Estimation of Pancreatic IRI Output Rate and Its Relation to Glucose Tolerance in Normal Anaesthetized Dogs

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Summary. The pancreaticoduodenal and portal venous blood flows were recorded electromagnetically in anaesthetized dogs. Blood glucose and IRI were measured in the arterial, portal, and peripheral venous as well as in the intestinal venous blood. By a mathematical model the actual net IRI output of the whole pancreas was estimated. Under basal conditions it is 10.2 ± 2.4 mU/min ($n = 30$; 26 kg mean body wt.). After i.v. glucose injection, IRI output is rapidly enhanced. The biphasic nature of this reaction was unequivocally demonstrated by consideration of the ratio IRI output : blood glucose. Pancreaticoduodenal blood flow increases transiently in relation to the increased blood glucose concentration. The IRI secretion rate is well correlated with the blood glucose concentration and to the amounts of glucose or of blood reaching the whole pancreas. It is also correlated with the portal IRI concentration. The overall peripheral venous or arterial IRI concentrations are correlated with the IRI secretion rate, but not in all

individual experiments. The different phases of IRI output (basal rate, stimulated output 1–10 min and 10–60 min) show no influence on each other, nor are they correlated with the peripheral IRI concentration area. Basal IRI output is negatively correlated with the glucose assimilation constants. These constants or the peripheral BG areas, however, are independent of the stimulated IRI output rate. However, both the assimilation constants and the peripheral BG areas are related to the peripheral IRI concentration areas. Hepatic uptake of insulin and dynamics of pancreatic blood flow seem to contribute considerably to the estimated correlation pattern.

Key words: Insulin secretion rate, pancreatic blood flow, mathematic model, IRI concentration, blood glucose, glucose assimilation, dog.

By means of insulin analyses in peripheral venous blood during diagnostic tests the description of well defined groups of patients and their allocation to hypothetical developmental stages of diabetes mellitus are possible [8]. However, due to the hepatic uptake of insulin, these measurements cannot give an exact pancreatic insulin secretion rate [11].

There have been attempts to estimate the rate of insulin secretion by indirect methods: the evaluation of the rate of degradation of insulin under steady state conditions [2, 11, 45]; the comparison of plasma IRI values after a rapidly acting secretory stimulus with those after an exogenous insulin load [41]; and the estimation according to a "reciprocal" indicator dilution principle with insulin as an indicator [46]. Repeated estimations, however, are not possible by these methods.

Insulin release *in vivo* can be evaluated better from the pancreatic blood flow and the pancreatic arteriovenous difference of insulin concentration. Kanazawa *et al.* [21], Lefebvre and Luyckx [24] and Porte *et al.* [33] estimated the IRI secretion rate of anaesthetized dogs by sampling superior pancreaticoduodenal vein. In that experimental arrangement, however, the pancreatic blood stream could be altered and only a part of the pancreas is considered.

Data on pancreatic blood flow under sufficiently physiological conditions can be obtained with the electromagnetic method [37]. We measured pancreaticoduodenal and portal flows by this method [12]. Blood samples were obtained from the portal vein instead of the pancreaticoduodenal vein, for the calculation of insulin secretion. The actual net IRI output was estimated by a mathematic model. In this paper we consider the relationship between IRI output and concentration as well as the influence upon it of blood glucose concentration and of whole pancreatic glucose supply in normal anaesthetized dogs.

Material and Methods¹

Experimental Design

16 Alsatian dogs of both sexes were anaesthetized using intubation and artificial breathing (hexobarbital sodium/nitrous oxide/oxygen, relaxation with Myorelaxin®, constant i.v. infusion of 0.9% saline 2.0

¹ Abbreviations: BG = blood glucose, IRI = immunoreactive insulin activity, Indices: art = arterial, ven = peripheral venous, int = intestinal venous, port = portal venous. F_1 in the formulas = blood flow through the A. pd. sup.

ml/min): mean body wt. was 26.6 ± 0.8 kg, starvation 20 hrs at the beginning of anaesthesia, mean time from the beginning of anaesthesia to the injection of glucose 180 min. Heparin was not used.

During laparotomy the animals were prepared in the following way: flowprobes of an electromagnetic flowmeter at the superior pancreaticoduodenal artery and, in some experiments, at the trunk of the portal vein; catheters for drawing blood in the portal vein within the liver via the splenic vein, in the ileocolic or jejunal veins ("intestinal veins"), and in the femoral and the saphenous veins; a catheter for recording the blood pressure in the splenic artery up to the coeliac artery. The operative procedure has been described in detail by Fischer *et al.* [12].

