Diabetologia 13, 269–272 (1977)

Diabetologia

The Mechanism of Insulin Secretion after Oral Glucose Administration

V. Portal Venous IRI Concentration in Dogs after Ingestion of Glucose*

H. H. Hommel and U. Fischer

Central Institute for Diabetes "Gerhardt Katsch" Karlsburg, GDR

Summary. Concentrations of immunoreactive insulin activity and of blood glucose were measured in portal and peripheral venous blood in six conscious dogs after oral administration of 1.0 g/kg glucose. Portal venous samples were obtained either by chronic catheterization or by direct puncture of the portal vein through a London-cannula. Portal venous IRI was already significantly increased 5 min after the onset of the stimulus. Peripheral venous IRI pattern reflected this early increase, but the peripheral venous blood glucose level was unchanged. The results indicate that the early peripheral venous IRI increase reflects a pancreatic insulin secretory reflex.

Key words: Insulin secretion, oral glucose, reflex insulin secretion, portal vein, dog.

The connection between the vegetative nervous system and the islets of Langerhans is well established [14, 28, 29]. Some studies involved the central nervous system in the regulation of pancreatic insulin secretion [16, 23, 25]. On the one hand, the possible physiological importance of these mechanisms is underlined by an increase of plasma insulin concentration due to imaginary food ingestion under hypnosis [8] and by specially conditioned reflexes [22, 30]. On the other hand an unconditioned insulinogenic reflex was demonstrated in the first phase after oral glucose intake [4, 5, 9, 24]. This reflex, however, was only shown by IRI measurements in the peripheral venous blood.

It is the purpose of this paper to substantiate this phenomenon by portal venous IRI measurements as a real variation of pancreatic insulin secretion.

Material and Methods

6 trained Alsatian dogs with a mean age of 30 ± 6 months and a mean body weight of 28.8 ± 1.8 kg were used in a total of 8 tests. The experimental conditions and the training pattern were extensively described by Fischer et al. [4].

Operations

In 3 dogs during laparotomy under N_2O/O_2-intubation anaesthesia, heparin-filled polyethylene catheters were introduced into the portal vein via a venous branch of the splenic vein with blood flow maintained through the splenic vein. The catheter tip was placed at the entrance to the liver. The other end was brought through the abdominal wall and implanted on the neck in a plastic capsule with a metallic cover [10]. The experiments were performed 4 to 19 days after the operation. Before the tests the patency of the catheters was ensured by flushing or by introducing a stylette.

In 3 additional dogs the portal vein was prepared between the pancreatic vein and the liver and encompassed by a modified London-cannula [18]. The other end was brought through the abdominal wall and fixed.

After removing the obturator of the cannula, direct puncture of the portal vein was possible using a Longwell-Teflon-Catheter (18G × 6″). This procedure could always be carried out without any bleeding.

* Investigations supported by the research project "Diabetes mellitus and diseases of lipid metabolism" of the Ministry of Health of the GDR

