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Metabolism of Glucose in Hyper- and Hypo-thyroid Rats *in vivo*

MINOR ROLE OF ENDOGENOUS INSULIN IN THYROID-DEPENDENT CHANGES IN GLUCOSE TURNOVER

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1. Rates and rate coefficients of glucose utilization and replacement (glucose turnover) as well as its recycling were determined in rats by using [U-^{14}C]- and [2-^{3}H]-, [3-^{3}H]- or [6-^{3}H]-glucose. 2. In euthyroid rats, the blood concentration of glucose was 1.5 times and its turnover rate was 2 times as high in the fed state as in the starved state; consequently the rate coefficient, a measure of the capacity of rats to utilize blood glucose, was also higher in the former than in the latter. 3. Induction of mild diabetes by streptozotocin exerted little influence on the content and turnover of blood glucose in the starved state, whereas it caused hyperglycaemia and a decrease in the rate coefficient after feeding. 4. Induction of hyperthyroidism caused increases in rates and rate coefficients of glucose turnover to substantially the same extent whether or not the plasma concentration of insulin was lowered by treatment with streptozotocin or injection with anti-insulin serum. 5. It is concluded that thyroid hormones are capable of enhancing glucose turnover in the starved state independently of endogenous insulin, which plays a significant role in increasing glucose utilization in the fed state.

The preceding paper (Okajima & Ui, 1979*a*) showed that blood glucose turned over more rapidly in hyperthyroid and more slowly in hypothyroid than in euthyroid rats. The metabolism of blood glucose is known to be under the influence of various endocrine and neural factors such as pancreatic hormones and adrenergic amines, the function and secretion of which would in turn depend on the thyroid state. In fact, the adrenergic regulation of insulin secretion has been reported to be affected by changes in the thyroid state (Okajima & Ui, 1978); the β-adrenergic stimulation was enhanced and impaired in hyperthyroid and hypothyroid rats respectively.

Thus endogenous insulin would be somewhat responsible for the thyroid-dependent increase in the rate of glucose turnover, since it could accelerate the tissue utilization of blood glucose. The purpose of the present paper is to study the role of endogenous insulin in determining the steady-state rate of glucose turnover.

Experimental

Animal experiments

Male albino rats (body wt. 150–250g) of the Wistar-derived strain were used. They had been starved for 20h before experiments unless otherwise specified. Rats were rendered hyperthyroid or hypothyroid as described by Okajima & Ui (1978). Mild diabetes was induced by injecting a freshly prepared solution of streptozotocin (4.5mg/100g body wt.) intravenously into rats by the procedure described elsewhere (Katada & Ui, 1977*a*). The rats with hyperglycaemia above 300mg/100ml in the fed state and with the normal glucose concentration below 100mg/100ml after 20h starvation were used for experiments.

The rate of glucose turnover in the steady state (i.e. without periodical changes in the blood glucose concentration) was determined, based on the decay of labelled blood glucose, by means of the monoexponential analysis with whole blood specimens withdrawn from the tail vein at 30, 45, 60, 75 and 90min after the injection of a tracer. [U-^{14}C]Glucose or [2-^{3}H]-, [3-^{3}H]- or [6-^{3}H]-glucose was used as the tracer (Okajima & Ui, 1979*a*). When the concentration of blood glucose was gradually changed during the experimental period, the rate of glucose inflow into the rapidly mixing pool (the inflow rate, R_{inflow}) and the rate of glucose removal from the pool (the outflow rate, $R_{outflow}$) were calculated separately according to the equations described by Shikama & Ui (1975*a*).

The glucose-tolerance test was carried out by an intravenous loading of a 50% (w/v) solution of glucose in pentobarbital-anaesthetized rats. Hyper-

glycaemia induced by the glucose loading was usually so transient as to be decreased progressively until the normal glucose concentration was recovered within 1h. Since this recovery obeyed first-order kinetics, the rate constant (k, %/min) was calculated as $-2.303 \times b \times 100$, where b is the slope of the semi-logarithmic plot of the blood glucose concentration against time. [^{14}C]Bicarbonate was also injected intravenously to study the production of [^{14}C]-glucose by gluconeogenesis (Shikama & Ui, 1975*a*,*b*).

