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Pancreatic Fate of 6-Deoxy-6-[^{125}I]Iodo-D-Glucose

In Vivo Experiments

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The fate of 6-deoxy-6-[^{125}I]iodo-D-glucose (6-DIG), injected intravenously, was compared in control rats and animals that had received streptozotocin and were then treated with insulin or not. In the control rats, the measurement of plasma radioactivity suggested that, after an initial and rapid (up to min 10) distribution phenomenon (*K* value: 12.2×10^{-2} min^{-1}), the clearance of the iodinated hexose occurred mainly by glomerular filtration (*K* value: 0.2×10^{-2} min^{-1}). Three minutes after the injection of 6-DIG, the radioactive content of muscle, liver, and pancreas, relative to the paired value in blood, was lower in untreated diabetic rats than in control animals. In the case of muscle and liver, such a difference was no longer observed when the treatment of the diabetic rats by insulin resulted in restoration of normoglycemia. In the pancreas, however, the radioactive content, whether expressed relative to the paired blood or liver value, remained significantly lower in the insulin-treated diabetic rats than in the control animals. No significant difference between control and diabetic rats, in terms of pancreatic radioactivity, was observed 10 min after the injection of 6-DIG. These findings indicate that advantage can be taken from the vastly different time course for 6-DIG uptake by pancreatic acinar and islet cells, as recently documented in vitro, to label preferentially the endocrine moiety of the pancreatic gland shortly after 6-DIG injection.

Key Words: 6-Deoxy-6-[^{125}I]iodo-D-glucose; streptozotocin-induced diabetes; liver; muscle; pancreas.

Introduction

The uptake of 6-deoxy-6-[^{125}I]iodo-D-glucose (6-DIG) by isolated islets and acinar tissue from the rat pancreas was recently characterized in experiments conducted in vitro *(1)*. The vastly different time course for the uptake of the D-glucose analog by the endocrine and exocrine moieties of the pancreatic gland suggested that the iodinated hexose could conceivably be used to label in vivo the endocrine pancreas. This proposal was investigated in the present study by comparison between the results recorded after intravenous injection of 6-DIG to control rats and animals in which the islet insulin-producing cells had been destroyed by a prior injection of streptozotocin.

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Results

Short- and Mid-Term Experiments

A first series of five experiments was conducted in 24 control rats, 24 animals injected intravenously with streptozotocin (0.25 μmol/g body wt) and examined 3–4 d thereafter, and 12 STZ rats treated with insulin. The latter animals received 5 U of insulin (Insulatard, Novo Nordisk, Bagsvaerd, Denmark) subcutaneously in the morning 3 and 4 d after the injection of streptozotocin and again 5 U of insulin at 6 PM 4 d and at 9 AM 5 d after the administration of streptozotocin. They were injected with 6- DIG 60–120 min after the last insulin administration.

Whereas the control rats steadily gained weight, the STZ rats lost 1.4 ± 0.5 g/d (n = 36; $p < 0.02$) over the period of 3–4 d following the injection of streptozotocin.

The plasma D-glucose concentrations were much higher in the untreated STZ rats than in the control rats (Table 1). The modality of insulin treatment used in this first series of experiments resulted in an abnormally low ($p < 0.001$) plasma D-glucose concentration.

In the first experiments conducted in 12 animals in each group, the 6-DIG injected intravenously (16-26 μCi or 0.03-0.09 μmol/rat) was not purified prior to its injection (Table 2).

In both control and STZ rats, whether treated with insulin or not, the plasma radioactivity was quite variable 3 min after injection of 6-DIG. More reproducible results were obtained at min 10. For instance, they yielded an apparent distribution space of 0.89 ± 0.08 mL/g body wt (n = 12) in control rats and 0.83 ± 0.06 mL/g body wt (n = 12) in

Table 1
Biological Data in Either Control Animals or STZ Rats, Treated with Insulin or Not, and Examined 3 or 10 min after the Injection of 6-DIG