The animals were injected intravenously with 0.125, 0.25 or 0.5 g/kg glucose within 25 sec (1.25 ml/kg of solutions with 10, 20 or 40 g glucose in 100 ml). BG and plasma IRI concentrations in the peripheral vein (BG_{ven} , IRI_{ven}), portal vein (BG_{port} , IRI_{port}), intestinal veins (BG_{int} , IRI_{int}) and in the femoral artery (BG_{art} , IRI_{art}) have been analyzed simultaneously at the following times: - 15, - 1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 60 and 90 min (for the analytical methods cf. Fischer *et al.* [15]).

Pancreaticoduodenal and portal blood flows (square wave flowmeter Nycotron A/S, Drammen, Norway), heart frequency and mean arterial blood pressure (Biometer BM 101 RFT, VEB Meßgeräte-werk Zwönitz, GDR) were continuously recorded (Motorkompensator MK, VEB Medizingerätewerk "Erich Weinert", Magdeburg, GDR).

Methodological Observations

General anaesthesia and laparotomy can be followed by a depression of insulin secretion and of glucose tolerance [13]. Part of this depression is produced by autonomic blocking agents used for premedication. Therefore these drugs have been omitted from our experiments.

The integrity of the pancreatic vascular nervous system was proved by the normal reaction of the blood flow to irritation of the arterial chemoreceptors by intravenous injection of potassium cyanide (short lasting increase and long lasting decrease thereafter). Blood flows through both the superior mesenteric and the common hepatic arteries were not altered by the whole experimental arrangement. Portal venous flow can only be measured by this method when no catheter is inserted into this vessel. Therefore, data on portal venous and simultaneous pancreaticoduodenal arterial flows were obtained in a group of preliminary experiments without analysis of IRI_{port} . The ratio

between both these flow rates was not significantly altered by the test [12].

IRI_{int} is significantly smaller than IRI_{ven} or IRI_{art} [12]. Therefore, in this arrangement the estimation of IRI_{int} has been necessary. Neither in the different catheters nor at the different times before and after the tests did the hematocrit show significant alterations [12]. Thus, for these evaluations the mean of all hematocrit measurements has been used (49.5 ± 0.5 , $n = 168$). - After the injection of China ink into the v. pancreaticoduod. sup. we found the color evenly distributed in all parts of the liver. This fact indicates a turbulent blood stream in the portal vein under these conditions and a sufficient mixing of the pancreaticoduodenal stream with the other splanchnic blood.

Estimation of the IRI Output Rate

Several constants had to be used for the mathematic evaluation. They had been estimated experimentally: The part of the pancreas supplied by the superior pancreaticoduodenal artery amounts to $58 \pm 2\%$ of the wet weight (injection of China ink). The reciprocal value of this is the constant K_1 .

According to preliminary estimations less than 5% of the pancreaticoduodenal flow passes through the duodenal mucosa. That part has been neglected. - The part of the whole portal blood flow reaching the splanchnic area via the superior pancreaticoduodenal artery amounts to $9.5 \pm 0.4\%$. The reciprocal value of this is the constant K_2 . It does not change significantly after glucose injection [12]. $K_4 = (100 - \text{hematocrit})/100 = 0.505$.

The actual net IRI output of the whole pancreas is - as an approach - the difference between the amount of IRI passing the trunk of the portal vein and the amounts reaching the whole pancreas at its arterial side and leaving the non-pancreatic organs of the splanchnic area:

The portal entrance of the liver is passed by
 $F_1 \cdot K_2 \cdot IRI_{port} \cdot K_4 [\mu U/min]$ (I).

The whole pancreas is reached by
 $F_1 \cdot K_1 \cdot IRI_{art} \cdot K_4 [\mu U/min]$ (II).

All other organs of the splanchnic area deliver venously

$(F_1 \cdot K_2 - F_1 \cdot K_1) \cdot IRI_{int} \cdot K_4 [\mu U/min]$ (III).

The difference (I) - (II) - (III) is

$F_1 \cdot K_4 [K_2 (IRI_{port} - IRI_{int}) + K_1 (IRI_{int} - IRI_{art})] [\mu U/min]$ (IV).

The amount of glucose reaching the whole pancreas arterially is

$F_1 \cdot BG_{art} \cdot K_1/100 [mg/min]$ (V).