For the purpose of determining the plasma concentration of insulin, 0.1ml of whole blood taken from the tail vein was quickly mixed with 0.9% NaCl containing heparin. After centrifugation (700*g*, 10min) the supernatant was obtained as diluted plasma and was assayed for immunoreactive insulin by the method described elsewhere (Okajima & Ui, 1978).

Materials

Sources of reagents are as follows: streptozotocin, a gift from Dr. M. Yajima, Kakenyaku Kako Co., Shiga, Japan; bovine crystalline insulin, a gift from Lilly Research Laboratories, Indianapolis, IN, U.S.A., through the courtesy of Dr. O. K. Behrens and Dr. W. N. Shaw. ^{125}I-labelled insulin was purchased from Dainabot Radioisotope Laboratories, Tokyo, Japan. Guinea-pig anti-insulin antiserum was prepared as reported by Shikama & Ui (1976). Sources of other reagents are as in the preceding paper (Okajima & Ui, 1979*a*).

Results

Rates of glucose turnover in the fed and starved states

Since feeding is known to stimulate insulin secretion, the role of the secreted insulin in determining the rate of glucose turnover was first studied by comparing the rates in the starved and fed states. There was no periodical change in the blood glucose concentration in either the starved or the fed state during the period of experiment in which decay of labelled blood glucose was followed after a single injection with [U-^{14}C,3-^{3}H]glucose. Kinetic parameters calculated for glucose turnover, together with the plasma insulin concentration, are shown in Table 1. The rate of glucose turnover (R) was roughly twice as high in the fed state as in the starved state, regardless of whether decay of ^{14}C or ^{3}H was used for calculation. The difference between R_c and R_{3H} was then used for calculation of the glucose recycling via the Cori cycle (and the glucose–alanine cycle). The contribution of futile cycles between fructose 6-phosphate and fructose 1,6-bisphosphate to the glucose recycling was found to be minimal (Okajima & Ui, 1979*a*). The recycling was markedly suppressed in the fed state, clearly indicating that intestinal absorption of the nutrients, rather than hepatic gluconeogenesis, was responsible for blood glucose supply in the fed state.

Concentrations of blood glucose and plasma insulin in the fed state were 1.5- and 2.5-fold respectively those in the starved state (Table 1). The increase in blood glucose would have enhanced removal of the glucose by tissues, owing to a mass-action effect (Kusaka & Ui, 1977). The rate coefficient, k', was therefore calculated as a measure of the glucose turnover corrected for by the blood glucose concentration or of the capacity of the rat to take up glucose into its cells; it was still higher, by 30–40%, in the fed state than in the starved state. Thus the increased rate of glucose turnover in the fed state was considerably, but not totally, accounted for by the mass-action effect of hyperglycaemia. The residual increase not accounted for by hyperglycaemia would be due to increased capacity for tissue glucose uptake dependent on the action of insulin secreted in the fed state. The relative roles of insulin and changes

Table 1. *Concentrations of blood glucose and plasma insulin, rates and rate coefficients for glucose turnover and glucose recycling in starved and fed euthyroid rats*

Blood samples (0.1ml) were taken from the tail vein of starved rats injected intravenously with [U-^{14}C,3-^{3}H]glucose (0.5μCi of ^{14}C and 5μCi of ^{3}H per 100g body wt.) at 30, 45, 60, 75 and 90min after the injection. Specific radioactivity of glucose in the sample was used for calculation of rates (R_c and R_{3H}) and rate coefficients (k'_c and k'_{3H}) for glucose turnover by the monoexponential method as described by Okajima & Ui (1979*a*). The glucose concentrations in blood samples were averaged to obtain a representative value for each rat, whereas the plasma insulin concentration was determined at 90min. The percentage glucose recycling was calculated based on the difference between R_c and R_{3H} as described previously (Okajima & Ui, 1979*a*). Mean values ± S.E.M. from eight (starved) or nine (fed) rats are given. Significance of difference between starved and fed: $^{*}P<0.05$, $^{**}P<0.01$.