Rats	Control	STZ	STZ + insulin
Body weight (g)	196 ± 3 (24)	173 ± 6 (24)	183 ± 5 (12)
Plasma D-glucose concentration (m*M*)	10.2 ± 0.2 (24)	25.7 ± 0.8 (24)	6.7 ± 0.8 (12)
Muscle/blood radioactive ratio (%)			
min 3	20.2 ± 2.1 (6)	13.1 ± 0.9 (6)	16.3 ± 1.4 (6)
min 10	21.7 ± 1.8 (6)	22.4 ± 3.0 (6)	24.6 ± 0.9 (5)
Liver wet wt			
g	6.50 ± 0.15 (24)	6.05 ± 0.19 (24)	9.30 ± 0.27 (12)
% of body wt	3.35 ± 0.07 (24)	3.50 ± 0.08 (24)	5.09 ± 0.28 (12)
Liver/blood radioactive ratio (%)			
min 3	116.1 ± 15.1 (12)	85.8 ± 4.7 (11)	90.4 ± 13.2 (6)
min 10	202.7 ± 11.7 (12)	149.1 ± 8.8 (11)	172.1 ± 5.6 (6)
Pancreas wet wt			
mg	728 ± 20 (24)	668 ± 24 (24)	765 ± 46 (12)
‰ of body wt	3.70 ± 0.10 (24)	3.88 ± 0.15 (24)	4.11 ± 0.28 (12)
Pancreas/blood radioactive ratio (%)			
min 3	41.0 ± 3.2 (11)	27.0 ± 1.0 (11)	30.6 ± 1.5 (6)
min 10	50.4 ± 3.1 (12)	57.0 ± 4.4 (11)	57.8 ± 3.9 (6)

Table 2
Characteristics of the Solution of 6-DIG Injected Intravenously

Batch	Radioactivity	Contamination[a]	Purification	Rats	Sacrifice	6-DIG injected		
(Nr.)	(Ci/g)	(%)	(yes or no)	(type)	(min)	μCi/rat	μmol/rat	volume (μL)
1	1.00	N.D.[b]	No	STZ	3–10	26.0	0.09	150
2	1.82	N.D.[b]	No	Control	3–10	16.0	0.03	150
2	1.82	N.D.[b]	No	STZ + insulin (4)[c]	3–10	16.0	0.03	150
2	1.82	6.8	Yes	Control	3–10	16.0	0.03	300
2	1.82	6.8	Yes	STZ	3-10	16.0	0.03	300
3	1.00	7.4	Yes	Control	3	14.3	0.05	300
3	1.00	6.5	Yes	STZ + insulin (2)[c]	3	14.3	0.05	300
3	1.00	7.4	Yes	STZ + insulin (3)[c]	3	14.3	0.05	300
3	1.00	15.3	Yes	Control	60	14.3	0.05	300
4	1.00	1.5	Yes	STZ + insulin (6)[c]	3	9.1	0.03	300
5	1.00	1.5	Yes	Control	1,440	14.6	0.05	300

[a]The contamination by radioactive acidic molecules was measured in the purification procedure and, hence, does not concern the injected 6-DIG.
[b]N.D.: not determined.
[c]The number of insulin injections is indicated in parentheses.

untreated STZ rats. The paired ratio in the radioactive content of whole blood/plasma, which was virtually identical at min 3 and 10 in each set of experiments, ranged between the extreme values of 74.7 ± 1.9 and 98.7 ± 2.6% ($n = 4$–5), and it was found to depend on the purity of the injected material, being lowest when the anionic fraction of the inoculate was highest. Hence, the radioactive content of the different organs under consideration was always expressed relative to the paired blood, rather than plasma, value.

In the muscle of control rats, the radioactive content, relative to the paired blood value, was not significantly different at min 3 and 10, averaging, respectively, 20.2 ±.1 and 21.7 ± 1.8% ($n = 6$ in both cases). At min 3, the muscle radioactive content was much lower ($p < 0.005$) in the untreated STZ rats, not exceeding 13.1 ± 0.9% ($n = 6$) of the paired blood value. Such was not the case, however, at min 10 (Table 1). Indeed, in the diabetic rats, the muscle radioactive content was significantly higher ($p < 0.005$) at

min 10 than at min 3, at variance with the situation observed in control rats. In the STZ rats treated with insulin, the readings were no more significantly different from those made at the same time in control rats. Nevertheless, in the former animals, a significant increase ($p < 0.005$) was observed between min 3 and 10.

The liver wet wt, whether expressed in absolute terms of relative to paired body wt, was not significantly different in control and untreated STZ rats, but strikingly increased ($p < 0.001$) in the STZ rats treated with insulin.