Additionally, the following parameters were calculated: K = glucose assimilation constant [9];

Fig. 1. Mean pancreaticoduodenal blood flow, BG_{art} and IRI_{port} in anaesthetized dogs before and after iv. injection of 0.5 (—, $n = 7$), 0.25 (---, $n = 5$) or 0.125 (—, $n = 4$) g/kg glucose. Evaluation of the blood flow: value at -1 min = 100%, from -5 to $+15$ min the value for each min was taken from the registered curves, for the remaining time one value was obtained for every 5 min

Fig. 2. Mean arterial blood glucose concentration and estimated glucose inflow into the whole pancreas (lower part), and portal venous IRI concentration and estimated IRI output from the whole pancreas (upper part) in 7 dogs before and after the rapid injection of 0.5 g/kg glucose

areas of BG from the time of glucose injection up to the BG normalization, and of IRI (0–10 and 10–60 min) in the peripheral venous and arterial blood.

All estimates were made on the computer Cellatron 8205 (VEB Kombinat Centronik, Meiningen, GDR). Statistical distribution as well as multiple correlations of analytic data and of calculated parameters have been investigated.

The mean values $\pm$ SEM are given. Significance levels of $P < 0.01$ and of $P < 0.05$ were required.

Results

Before the tests the BG pattern at the different points showed the well known arteriovenous concentration difference of about 10 mg/100 ml. From 2–15 min after the injection of glucose this difference was enhanced. Its alteration, however, was very small. In 357 non-selected pairs of data (before and after the injection of all doses of glucose) the BG values in the various explored vessels are related by the following equations:

$$BG_{art} = 1.04 \cdot BG_{ven} + 1.0 \quad (r = 0.95)$$

$$BG_{int} = 0.99 \cdot BG_{art} + 2.2 \quad (r = 0.96)$$

$$BG_{art} = 0.97 \cdot BG_{port} + 10.2 \quad (r = 0.93).$$

Therefore only BG_{art} is given in Figs. 1 and 2. Immediately after an increased BG the pancreaticoduodenal blood flow rose rapidly (Fig. 1). Thus the increase is not proportional to the actual BG level, as can be seen by the alteration of their ratio (Fig. 5).

Some dependence, however, of the relative flow increase (both amount and duration) on the injected dose is to be seen.

The actual glucose supply (= inflow into the whole pancreas) has been estimated (one group is presented in Fig. 2 as an example) because at present that of the islets of Langerhans cannot be analyzed directly. With respect to the small portion of the endocrine tissue of the whole pancreas and provided that the specific blood supply of the endocrine and of the exocrine tissues are similar, about 2–4% of the amounts of glucose given in Fig. 2, are at the disposal of the islets of Langerhans.

The IRI concentrations in the various vessels are related by the following equations ($n = 250$ non-selected pairs of data in the range from 2–237 $\mu\text{U/ml}$ of IRI_{art}):

$$IRI_{art} = 0.97 \cdot IRI_{ven} + 5.4 \quad (r = 0.90);$$

$$IRI_{int} = 0.51 \cdot IRI_{art} + 21.7 \quad (r = 0.83);$$

$$IRI_{art} = 0.36 \cdot IRI_{port} + 17.7 \quad (r = 0.60);$$

Fig. 3 shows these relations after the injection of 0.5

Fig. 3. Arterial (○), portal venous (●), peripheral venous (×) and intestinal venous (•) plasma IRI concentrations in anaesthetized dogs before and after iv. injection of 0.5 g glucose per kg

Table 1. Glucose assimilation constants of the arterial (K_{art}) and peripheral venous (K_{ven}) blood glucose data, arterial and peripheral venous BG areas [$\text{mmoles} \cdot \text{min/l}$] up to the time of BG normalization, arterial and peripheral venous IRI areas for 1–10 and 10–60 min [$\mu\text{U} \cdot \text{min/ml}$], and additional IRI output (stimulated minus basal rate) during the test 1–10 min [mU/10 min] and 10–60 min [mU/50 min] in anaesthetized dogs after intravenous injection of different doses of glucose

	0.5 g/kg		0.25 g/kg		0.125 g/kg	
n	7		5		4	
	mean	SEM	mean	SEM	mean	SEM
body wt. [kg]	25.3	1.0	27.0	1.4	27.4	2.4
K_{art}	2.0	0.2	1.8	0.2	1.5	0.3
K_{ven}	1.8	0.1 ^a	1.2	0.1	1.1	0.1
BG-area _{art}	211	30 ^a	72	22	53	7
BG-area _{ven}	205	20	98	30	49	13
IRI-area _{art}						
0–10 min	420	120	500	250	150	90
10–60 min	3170	970	2390	1380	270	150 ^a
IRI-area _{ven}						
0–10 min	390	110	540	230	160	80
10–60 min	3120	960	2830	1500	600	260 ^a
additional IRI output						
1–10 min	381	143	405	101	345	52
10–60 min	758	259	491	271	578	611

^a significant differences to the other data of that line ($p < 0.01$)

g/kg glucose. During the rapid alteration in the first test phase all other concentrations cannot exactly reflect the portal one. The difference of IRI_{int} from the other values increased after stimulation of insulin secretion. The animals loaded with smaller doses of glucose reacted in a similar way.