	Blood glucose (mg/100ml)	Turnover rate (mg/min per 100g body wt.)		Rate coefficient (ml/min per 100g body wt.)		Glucose recycling (%)	Plasma insulin (μunits/ml)
		R_{3H}	R_c	k'_{3H}	k'_c		
Starved	71 ± 2	0.57 ± 0.05	0.43 ± 0.04	0.80 ± 0.05	0.60 ± 0.04	25 ± 1.4	20 ± 4.3
Fed	105 ± 2**	1.08 ± 0.09**	0.91 ± 0.08**	1.02 ± 0.08*	0.86 ± 0.07**	15 ± 1.5**	50 ± 5.0**

in the blood glucose concentration in determining glucose turnover are dealt with below in more detail.

Glucose turnover in mildly diabetic and hyperthyroid rats

A role of endogenous insulin in the hyperthyroid-induced increase in glucose turnover was next studied by decreasing the concentration of circulating insulin. Both the turnover rate and the rate coefficient determined with [U-^{14}C]glucose or [2-^{3}H]-glucose in the starved state markedly increased on induction of the hyperthyroid state (Table 2), in accordance with the previous results (Okajima & Ui, 1979*a*). A slight hyperglycaemia associated with a slight hyperinsulinaemia was also observed in starved hyperthyroid rats (Okajima & Ui, 1978). Induction of mild diabetes by streptozotocin was without effect on the starvation concentration of blood glucose (see Katada & Ui, 1976, 1977*a*), although the plasma insulin concentration was significantly lowered in either euthyroid or hyperthyroid rats.

In diabetic starved rats, there were no differences in concentrations of blood glucose and plasma insulin between euthyroid and hyperthyroid rats, but the turnover rate was still twice as high in the latter as in the former. Thus increased glucose turnover observed in hyperthyroid rats appeared to be independent of the ability of endogenous insulin to accelerate the blood glucose turnover.

Effect of anti-insulin serum on glucose turnover in euthyroid and hyperthyroid rats

Since insulin was still present, though at lower concentrations than normal, in streptozotocin-diabetic rats, more complete suppression of endogenous insulin was caused by treatment of starved rats with anti-insulin serum. Antiserum capable of neutralizing 1 unit of insulin was injected intravenously per 100g body wt., the amount probably being far in excess of that required for complete neutralization of the circulating insulin in view of the plasma content of less than 0.5munit/100g body wt. or of the baseline rate of 20–40μunits/min for the secretion *in vitro* from perfused rat pancreas (Katada & Ui, 1977*b*).

After the injection of the antiserum, there was a gradual increase in the blood concentration of glucose in euthyroid or hyperthyroid rats (Fig. 1). In contrast, no change in blood glucose concentration was caused by the normal guinea-pig serum used as the control. Since periodical changes in the glucose mass in a pool indicate that glucose entered the pool at a rate different from its outflow, the rates of inflow and outflow were calculated separately by combination of these changes in blood glucose concentration with concurrent changes in the specific radioactivity of blood glucose labelled with ^{14}C uniformly or with ^{3}H at the 2-position. These rates were rather constant during the 1h period shown in Fig. 1 in a rat; they were averaged within a group of rats receiving the same treatment, and were recorded in Table 3.

There was essentially no difference between the inflow rate and the outflow rate in the rats injected with the normal serum, reflecting the steady-state glucose turnover. The injection with anti-insulin serum caused a significant increase in the inflow rate of glucose in both euthyroid and hyperthyroid rats without a significant change in the outflow rate. Thus the antiserum-induced hyperglycaemia appeared to be primarily due to increased inflow of glucose into the blood glucose pool. With respect to the outflow from the pool, however, the rate should have increased by virtue of the mass-action effect of hyperglycaemia. The lack of increase in the outflow rate therefore implies that the utilization of blood glucose by peripheral tissues was in fact suppressed