In control rats, the liver radioactive content was not significantly different from that of whole blood at min 3, but twice higher at min 10. The paired liver/blood ratio in radioactivity was lower ($p < 0.05$ or less) in untreated STZ rats than in control animals, both at min 3 and 10. No significant difference in such a ratio was observed when comparing control and insulin-treated STZ rats.

The absolute (mg) and relative (‰ of body wt) values for the pancreas wet wt were not significantly different in control and diabetic rats, whether the latter animals were treated with insulin or not. At min 3, the paired pancreas/blood ratio in radioactive content was much lower ($p < 0.005$) in untreated STZ rats than in control animals. At the same time, the mean value recorded in insulin-treated STZ rats was still lower ($p < 0.02$) than that found in control animals, albeit somewhat higher ($p < 0.06$) than in the untreated STZ rats. At min 10, the pancreas/blood radioactive ratio was always higher ($p < 0.05$ or less) than at min 3, and failed to differ ($p > 0.14$ or more) in the three groups of rats.

In 3 of the 12 STZ rats treated with insulin, the plasma D-glucose concentration was close to the normal value (10.9 ± 1.2 m*M*; $n = 3$). The two readings for the paired pancreas/blood ratio in radioactivity recorded at min 3 in these euglycemic insulin-treated STZ rats (28.8 and 29.1%) were well below the lower limit of the 95% confidence interval for the mean value in control rats (i.e., 34.5%).

At min 3, the lower radioactive content of the pancreas in the untreated STZ rats, as compared to control animals, is likely to be attributable to the greater isotopic dilution of 6-DIG by plasma D-glucose in these severely hyperglycemic animals. Inversely, in the insulin-treated STZ rats, the abnormally low plasma D-glucose concentration may have favored the pancreatic uptake of 6-DIG. In light of these considerations, a further series of experiments was conducted in control rats and STZ animals treated with insulin. All measurements were made 3 min after injection of the iodinated hexose. Three modifications of the experimental procedure were introduced. First, in order to minimize the risk of hypoglycemia in the STZ rats, they received, in the first two sets of experiments, only two or three injections of insulin (5 U/rat) before the injection of 6-DIG. Second, the 6-DIG was always purified by anion exchange chromatography before each experiment. Finally, the erythrocyte radioactive content was also measured.

Short-Term Experiments

Three groups of 11–12 rats each were used as either control animals or STZ rats treated with insulin in the first experiments in this series. They were injected intravenously with 6-DIG (14.3 μCi or 0.05 μmol/rat) from the same batch and were examined 3 min thereafter.

In 12 control rats examined 3 min after the intravenous injection of 6-DIG (Table 3), the results were not vastly different from those recorded in the first series of experiments. Most important, the paired pancreas/liver ratio in radioactivity averaged 37.9 ± 3.3% ($n = 11$), as compared ($p > 0.45$) to 33.0 ± 5.0% ($n = 12$) in the first series of experiments.

The STZ rats that received either only one injection of insulin (5 U) on d 3 and 4 or one injection of insulin on d 4 and two injections of insulin on d 5 after streptozotocin administration remained severely hyperglycemic (Table 3) when killed on d 5 (two injections) or d 6 (three injections) after administration of the β-cytotoxic agent. It should be emphasized, however, that these animals were heavier and originated from a different firm than those used in the first series of experiments. Nevertheless, in this second series of experiments, the animals injected with STZ lost 2.9 ± 0.9 g per day over the period of 3–4 d preceding the onset of insulin treatment and, over the 2 d period of insulin treatment, then gained +12.0 ± 2.0 g ($n = 12$) and +19.2 ± 1.8 g ($n = 11$) when they had received two and three insulin injections, respectively. Moreover, the insulin treatment always resulted in a marked increase ($p < 0.005$ or less) of liver wet wt (Table 3).