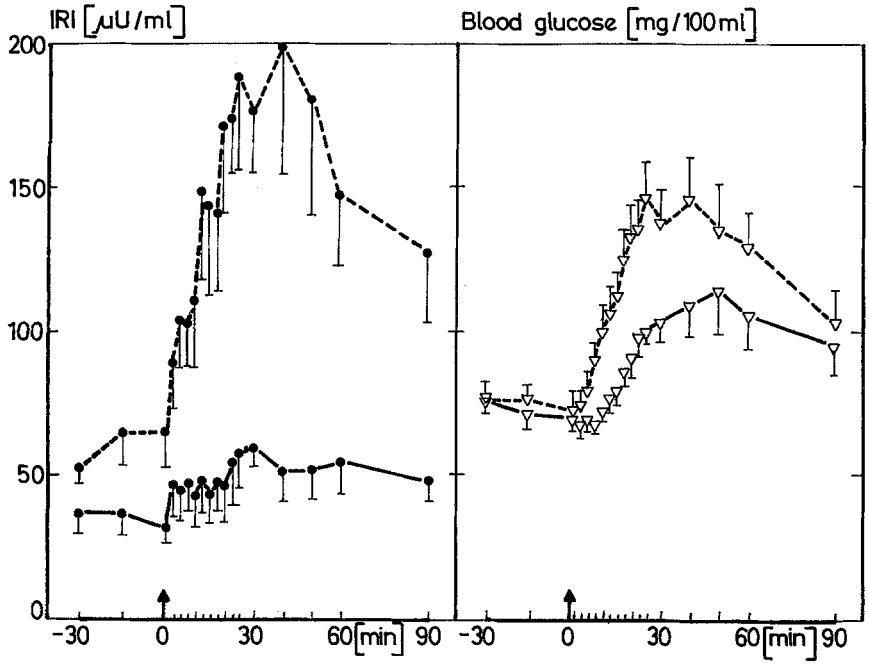

Fig. 1. IRI (•) and blood glucose (▽) concentrations in the peripheral (——) and portal venous (-------) blood after oral glucose application (1.0 g/kg). Results of 8 experiments in 6 dogs.

Tests

After a mean interval of 9 days from the operation the conscious dogs were studied in a Pavlov-frame in an isolated room. Wound healing proceded without any complication and the animals had been eating 1000 g cooked beef and 500 g bread once a day for at least 3 days. The tests began at 7.30 a.m. after a starvation period of 21 hrs. 60 min before the start the portal catheters were made patent and a leg vein was cannulated. Blood specimens from both vessels were drawn simultaneously at −30, −15, −2, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 30, 40, 50, 60 and 90 min. In the interval between −2 and zero time, 1.0 g/kg glucose, dissolved in 50 ml tap water, was given orally through a plastic tube. The animals showed no defensive behaviour.

Analyses and Calculations

The peripheral and portal venous concentrations of blood glucose were measured colorimetrically with glucose oxidase [15], and plasma immunoreactive insulin activity (IRI) was estimated by the back titration principle with alcoholic precipitation (cf. 4). The mean ± SEM of the measured and calculated values are given. The calculation of the areas under the curves was described by Fischer et al. [4]. The differences were evaluated by the t-test ($p < 0.01$).

Results

There was no difference in the IRI or glucose values from the two sampling sites in the portal vein. Therefore the data obtained by both techniques were combined (Fig. 1). Portal vein blood glucose was significantly raised after 7.5 mins and a maximum was reached after 25 mins. The increase in peripheral venous blood glucose was delayed to 10 mins. The difference in relation to the initial values became significant at 15 min. Portal venous IRI, however, was already increased in the first postloading specimen in spite of the lack of any measurable peripheral blood glucose rise. The IRI rise was significant after 5 min. This early glucose-independent insulin secretion was confirmed by the integrated areas of the concentration curves (Table 1).

Portal (y) and peripheral (x) IRI concentrations were significantly correlated and related by the following equation:

$y = 106 + 0.56x$ ($r = 0.54$, $n = 144$, 0–90 min).

This correlation became more obvious when the logarithms of the measured values were used for the calculation:

$y = 0.5 + 2.69x$ ($r = 0.84$).

None of the variables derived from the portal or peripheral venous blood glucose (concentration, concentration difference, integrated area) were correlated with the IRI pattern.

The fasting Portal to peripheral IRI ratio was 2.5 ± 0.3.

The ratio increased after the onset of stimulation and was at a maximum at 20 and 22.5 mins when it averaged 6.0 ± 0.9. The differences in relation to the pretest values were significant between 10 and 25 mins. The initial values were not reached again within the observation period.

Discussion

Oral glucose administration led to a prompt and significant increase in peripheral IRI before any change in blood glucose level. This increase occurred not only in the peripheral but also in the portal venous blood. In a few unpublished experiments we observed similar IRI increases in arterial blood of dogs bearing carotid loops. This excludes a nonpancreatic origin of the early peripheral venous IRI increase after glucose, after feeding [3, 24] or drinking [26].

Recent experiments in vagotomized or atropinized dogs with or without oesophageal fistulas indicated neural trigger mechanisms for peripheral venous IRI increase after ingestion of glucose or meat [6]. An insulin secretory reflex was previously demonstrated in humans by Karamanos et al. [13] and in rats by Louis-Sylvestre [17]. A portal IRI increase shortly before any increase of glucose concentration was shown in a few oral glucose tolerance tests in humans using umbilical catheterization [20]. The difference between portal and peripheral venous plasma insulin concentration is a possible indicator of hepatic insulin absorption, assuming a constant blood flow. This difference is small during the early reflex period and rises with increasing insulin concentration in the later test phase. Insulin degradation does not only take place in liver [12], but also in muscle and fat tissues [7] as well as in the heart-lung-system [1, 20]. The newly secreted insulin first passes, regarding the insular vascular system [2, 19], the exocrine pancreas. A modulation of the primary IRI secretion pattern can already take place there. In spite of the proof of an insulinogenic reflex, glucose appears to be the major stimulus for insulin secretion in the later test phase. A direct correlation between plasma insulin and glucose levels is to be expected. After an oral glucose tolerance test the portal and peripheral venous IRI values correspond well, but only by a direct linear logarithmic relationship over the range studied (up to about 300 μU/ml). The linearity of correlation would imply the lack of any saturability of the insulin removal mechanisms within the limits investigated. The observations of Horowitz et al. [11], using intravenous infusions of glucose and arginine, showed no significant correlations. Simultaneous estimation of pancreatic and hepatic blood flow and IRI concentration differences across both these organs are essential for the calculation of net insulin balances.