Table 2. *Effects of hyperthyroidism on glucose turnover in starved non-diabetic and streptozotocin-induced diabetic rats*
Euthyroid and hyperthyroid rats were divided into two groups, one of which (diabetic) was rendered diabetic by intravenous injection of streptozotocin (4.5mg/100g body wt., 4 days before experiments), and the other (non-diabetic) served as non-diabetic control. [U-^{14}C,6-^{3}H]Glucose was injected in the starved state. Turnover rates, rate coefficients, concentrations of blood glucose and plasma insulin were determined as in Table 1. Mean values ± S.E.M. are given with the numbers of observations in parentheses. *($P<0.05$), **($P<0.01$): Significantly different from corresponding euthyroid control. †($P<0.05$): Significantly different from non-diabetic control.

Treatment	Blood glucose (mg/100ml)	Turnover rate (mg/min per 100g body wt.) R_{2H}	Turnover rate (mg/min per 100g body wt.) R_c	Rate coefficient (ml/min per 100g body wt.) k'_{2H}	Rate coefficient (ml/min per 100g body wt.) k'_c	Plasma insulin (μunits/ml)
(*a*) Non-diabetic						
Euthyroid (10)	75±3	0.71±0.03	0.48±0.03	0.95±0.02	0.65±0.04	21±1.7
Hyperthyroid (11)	90±3*	1.24±0.08**	0.75±0.07**	1.40±0.11**	0.86±0.08**	28±3.2
(*b*) Diabetic						
Euthyroid (8)	88±5	0.77±0.04	0.51±0.05	0.89±0.05	0.55±0.05	15±1.2†
Hyperthyroid (9)	87±5	1.41±0.10**	0.89±0.11**	1.67±0.18**	1.09±0.19**	13±1.6†

as a result of insulin insufficiency. In any case, glucose turned over more rapidly in hyperthyroid rats than in euthyroid rats even when the endogenous insulin was neutralized, confirming the above conclusion that the hyperthyroid-induced increase in glucose turnover was largely independent of endogenous insulin activity.

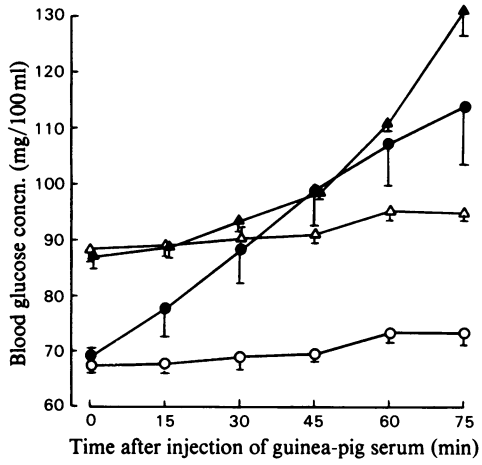

Fig. 1. *Effect of anti-insulin serum on the blood concentration of glucose*

Euthyroid (○, ●) and hyperthyroid (△, ▲) rats were injected intravenously with normal guinea-pig serum (○, △) or with anti-insulin serum (●, ▲) immediately before they were injected with [U-^{14}C,2-^{3}H]-glucose. The volume of the serum injected was 0.5ml/100g body wt. Mean values±S.E.M. from five rats are shown by symbols with vertical bars attached.

Increased incorporation of [^{14}C]bicarbonate into blood glucose in hyperthyroid rats treated with anti-insulin serum

Increased turnover of blood glucose in the starved state reflects enhanced gluconeogenesis (associated with the increased peripheral glucose utilization), since gluconeogenesis is the major source of blood glucose during starvation. Activation of gluconeogenesis in the hyperthyroid state was substantiated in the preceding paper by measuring the incorporation of [^{14}C]bicarbonate into blood glucose during a glucose-tolerance test (Okajima & Ui, 1979*a*). Similar experiments were repeated with rats deprived of their endogenous insulin by the antiserum treatment as shown in Fig. 2. Hyperglycaemia induced by glucose load was maintained for longer than 40min owing to insufficiency of insulin; the hyperglycaemia was of similar degree in euthyroid and hyperthyroid rats (Fig. 2*a*). Not only the ^{14}C content but also the specific radioactivity of blood glucose was higher in hyperthyroid than in euthyroid rats (Figs. 2*b* and 2*c*), demonstrating that more [^{14}C]glucose was produced in the hyperthyroid state. Production of more glucose without difference in the blood glucose concentration implies that more glucose was concurrently removed. Thus it is concluded that, even when hyperglycaemia develops by virtue of insulin deficiency, the hyperthyroid state is characterized by a rapid turnover of blood glucose.