In these animals, the paired erythrocyte/plasma ratio in radioactivity (69.9 ± 1.8%; $n = 19$) appeared somewhat higher, albeit not quite significantly so ($p < 0.06$), than in control rats. Inversely, the paired muscle/blood and liver/blood ratios in radioactivity tended to be lower in these STZ rats than in control animals. Such differences failed, however, to achieve statistical significance. Only the paired pancreas/blood radioactive ratio was significantly lower ($p < 0.03$ or less) in the diabetic rats than in the control animals. In the STZ rats, the mean values for the pancreas/blood radioactive ratio recorded, respectively, in the least and most severely hyperglycemic animals (plasma D-glucose concentration : 18.6 ± 1.4 and 34.9 ± 0.8 m*M*; $n = 4$–11) were not significantly different from one another (23.3 ± 2.5 and 25.7 ± 1.9%) and both significantly lower ($p < 0.03$ in both cases) than the mean value (33.0 ± 2.4%) found in the control rats with a plasma D-glucose concentration of 11.1 ± 0.2 m*M* ($n = 12$).

The last group of STZ rats received each day and for three successive days, two injections of 6 U of insulin each and were killed about 16 h after the last injection. These animals lost 11.9 ± 1.5 g over the period of 3 d following the administration of streptozotocin, and then gained 29.8 ± 2.4 g ($n = 12$ in both cases) over the next 3 d when treated with insulin. Their plasma D-glucose concentration aver-

Table 3
Biological Data in either Control Animals or STZ Rats Treated with Insulin, and Examined 3 min after the Injection of 6-DIG

Rats	Control	STZ + insulin (2)[a]	STZ + insulin (3)[a]	STZ + insulin (6)[a]
Body weight (g)	214 ± 3 (12)	218 ± 3 (12)	234 ± 4 (11)	243 ± 3 (12)
Plasma D-glucose concentration (m*M*)	11.1 ± 0.2 (12)	30.8 ± 1.9 (11)	28.2 ± 2.6 (9)	9.1 ± 2.2 (11)
Erythrocyte/plasma radioactive ratio (%)	63.3 ± 2.9 (12)	69.4 ± 2.5 (10)	70.3 ± 2.8 (9)	74.1 ± 5.7 (11)
Muscle/blood radioactive ratio (%)	22.1 ± 1.6 (12)	19.6 ± 2.2 (12)	17.9 ± 2.2 (11)	27.8 ± 1.4 (12)
Liver wet wt				
g	8.54 ± 0.20 (12)	10.12 ± 0.36 (12)	12.56 ± 0.49 (11)	12.39 ± 0.46 (10)
% of body wt	3.72 ± 0.24 (12)	4.62 ± 0.11 (12)	5.34 ± 0.18 (11)	5.06 ± 0.15 (12)
Liver/blood radioactive ratio (%)	87.1 ± 4.3 (12)	82.2 ± 6.5 (12)	74.6 ± 7.7 (11)	103.5 ± 3.8 (12)
Pancreas wet wt				
mg	967 ± 47 (12)	978 ± 45 (12)	1016 ± 37 (11)	1245 ± 48 (12)
‰ of body wt	4.47 ± 0.22 (12)	4.44 ± 0.18 (12)	4.32 ± 0.12 (11)	5.07 ± 0.24 (12)
Pancreas/blood radioactive ratio (%)	33.0 ± 2.4 (11)	25.0 ± 2.2 (12)	23.2 ± 2.4 (11)	28.6 ± 1.5 (12)

[a]Number of insulin injections.

aged 9.1 ± 2.2 m*M* (n = 12). As in the other groups of insulin-treated STZ rats, the liver wet wt, whether expressed in absolute values or relative to paired body wt, was much higher than in control rats (Table 3).

The dose of 6-DIG injected intravenously was 9.1 μCi (or 0.03 μmol/rat).

As judged from the plasma radioactive content, the apparent distribution space of 6-DIG (from a different batch than that used in the three first series of experiments in this second part of our study) averaged, excluding one abnormally high value (2.04 mL/g body wt), 0.36 ± 0.01 mL/g body wt (n = 10). The rather unusual reproducibility of the measurements made at min 3 in this group led us to calculate such a mean value, so that it could be compared to measurements made at a later time. For instance, by comparison with the tenth min readings mentioned above (0.86 ± 0.05 mL/g; n = 24), it was calculated that, assuming an exponential fall of plasma radioactivity according to the equation $R = R_0e^{-Kt}$, the K value would be close to 12.2 ± 1.3 × 10^{-2} min^{-1} during the early period after 6-DIG injection (3–10 min). Such a value is two orders of magnitude higher than that measured beyond the tenth min after 6-DIG injection (*see below*), indicating the participation of at least two distinct processes to the body distribution and/or clearance of 6-DIG.