The basal net IRI output rate at a mean interval of 180 min from the onset of anaesthesia amounted to 10.2 ± 2.4 mU/min in 30 animals (mean body wt. 26.0 ± 0.8 kg). This is about 280 $\mu\text{U/min} \cdot \text{g}$. After glucose injection it is enhanced rapidly (Figs. 2 and 4). The early increase does not clearly depend on the BG alteration (Table 1). This phase is followed by a plateau, the level and the duration of which seem to be related to hyperglycemia. The enhancement of IRI output, however, lasts longer than that of BG.

The biphasic insulin secretion shown in the concentration pattern of IRI_{port} (Fig. 3) seems to become obscured by the computation (Fig. 4). Fig. 5 demonstrates a distinct biphasic reaction if the relation of the estimated net IRI output to the actual BG concentration or to the blood flow is considered. In relation to the amount of glucose actually reaching the pancreas IRI output increases significantly only in the later test

phase. Before the glucose load, about $14 \cdot 10^{-6}$ moles IRI are liberated per mol glucose assumed to reach the endocrine pancreas. If the load is reduced, the difference of this ratio between both phases shown in Fig. 5 became smaller. Multiple correlations between all measured and calculated values have been investigated both for each individual experiment and for all data together. Net IRI output, glucose concentration, and pancreatic glucose supply are well correlated ($p < 0.01$). In Fig. 6 this fact is documented by the relationship between the relative IRI output rate and the relative glucose inflow into the pancreas. Pancreaticoduodenal blood flow and IRI output are loosely related. Both these parameters depend strongly on an additional factor: the BG alteration. Any IRI concentration represents IRI output rate in a varying portion of the individual tests only. The highest level of significance ($p < 0.01$) exists in the relation of IRI output to IRI_{port} . Peripheral venous or arterial IRI concentrations cannot give an exact figure of insulin secretion.

There is some correlation between these parameters in total, but it is absent in most of the individual experiments. This is demonstrated in Fig. 7 in two selected animals, only one of which has a significant

Fig. 4. Mean relative rate of IRI output from the canine pancreas after the rapid iv. injection of different doses of glucose. 100% = mean of the -15 and -1 min-values in the individual experiments

correlation of IRI_{ven} with IRI output whereas IRI_{port} is closely related to insulin secretion.

Finally, correlation analysis has been performed, independent of the dose administered, between pancreatic IRI output rate, and some parameters, usually estimated from the peripheral concentration curves (Table 1). There is no significant relation, either between the different phases of IRI output (basal rate, 1–10 min, 10–60 min), or between the IRI output on the one hand and the areas of IRI and BG or the glycemic assimilation constants on the other hand. Only the pancreatic IRI delivery rate in the anaesthetized fasted animal before any glucose injection is negatively correlated to the glucose assimilation constant ($p < 0.05$).

The 10–60 min IRI areas, but not those from 1–10 min, are positively correlated with the BG areas ($p < 0.05$): after the distribution of the injected glucose the amount of IRI reaching the peripheral circulation seems to increase with BG.

Discussion

The experimental design reported here allows repeated estimation of IRI output rate during one

in-vivo test. In contrast to the drainage methods, normal flow regulation and vascular integrity of the pancreas are preserved. The values represent the function of the whole organ (not only of one of its vascular regions). The estimated amounts of IRI output for anaesthetized dogs are comparable to the calculations by indirect methods of other authors [11, 20, 44]: 11–12 mU/min. The values obtained by drainage or bypass methods are considerably smaller, even in relation to the mean body weight (given in brackets) of the experimental animals used: Bor *et al.* [5] – 3.6 mU/min (15–20 kg), Lefèbvre *et al.* [24] – 4.4 mU/min (15–22 kg), Kanazawa *et al.* [21] – 3.9 mU/min (9–29 kg), Mandelbaum *et al.* [28] – 1.9 mU/min (15–20 kg), Bergman *et al.* [3] – 0.9 mU/min (2–3 kg), Loubatières *et al.* [27] – 4.0 mU/min and Porte *et al.* [33] – 2.5 mU/min (15 kg). Some of the values referred to were converted or they were taken from figures. The differences from the findings reported here can be accounted for by methodologic advantages in relation to the venous drainage methods, which are discussed in detail by Fischer *et al.* [12].