Sensitivity of hyperthyroid rats to glycaemic action of insulin

The above findings, that enhanced glucose turnover in hyperthyroid rats was rather independent of endogenous insulin activity, would suggest that hyperthyroid rats were less sensitive to the glycaemic

Table 3. *Effect of anti-insulin serum on the production rate and the utilization rate of glucose in euthyroid and hyperthyroid rats*

Starved euthyroid and hyperthyroid rats were injected intravenously with normal or anti-insulin serum as shown in Fig. 1. R_{Inflow} and $R_{outflow}$ were calculated at 15min intervals for each rat and were averaged to obtain representative values for each rat. The glucose space of 39.7% for euthyroid and of 36.7% for hyperthyroid rats (Okajima & Ui, 1979*a*) was used for calculation of these rates. Mean values±S.E.M. from five animals for each group are given. All the corresponding values are significantly different between euthyroid and hyperthyroid rats ($P<0.05$ or $P<0.01$). *The effect of antiserum is significant ($P<0.05$). †R_{Inflow} is significantly larger than $R_{outflow}$ ($P<0.05$).

Treatment	Glucose labelled with	Production rate (R_{Inflow}) (mg/min per 100g body wt.) 2-^{3}H	Production rate (R_{Inflow}) (mg/min per 100g body wt.) U-^{14}C	Utilization rate ($R_{outflow}$) (mg/min per 100g body wt.) 2-^{3}H	Utilization rate ($R_{outflow}$) (mg/min per 100g body wt.) U-^{14}C
(*a*) Euthyroid					
Normal serum		0.72±0.02	0.54±0.02	0.72±0.06	0.46±0.03
Anti-insulin serum		0.90±0.07*†	0.67±0.07*†	0.67±0.02	0.45±0.04
(*b*) Hyperthyroid					
Normal serum		1.17±0.14	0.65±0.09	1.12±0.12	0.60±0.08
Anti-insulin serum		1.44±0.10*†	0.94±0.09*†	1.14±0.08	0.63±0.07

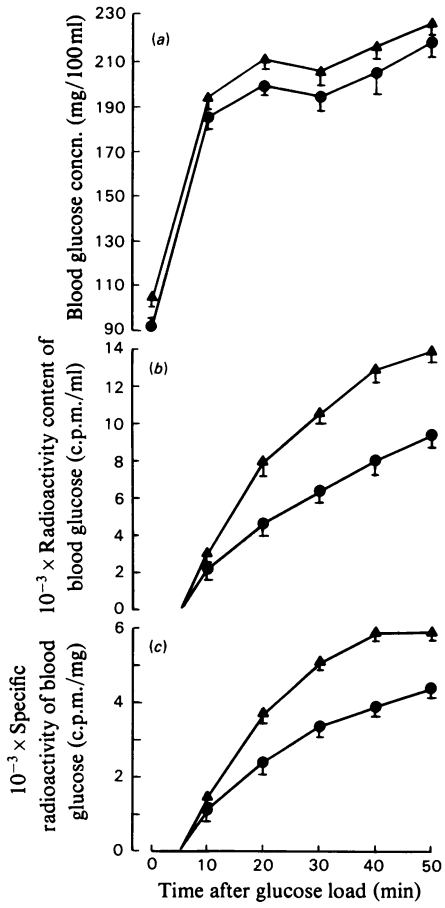

Fig. 2. *Changes in the blood glucose concentration and incorporation of [^{14}C]bicarbonate into blood glucose on glucose loading into euthyroid and hyperthyroid rats both treated with anti-insulin serum*