The paired erythrocytes/plasma, muscle/blood, and liver/blood ratios in radioactivity were all significantly higher in these insulin-treated STZ rats than in control animals ($p < 0.02$ or less), this being probably attributable to the occurrence of hypoglycemia (plasma D-glucose concentration : 3.41 ± 0.52 m*M*) in six of these rats.

The pancreatic radioactive content, expressed relative to the paired blood value, averaged 28.6 ± 1.5% (n = 12), a value not significantly lower ($p > 0.1$) than that found in control rats. The mean value for such a ratio in the six hypoglycemic rats, i.e., 30.7 ± 2.1%, was not significantly different ($p > 0.3$) from that found in the five normoglycemic or hyperglycemic insulin-treated STZ rats (plasma D-glucose concentration : 15.87 ± 2.44 m*M*), i.e., 28.3 ± 1.4%.

In these experiments, however, the paired ratio between pancreatic and hepatic radioactive content (27.6 ± 0.8%; n = 12) remained lower ($p < 0.005$), than in control rats (37.9 ± 3.3%; n = 11), as was also the case ($p < 0.01$) in the two groups of rats that had received a lower number of insulin injections (30.8 ± 0.9%; n = 23).

When pooling all available measurements made 3 min after the injection of 6-DIG in the present study, the following picture emerged (Fig. 1). In control rats, the plasma D-glucose concentration and paired pancreatic/blood ratio in radioactivity averaged, respectively, 10.59 ± 0.20 m*M* and 35.9 ± 2.2% (n = 23-24), as distinct ($P < 0.005$ or less) from 25.21 ± 1.12 m*M* and 27.0 ± 1.0% (n = 11-12) in untreated STZ rats. In the insulin-treated STZ rats, the corresponding values were 9.92 ± 2.06 m*M* and 26.3 ± 1.1% (n = 37-41), both values being again significantly different ($p < 0.001$) from those recorded in control rats. When only hypoglycemic, normoglycemic, and moderately hyperglycemic insulin-treated STZ rats (plasma D-glucose concentration below 22.0 m*M*) were taken into account, the mean plasma D-glucose concentration (9.72 ± 1.42 m*M*; n = 20) was no more significantly different ($p > 0.5$) from that found in control rats. Yet, the paired