Peripheral venous IRI concentrations are widely used as diagnostic criteria in tests of endocrine pancreatic function and of glucose tolerance. Despite several typical reaction patterns, their interpretation is difficult. According to our findings on anaesthetized animals, in the normal range such measurements give a rough correlation to IRI_{port} or to pancreatic IRI output.

Similar results were obtained by Cerasi and Luft [8] in man. In the individual case these values do not reflect the IRI secretion rate neither quantitatively nor qualitatively [2, 10, 18, 19, 26]. The lack of an exact relationship is due to the obligatory but inconstant metabolic loss of insulin in its passage through the liver [11, 16], and it is also due to the alteration of the pancreatic blood flow [14].

Some influence of pancreatic blood flow on the dynamics of insulin secretion can be observed when, during the measurement, the circulation is altered. Different secretory tests produce different variations of the pancreatic flow. They depend on simultaneous alterations of plasma osmolality (own unpublished results). During food ingestion as well as in an oral glucose load, some redistribution of splanchnic flow is to be expected [6, 23, 35, 36]. – Redistribution of flow within the pancreas between its exocrine and endocrine parts can also be expected under the influence of insulinogenic stimuli [42]. The method used here for calculation of IRI output, however, does not depend on such variations of the pancreatic microcirculation.

Glucose is well recognized as the major physiologic

stimulus acting directly on insulin secretion and there is a close relation between any alteration of BG and of insulin secretion [4, 22, 29]. In several cases this connection could also be demonstrated when using peripheral venous concentrations for mathematical evaluation [1, 17, 34].

In our experiments, such correlation appears independent of the use of the concentrations or of the amounts of glucose for correlation analysis. The correlation between IRI output and BG differs, however, in dependence on the test phase. This is demonstrated by the ratios of IRI output to glucose supply and to BG concentration, showing a biphasic alteration. During the early test phase with an extremely increased apparent IRI output, there is no alteration, or a small one only, of IRI delivered by the pancreas per mol glucose reaching it. In the later phase, this ratio is at least twice that of the pretest levels. These completely different phases are not clearly indicated

by the computed IRI secretion rate because there is no steady state level of BG and of IRI. Both these periods seem to correspond to the well known biphasic pattern of peripheral IRI concentration after several loads stimulating insulin secretion [8].

Relations between BG-dependent parameters and insulin secretion were observed in all statistical analyses performed. However, increased amounts of secreted IRI did not produce an increased action of insulin on BG level, glucose tolerance or glucose assimilation [10, 40]. In man, a defective early phase IRI increase may indicate pre-diabetes [7, 8]; and Lerner *et al.* [25] showed some interaction between the early IRI increase and the glucose assimilation constants. Other authors found no correlation, or a contrary one, between such parameters in the peripheral blood [1, 30, 39, 40]. In our experiments, there was also no proof that a higher IRI concentration or output in the early or in the late phase is

Fig. 5. Ratios of net pancreatic IRI output to BG, pancreatic inflow of glucose, or pancreaticoduodenal blood flow and of blood flow to BG in 7 anaesthetized dogs before and after i. v. injection of 0.5 g/kg glucose. For molar ratios a molecular wt. of 6000 of IRI has been assumed

followed by lower BG values or by an enhanced arterio-venous difference (unpublished data).

Any action of newly secreted insulin on glucose metabolism can possibly only be demonstrated by the glucose appearance and disappearance rates after injection of labelled substrates. — Thus, the pancreatic IRI output before the test is negatively correlated with the glucose assimilation constants which means that

the higher the insulin secretion in the resting and fasting anaesthetized animal the lower is the ability to assimilate an exogenous glucose load. Similar conclusions could be drawn from peripheral IRI analyses in diabetic and normal men [31].

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Fig. 6. Correlation of relative pancreatic glucose supply with net pancreatic IRI output after rapid i.v. injection of different doses of glucose. Each point represents the mean of one dose related group at a given time after the injection. 100% = mean of the -15 and -1 min-values in the individual experiments

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Fig. 7. Relations of IRI_{port} (●) and IRI_{ven} (○) to net pancreatic IRI output in 2 selected experiments, i.v. injection of 0.25 g/kg glucose. Left side: expt. 428, significant correlation of both IRI concentrations to output. Right side: expt. 429, significant correlation of IRI_{port} only to the output

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