A 50% (w/v) solution of glucose (0.15ml/100g body wt.) and anti-insulin serum (in the same volume as in Fig. 1) were injected intravenously into four euthyroid (●) or four hyperthyroid (▲) rats at zero time. [^{14}C]-Bicarbonate (10μCi/100g) was injected intravenously at 5min. Mean values±S.E.M. are shown by symbols with vertical bars attached.

action of insulin. Such was not actually the case; as shown in Fig. 3, insulin injected simultaneously with an intravenous glucose loading improved glucose tolerance in hyperthyroid rats to a larger extent than in euthyroid rats. The k value (%/min), the first-order rate constant for the disposal of injected glucose, was 2.44±0.25 for the euthyroid and 3.04±0.13 for the hyperthyroid rats after insulin injection, the difference being significant at the 5% level. Thus the glucose-utilization mechanism in peripheral tissues was capable of being responsive to insulin more readily in hyperthyroid than in euthyroid rats.

Significance of the blood glucose concentration as a determinant of the turnover rate

Since the higher rate of glucose turnover in the fed state than in the starved state was to a considerable extent explained by hyperglycaemia (Table 1), the steady-state rate estimated with [6-^{3}H]glucose for each starved rat was plotted against its blood glucose concentration in Fig. 4. The starvation concentration of blood glucose ranged from 56 to 90mg/100ml (mean±S.E.M., 72±1.3) for 34 euthyroid rats, from 65 to 101mg/100ml (87±1.8) for 22 hyperthyroid rats and from 55 to 90 (71±3.3) for 10 hypothyroid rats. In both euthyroid and hyperthyroid rats, rates of glucose turnover were proportional to blood glucose concentrations, with regression coefficients of +0.71±0.19 and +0.66±0.33 respectively (Fig. 4*a*). Each regression was significantly different from 0 at the 1% level, but was not different from the other. In contrast, there was no significant increase in the turnover rate as the blood

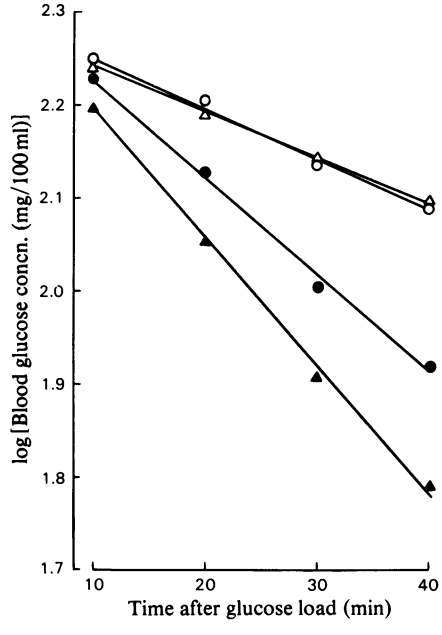

Fig. 3. *Effect of insulin on disposal of glucose injected*

A 50% solution of glucose was injected intravenously at zero time into four euthyroid (○, ●) and four hyperthyroid (△, ▲) rats, and the mean log of the blood glucose concentration was plotted against time. Linear regression lines were drawn by the least-squares fitting method. Insulin (0.02unit/100g body wt., ●, ▲) or 0.9% NaCl (○, △) was injected intravenously 5min after glucose loading.