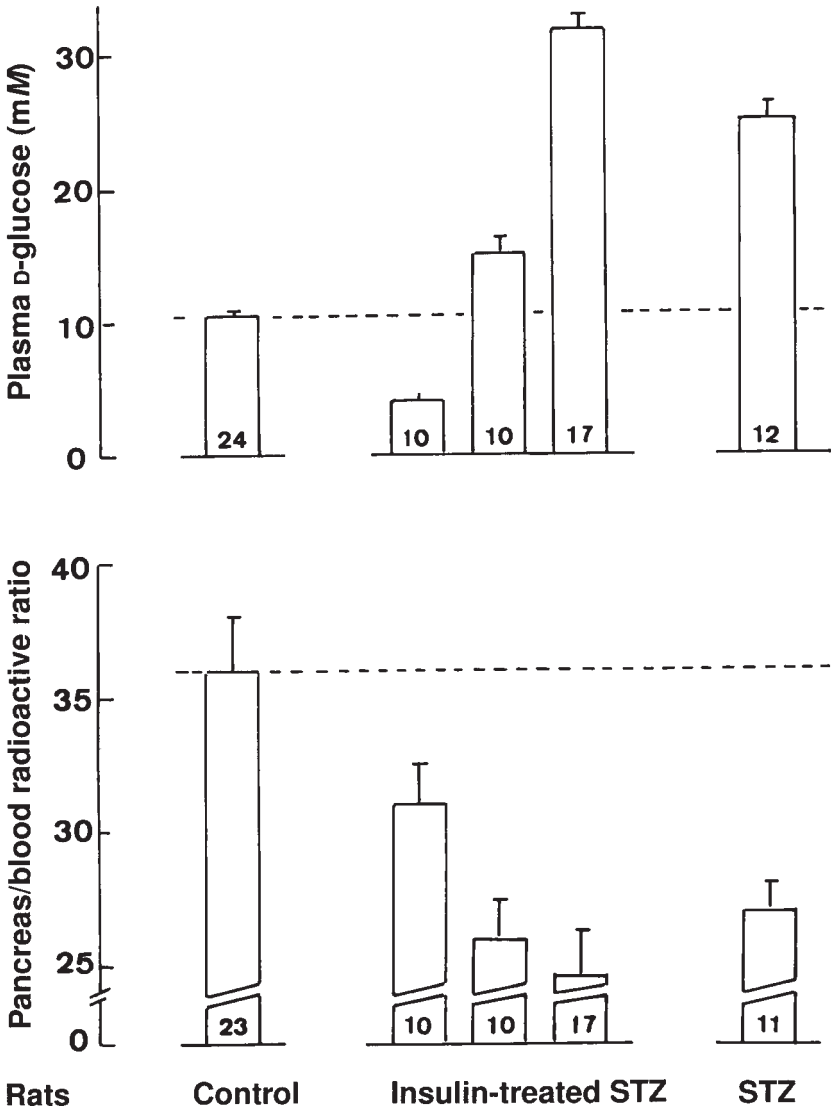

Fig. 1. Mean values (± SEM) for the plasma D-glucose concentration (upper panel) and paired pancreas/blood radioactive ratio (lower panel) in control rats, insulin-treated STZ rats, and untreated STZ rats examined 3 min after the intravenous injection of 6-DIG. The horizontal dotted lines refer to the mean values found in control rats. The number of individual observations is indicated at the bottom of each column. The insulin-treated STZ rats were, from left to right, hypoglycemic, normoglycemic or moderately hyperglycemic (plasma D-glucose concentration below 22.0 m*M*), and severely hyperglycemic.

pancreatic/blood ratio in radioactivity (28.4 ± 1.2%; $n = 20$) remained significantly lower ($p < 0.005$) than in control animals. Figure 1 illustrates the inverse relationship between plasma D-glucose concentration and paired pancreas/blood radioactive ratio in the insulin-treated STZ rats, and compares the situation found in these animals to that documented in either control or untreated STZ rats.

Long-Term Experiments

The last two sets of experiments in this study aimed at characterizing the fate of 6-DIG in normal rats, beyond the tenth min after its intravenous injection.

The plasma, blood, and erythrocyte radioactivity were first measured over 60 min after the injection of 6-DIG (14.3 μCi and 0.05 μmol/rat) in six normal rats (Table 4).

The plasma radioactivity at min 10 yielded an apparent distribution space averaging 0.70 ± 0.08 mL/g body wt ($n = 6$). Assuming an exponential decrease in plasma radioactivity (according to the equation $R = R_0 e^{-Kt}$), the measurements made between min 20 and 60 yielded a K value close to 0.2×10^{-2} min^{-1} (Fig. 2).

Already at the tenth min, the paired erythrocyte/plasma radioactive ratio averaged 88.3 ± 4.1% ($n = 6$), as compared to 88.4 ± 4.5% ($n = 6$) at min 20, 93.1 ± 1.8% ($n = 5$) at min 30, 93.8 ± 2.2% ($n = 5$) at min 45 and 85.0 ± 4.6% ($n = 6$) at min 60.

Expressed relative to the paired radioactivity of blood, that of muscle, liver, and pancreas averaged 68.6 ± 1.2%, 100.8 ± 3.2% and 69.2 ± 2.0%, respectively (Table 3), when the rats were killed 60 min after the injection of 6-DIG.

Table 4
Biological Data in Normal Rats Examined 60 min after the Injection of 6-DIG

Body weight (g)	225 ± 5 (6)
Plasma D-glucose (m*M*)	13.4 ± 0.2 (5)
Erythrocyte/plasma radioactive ratio (%)	85.0 ± 4.6 (6)
Muscle/blood radioactive ratio (%)	68.6 ± 1.2 (6)
Liver wet wt	
g	7.80 ± 0.26 (6)
% of body wt	3.46 ± 0.07 (6)
Liver/blood radioactive ratio (%)	100.8 ± 3.2 (6)
Pancreas wet wt	
mg	933 ± 40 (6)
‰ of body wt	4.14 ± 0.23 (6)
Pancreas/blood radioactive ratio (%)	69.2 ± 2.0 (6)