Table 1. Integrated areas of IRI and of blood glucose in peripheral and portal venous blood for different intervals after oral glucose administration (1.0 g/kg). Results of 8 experiments in 6 dogs

Time interval (min)	IRI μU · min/ml		Blood glucose mg · min/100 ml	
	m	SEM	m	SEM
Portal venous blood				
0–5	201	68	19	25
0–12,5	864	130	210	256
0–22,5	1364	348	706	227
0–90	7900	1050	4515	1164
Peripheral venous				
0–5	78	22	−4	39
0–12,5	232	106	75	47
0–22,5	320	130	191	75
0–90	1880	475	2605	652

Acknowledgements. Skilful technical assistance of Mrs. Karla Brüllke, Mrs. Helga Schröder, Mrs. Hannelore Buff and Mrs. Helga Goraczka is greatfully acknowledged.

References

1. Carlson, L. A., Kaijser, J., Rossner, S., Wahlquist, M. L., Wide, L.: Changes in insulin immunoreactivity across the circulation in man during infusion of glucose and a fat emulsion. Eur. J. Clin. Invest. **5**, 57–62 (1975)
2. Ferner, H.: Das hyperglykämisierende Prinzip des Pankreas, sowie über Gefäßverhältnisse und Innervation der Insel. Acta Neurovegetat. **9**, 47–60 (1954)
3. Fischer, U., Hommel, H., Fiedler, H., Bibergeil, H.: Reflex mechanism on insulin secretion. Endocrinol. Exp. (Bratisl.) **8**, 137–146 (1974)
4. Fischer, U., Hommel, H., Ziegler, M., Michael, R.: The mechanism of insulin secretion after oral glucose administration. I. Multiphasic course of insulin mobilization after oral administration of glucose in conscious dogs. Differences to the behaviour after intravenous administration. Diabetologia **8**, 104–110 (1972)
5. Fischer, U., Hommel, H., Ziegler, M., Jutzi, E.: The mechanism of insulin secretion after oral glucose administration. III. Investigations on the mechanism of a reflectoric insulin mobilization after oral stimulation. Diabetologia **8**, 385–390 (1972)
6. Fischer, U., Hommel, H., Nowak, W., Sill, U., Lippert, H., Hahn v. Dorsche, H.: Der Einfluß der Vagotomie auf die Glukosetoleranz sowie die Reaktionen von Plasmainsulin und exokriner Pankreasfunktion nach Glukosebelastung oder Nahrungsaufnahme bei Hunden. Acta Biol. Med. Ger. **35**, 1279–1291 (1976)
7. Garratt, J., Butterfield, W. J. H., Abrams, M. E., Sterky, G., Whichelow, M. J.: Effect of exercise on peripheral uptake of