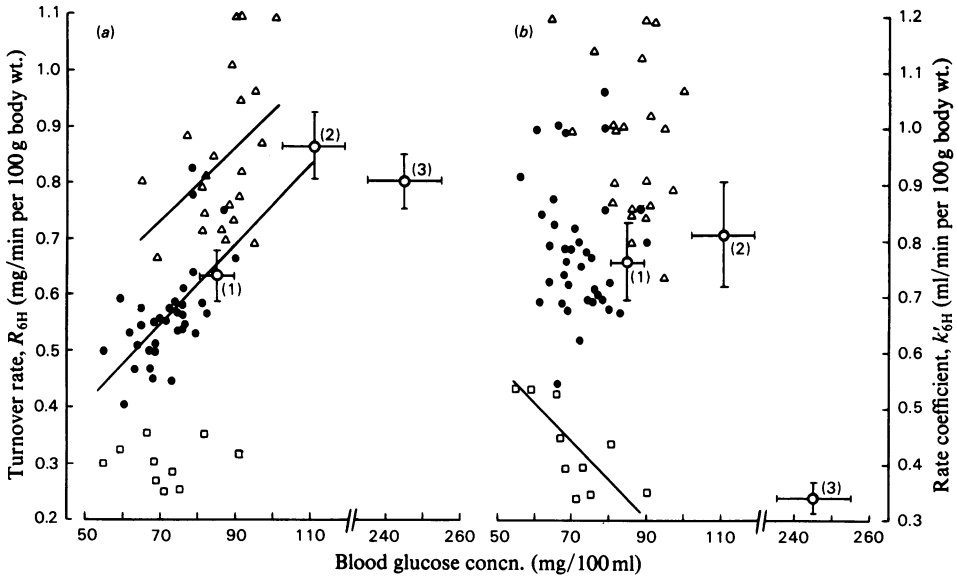

Fig. 4. *Dependence of rates and rate coefficients of glucose turnover on blood glucose concentrations*
Euthyroid (●), hyperthyroid (△) and hypothyroid (□) rats were injected with [6-^{3}H]glucose, and rates (*a*) and rate coefficients (*b*) calculated for each rat were plotted against its blood glucose concentration. Open circles represent means ± S.E.M. for rates (*a*) and for rate coefficients (*b*) with respect to glucose turnover in streptozotocin-induced diabetic rats as plotted against means ± S.E.M. for their blood glucose concentrations. Open circle (1), after 20h starvation (seven rats); open circle (2), after 9h starvation (five rats); open circle (3), after 3h starvation, i.e. in the post-absorptive state (ten rats). Regression lines for euthyroid and hyperthyroid (*a*) and for hypothyroid (*b*) are shown with respect to non-diabetic rats.

glucose concentration increased in hypothyroid rats; the regression coefficient of $+0.03 \pm 0.13$ was non-significant.

The rate coefficient, k'_{6H}, which is a measure of the capacity of the rat to take up glucose into its cells, was independent of the blood glucose concentration in the euthyroid and hyperthyroid states (Fig. 4*b*), suggesting that dependency of glucose-utilization rates on blood glucose concentrations was solely due to its mass-action effect. Thyroid was apparently required for the glucose-utilization capacity to be maintained normal, as evidenced by an inverse relationship between k' and blood glucose concentrations in hypothyroid rats.

The role of insulin in determining the glucose-utilization rate was further studied with diabetic euthyroid rats. Mildly diabetic rats were analysed for blood glucose concentrations, turnover rates and rate coefficients in the starved state [20h starvation, depicted by an open circle (1) in Fig. 4], after short-term starvation [9h, open circle (2)] and in the post-absorptive state [3h after the cessation of free access to food, open circle (3)]. The mean glucose concentration (85 ± 4.3 mg/100ml) of the diabetic rats after 20h starvation was within the concentration range of starved non-diabetic rats. When starvation was shortened to 9h, however, a slight but significant hyperglycaemia (111 ± 8.3) developed. As shown in Fig. 4(*a*), the relationship between blood glucose concentrations and turnover rates in starved diabetic rats was essentially on the same linear regression as that drawn for non-diabetic starved rats, regardless of whether starvation lasted for 9 or 20h. Thus diabetic rats were capable of utilizing glucose at a normal rate under these conditions.

In the post-absorptive state, hyperglycaemia developed up to 205 ± 10.8 mg/100ml in diabetic rats without concomitant increase in turnover rates beyond the rates after the 9h starvation. The capacity of the diabetic rat to metabolize glucose was much lowered under these conditions (Fig. 4*b*). Thus rats were capable of utilizing blood glucose independently of endogenous insulin when its replacement rate was at such a low rate as in the starved state. When intestinal absorption of the nutrients increased the replacement, however, insulin became essential for blood glucose to be taken up by peripheral tissues at a proportional rate.