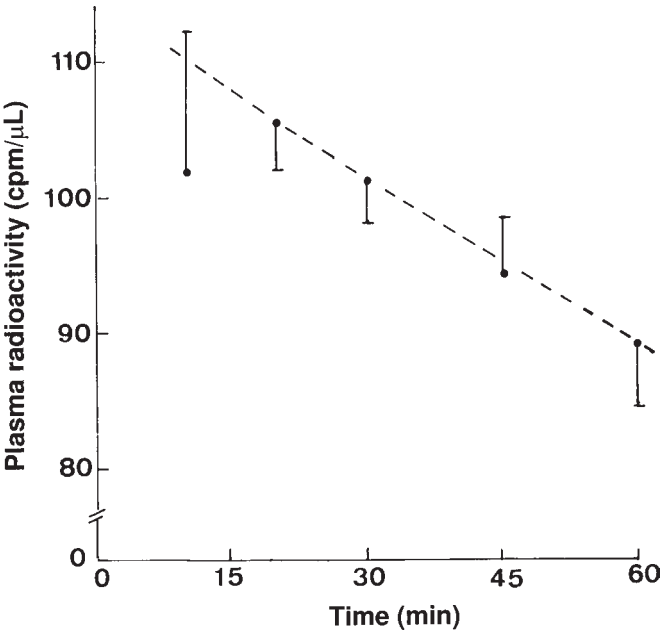

Fig. 2. Time course for the changes in plasma radioactivity after intravenous injection of 6-DIG (14.3 μCi or 0.05 μmol per rat). Mean values (± SEM) refer to six measurements at each time point. The line defining the fall in radioactivity (*R*) was calculated by regression analysis of the last four mean measurements made, according to the equation $R = R_0 e^{-Kt}$.

In the last set of experiments, three normal rats (200 ± 3 g body wt) were examined 24 h after the intravenous injection of 6-DIG (14.6 μCi and 0.05 μmol/rat). Over this period, they gained 10.3 ± 3.0 g body wt. At killing their plasma D-glucose concentration averaged 9.55 ± 0.40 m*M*. As judged from the plasma radioactivity, the apparent volume of distribution averaged 8.36 ± 1.82 mL/g body wt, as compared to 0.89 ± 0.08 mL/g body wt ($n = 12$) only 10 min after the injection of DIG to normal rats (see above). These data yielded a *K* value close to 0.16 ± 0.02 × 10^{-2} min^{-1}, in fair agreement with the value derived from the measurements made during the period of 60 min following the intravenous injection of 6-DIG (Fig. 2). The erythrocyte/plasma paired ratio in radioactivity averaged, in these three rats, 65.3 ± 7.9%, a value significantly lower ($p < 0.025$) than that recorded 10 min after the injection of 6-DIG in the experiments illustrated in Fig. 2 (88.3 ± 4.1%; $n = 6$). Relative to the paired plasma radioactivity, that of other organs (cpm/mg wet wt) averaged 5.5 ± 1.2% in brain, 21.5 ± 1.2% in muscle, 51.4 ± 5.2% in pancreas, 60.7 ± 2.3% in liver, and 86.5 ± 5.1% in kidney. In these experiments, the liver, kidney, and pancreas wet wt averaged, respectively, 4.14 ± 0.08 %, 0.42 ± 0.01% and 0.47 ± 0.02% of paired body wt.

The *K* value mentioned above, the high radioactive content of the kidney, and the presence of a large amount of radioactivity in the urine (data not shown) are all compatible with the view that 6-DIG is mainly eliminated from the body by glomerular filtration.

Discussion

The present study affords essentially three novel pieces of information. First, it indicates that the disappearance of 6-DIG from the plasma, after its intravenous injection, involves first a rapid distribution phenomenon completed within 10 min and occurring in an apparent volume close to the whole body weight, and then a much slower clearance tentatively ascribed to the elimination of 6-DIG by glomerular filtration.

Second, except for a transient (min 10) accumulation of 6-DIG in the liver, the radioactive content of all organs here under consideration (erythrocytes, muscle, liver, and pancreas) was close to or remained frankly lower than that of plasma (or blood). This obviously represents a rather unfavorable situation in the perspective of using 6-DIG for the noninvasive imaging of these organs, e.g., by single-photon emission computer tomography *(2)*. Nevertheless, 6-DIG could conceivably be used to assess, by a noninvasive method, the participation of the liver to disorders of glucose homeostasis.

