample preparation for IGF-1 radioimmunoassay. The lower IGF-1 plasma concentrations and splanchnic production after ingestion of guar gum was in agreement with the sensitivity of IGF-1 secretion level to the nutritional status observed in man, calf, rat and pig (Prewett *et al*, 1982; Isley *et al*, 1983; Coxam *et al*, 1989; Buonomo and Baile, 1991). Moreover, it was the result of the previous adaptation to guar gum diet and not an acute effect.

In conclusion, our results demonstrated that guar gum strongly inhibited the *in vivo* absorption of glucose as well as the production of insulin and GIP without changing the hepatic extraction coefficients of these nutrient and hormones. The latter demonstration suggested that the intestinal mechanisms of action of guar gum were sufficient to regulate the latter metabolic effects. These observations could be of interest when dealing with human diet manipulations in certain nutritional pathological states. Furthermore, we have shown that the gut is a net producer of IGF-1 and that the liver has a net uptake of this peptide.



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