Discussion

The stimulation of peripheral glucose utilization induced by the injection of insulin into starved rats was associated with increased release of glucose into the circulation, leading to increased turnover of blood glucose (Kusaka & Ui, 1977). The present results demonstrate that endogenous insulin secreted in response to feeding was also effective in accelerating the blood glucose turnover; the increase in turnover rate owing to food intake was associated with an increase in k' (Table 1), a measure of the capacity for peripheral glucose utilization, which was dependent on insulin, as evidenced by its marked decrease on induction of diabetes (Fig. 4).

It should be noted that insulin played only a minor role in the starved state, despite its importance in fed or post-absorptive rats, in determining the rate of glucose turnover. In fact, blood glucose turned over in diabetic rats at substantially the same rate as in non-diabetic rats, unless they were given food or glucose. Instead, the turnover of blood glucose in the starved state was highly dependent on thyroid activity; it was doubled in the hyperthyroid and halved in the hypothyroid state. This action of the thyroid appeared not to be mediated by endogenous insulin, since suppression of endogenous insulin did not decrease hyperthyroid-induced increases in turnover rates (Tables 2 and 3, Fig. 2).

In euthyroid or hyperthyroid rats, dependence of turnover rates on blood glucose concentrations in the starved state (Fig. 4*a*) was accounted for by a mass-action effect of blood glucose on glucose utilization, since k' was independent of blood glucose concentrations in these rats (Fig. 4*b*). This result appears to be at variance with the reports (Heath *et al.*, 1977*a*,*b*) that rate coefficients for glucose utilization were inversely correlated with plasma glucose concentrations in rats anaesthetized with halothane. The discrepancy would be explained by differences in experimental conditions such as anaesthesia, room temperature etc. In our study, there was an inverse relationship between k' and the blood glucose concentration only if rats had been rendered hypothyroid (Fig. 4*b*), suggesting that thyroid hormones might be also involved in the disagreement. The rather large scatter of individual k' values (Fig. 4*b*) would have confirmed their conclusion that the overall sensitivity of the tissues to insulin is surprisingly variable between individual animals (Heath *et al.*, 1977*a*).

The potency of insulin to enhance disposal of glucose was greater in hyperthyroid than in euthyroid rats (Fig. 3). Lenzen *et al.* (1975) reported that tolbutamide injected in hyperthyroid rats caused insulin secretion to the same extent as, but a more pronounced hypoglycaemia than, in euthyroid rats. Thus hyperthyroidism was characterized by enhanced sensitivity to the hypoglycaemic action of endogenous and exogenous insulin. Insulin sensitivity would have reflected the concentration of insulin receptors on target cells, which is known to be inversely related to the concentration of circulating insulin (Soll *et al.*, 1975*a*,*b*). The secretion of insulin in response to nutrients such as glucose (Renauld *et al.*, 1971; Cavagnini *et al.*, 1974; Lenzen *et al.*, 1976; Okajima & Ui, 1978) and arginine (Imura *et al.*, 1976; Shima *et al.*, 1976) was reported to be severely impaired in hyperthyroidism. Though the insulinaemic action of β-adrenergic agents was conversely enhanced by hyperthyroidism (Okajima & Ui, 1978), nutritional stimuli might be more intense and more frequent than sympathetic stimuli to cause a normal daily rhythm of insulin secretion. Moreover, circulating insulin would undergo rapid breakdown in hyperthyroidism (Orsetti *et al.*, 1974). Thus the total quantity of circulating insulin throughout the entire course of animal maintenance would be smaller in hyperthyroidism than in euthyroidism, increasing the concentration of insulin receptors on target cells and hence sensitivity to insulin. Involvement of other factors probably interfering with insulin action, such as somatotropin and catecholamines, would also be possible.

Although the present results clearly showed that thyroid-dependent stimulation of glucose turnover was not mediated by insulin action, the manner in which thyroid hormones could stimulate glucose metabolism is still unknown. A possible role of catecholamines is discussed in the following paper (Okajima & Ui, 1979*b*).

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