Last, and most important, the present results unambiguously indicate that the difference in the time course for 6-DIG uptake by pancreatic acinar and islet cells, as recently documented in vitro *(1)*, results, 3 min after the intravenous injection of 6-DIG, in a higher pancreatic uptake of the iodinated hexose by the whole pancreatic gland of control rats, as distinct from animals that became diabetic as a result of the destruction of insulin-producing cells by streptozotocin. This difference was observed even when comparing control rats to diabetic animals displaying a normal mean plasma D-glucose concentration, as a result of insulin treatment. Assuming that the net uptake of 6-DIG by the exocrine moiety of the pancreas was iden-

tical in the control rats and the normoglycemic STZ rats and that the endocrine pancreas only accounts for 1.0% of the total pancreatic mass, it was calculated that, per unit wet wt, the radioactivity content of the pancreatic islets was, 3 min after the injection of 6-DIG, about 26 times higher (26.2 ± 8.9; *df* = 41) than that of the acinar cells. This is in fair agreement with the results of experiments conducted in vitro *(1)*.

It is obvious that the difference between the pancreatic measurements made in control and euglycemic STZ rats is not sufficiently pronounced to allow, even shortly after the injection of 6-DIG, a reliable assessment of the mass of the endocrine pancreas by noninvasive imaging of the pancreatic gland. Moreover, and as already mentioned, the quantitative aspects of such an imaging might be hampered by the low ratio between pancreatic and blood radioactivity.

The present study draws attention, therefore, to two major requirements for selective imaging of the endocrine pancreas by a radioactive monosaccharide. First, the monosaccharide under consideration should be efficiently taken up by endocrine islet cells, while being virtually excluded from pancreatic acinar cells. The specific expression of the GLUT2 gene in islet B-cells may provide a favorable opportunity in this perspective. Second, as it is the case with 2-deoxy-2-fluoro-D-glucose in most cell types, the monosaccharide should be able to undergo phosphorylation in order to allow for the accumulation of its phosphate ester in amounts largely exceeding the limited pool of intracellular unesterified monosaccharide. Here again, the presence in islet B-cells of glucokinase, as distinct from other hexokinase isoenzymes, could conceivably represent a favorable attribute.

Materials and Methods

All experiments were conducted in female Wistar rats given free access to food and tap water throughout the experimental procedure. They were purchased from B & K Ltd. (Hull, UK) for the five first experiments listed in Table 2, and from Iffa Credo (L'Arbresle, France) for the last six experiments in the same table. Streptozotocin (Sigma, St. Louis, MO), freshly dissolved in saline, was injected (0.25 μmol/g body wt) in a tail vein, without anesthesia, the animals being placed in a restraining box. Some of these diabetic animals (STZ rats) were treated with insulin, as described above.

The 6-deoxy-6-[^{125}I]iodo-D-glucose (6-DIG) was kindly provided by M.L. Mauclaire (CIS bio international, Gif-sur-Yvette, France). Its contamination by radioactive acidic metabolites was assessed by ion exchange chromatography. Except in the first three experiments, the material injected corresponded to that purified by this procedure and further diluted with an equal volume of a NaCl solution (0.31 *M*). The animals were injected with 0.15–0.30 mL (Table 2) in a tail vein, without anesthesia, the end of this injection being taken as time zero.

At stated times after the injection of 6-DIG, the animals were stunned and decapitated. Blood was collected in heparinized tubes for measuring blood, plasma and erythrocyte radioactivity, and plasma D-glucose concentration *(3)*. The rats were then immediately dissected for removal of the whole pancreas (cut in two fragments) and for sampling of the liver and muscle. In one set of experiments, a kidney and a piece of brain were also collected. All the samples were weighed and examined for their radioactive content. The remaining part of the liver was also weighed.

In one series of experiments, blood samples were collected from the severed tip of the tail at time intervals after the injection of 6-DIG.

All results are presented as means ± SE, together with the number of individual observations (*n*) or degree of freedom (*df*). For all results representing a ratio between two variables, a geometric mean was used, the SE mentioned in the text and tables representing the mean of the upper and lower deviation from the geometric mean *(4)*. The statistical significance of differences between mean values was assessed by the use of Student's two-tailed *t*-test.

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