131-I-insulin and glucose in non-diabetics. Metabolism **21**, 36–47 (1972)
8. Goldfine, I. D., Abraira, C., Gruenewald, D., Goldstein, M. S.: Plasma insulin levels during imaginary food ingestion under hypnosis. Proc. Soc. Exp. Biol. Med. **133**, 274–276 (1970)
9. Hommel, H., Fischer, U., Retzlaff, K., Knöfler, H.: The mechanism of insulin secretion after oral glucose administration. II. Reflex insulin secretion in conscious dogs bearing fistulas of the digestive tract by sham-feeding of glucose or tap water. Diabetologia **8**, 111–116 (1972)
10. Hommel, H., Fischer, U., Gottschling, H.-D., Bergos, O. V.: The mechanism of insulin secretion after oral glucose administration. VI. The influence of stomach and of small intestine (russ.). Physiol. J. SSSR (Setschenov) **62**, 1506–1513 (1976)
11. Horwitz, D. L., Starr, J. I., Mako, M. E., Blackard, W. G., Rubenstein, A. H.: Proinsulin, insulin and C-peptide concentrations in human portal and peripheral blood. J. Clin. Invest. **55**, 1278–1283 (1975)
12. Kaden, M., Curtin, R., Carey, L., Taylor, F., Field, J. B.: Evaluation of factors regulating hepatic extraction of insulin. Diabetes **20**, 341–342 (1971)
13. Karamanos, B., Butterfield, W. J. H., Asmal, A. C., Cox, B. D., Whichelow, M. J.: The pattern of the early insulin response to oral glucose. Postgrad. Med. J. **47**, 440–443 (1971)
14. Kobayashi, S., Fujita, T.: Fine structure of mammalian and avian pancreatic islets with special reference to D cells and nervous elements. Z. Zellforsch. **100**, 340–363 (1969)
15. Köhler, P.: Verbesserte Glukoseoxydasemethode zur Blutzuckerbestimmung im Routinebetrieb des klinischen Laboratoriums. Z. Gesamte Inn. Med. **17**, 674–676 (1962)
16. Kuzuya, T.: Regulation of insulin secretion by the central nervous system. II. The role of the hypothalamus and the pituitary gland upon insulin secretion. J. Jpn. Soc. Intern. Med. **51**, 65–74 (1962)
17. Louis-Sylvestre, J.: Preabsorptive insulin release and hypoglycemia in rats. Am. J. Physiol. **230**, 56–60 (1976)
18. London, E. S., Kotschneff, N.: Der Mechanismus der alimentären Hyperglykämie. I. Die Rolle der Zuckerresorption aus dem Darm und der Inkretion des Pankreas. Z. Gesamte Exp. Med. **101**, 767–775 (1937)
19. Malaisse-Lagae, F., Ravazzola, M., Robberecht, P., Vandermeers, A., Malaisse, W. J., Orci, L.: Exocrine pancreas: Evidence for topographic partition of secretory function. Science **190**, 795–797 (1975)
20. Reyes-Leal, B., Castro, A., Bernal, B., Guadiola, O.: Le role du duodenum dans l'insulino-sécretion. Sem. Hop. Paris **49**, 1611–1617 (1973)
21. Rubenstein, A. H., Zwi, S., Miller, K.: Insulin and the lung. Diabetologia **4**, 236–238 (1968)
22. Siegel, S.: Conditioning of insulin glycemia. J. Comp. Physiol. Psychol. **75**, 233–241 (1972)
23. Steffens, A. B., Mogenson, G. J., Stevenson, J. A. F.: Blood glucose, insulin, and free fatty acids after stimulation and lesions of the hypothalamus. Am. J. Physiol. **222**, 1446–1452 (1972)
24. Strubbe, J. H., Steffens, A. B.: Rapid insulin release after ingestion of a meal in the unanaesthetized rat. Am. J. Physiol. **229**, 1019–1022 (1975)
25. Toivola, P. T. K., Cale, C. C., Goodner, C. J., Werrbach, J. H.: Central alpha-adrenergic regulation of growth hormone and insulin. Hormones **3**, 193–213 (1972)
26. Vinik, A. J., Kalk, W. J., Keller, P., Beaumont, P., Jackson, W. P. U.: Overactivity of the entero-insulinar axis in maturity-onset diabetes. Lancet **1973 II**, 183–185
27. Waddell, W. R., Sussmann, K. E.: Plasma insulin after diversion of portal and pancreatic venous blood to vena cava. J. Appl. Physiol. **22**, 808–812 (1967)
28. Watari, N., Taukagoshi, N., Honma, Y.: The correlative light and electron microscopy of the islet of Langerhans in some lower vertebrates. Arch. Histol. Jpn. **31**, 371–392 (1970)
29. Woods, S. C., Porte jr., D.: Neural control of the endocrine pancreas. Physiol. Rev. **54**, 596–619 (1974)
30. Woods, S. C., Shogren, R. E.: Glycemic response following conditioning with different doses of insulin in rats. J. Comp. Physiol. Psychol. **81**, 220–225 (1972)

Received: August 12, 1976, and in revised form: February 28, 1977

Dr. sc. med. H. H. Hommel
Department of Experimental Diabetes Research
Central Institute for Diabetes
"Gerhardt Katsch"
DDR-2201 Karlsburg
German Democratic Republic