Effects of Streptozocin-Induced Diabetes and Food Restriction on Quantities and Source of T_4 and T_3 in Rat Tissues

JANNY P. SCHRÖDER-VAN DER ELST AND DAAN VAN DER HEIDE

Diabetes mellitus and fasting are both associated with low plasma thyroid hormone concentrations and loss of body weight. To discriminate between the separate effects of energy shortage and insulin, we studied control rats, diabetic rats (DM), DM rats treated with insulin (DMI), and rats after modified fasting (MF1 and MF2; 70 and 30% of normal daily food intake, respectively). In double-isotopic equilibrium experiments, we determined the tissue thyroxine (T_4) and triiodothyronine (T_3) concentrations and the contribution of local T_4-to-T_3 conversion to total T_3 in rat tissues; thyroidal T_4 and T_3 secretion and extrathyroidal T_3 production were calculated. In DM and DMI rats, plasma T_4 and T_3 decreased; in MF1 and MF2 rats, only plasma T_4 decreased. Thyroidal T_4 secretion decreased, whereas that of T_3 remained normal. The decrease in tissue T_4 in MF and DM rats paralleled the decrease in plasma T_4. Although plasma T_3 did not differ in DM and DMI rats, total T_3 concentrations in all tissues were not the same due to changed uptake of T_3 from plasma and local T_4-to-T_3 conversion; these changes were not found in several tissues of MF1 and MF2 rats. Our results suggest that the decrease in tissue T_4 during diabetes mellitus is due to the decrease in plasma T_4 caused by the decreased thyroidal secretion, possibly due to intracellular energy shortage. The changes in tissue T_3 during diabetes mellitus are only partly attributable to the same phenomenon; in several tissues, the decrease in T_3 seems more related to the lack of insulin. *Diabetes* 41:147–52, 1992

From the Department of Metabolic Diseases and Endocrinology, University Hospital, Leiden; and the Department of Human and Animal Physiology, Agricultural University, Wageningen, Netherlands.

Address correspondence and reprint requests to Dr. D. van der Heide, Department of Human and Animal Physiology, Agricultural University, Haarweg 10, 6709 PJ Wageningen, Netherlands.

Received for publication 21 March 1991 and accepted in revised form 14 October 1991.

Diabetes and fasting are both associated with a deficiency of thyroid hormones and a loss of body weight; plasma thyrotropin (TSH) levels are markedly decreased (1–4). Changes in the peripheral metabolism of thyroid hormones have been established both in vivo and in vitro (5–11). In recent reports, thyroid hormone appears to be involved in the regulation of glucose transport; muscle-fat glucose transporter protein and mRNA abundance in muscle were found to be dependent on thyroid status (12–14). Because plasma thyroid hormone levels do not always lead to corresponding intracellular concentrations (15,16), due to changes in local thyroxine (T_4) to triiodothyronine (T_3) conversion (17–19), it is important to be informed about tissue thyroid hormone concentrations. For this reason, we studied the effect of diabetes on the tissue concentrations in relation to the decrease in thyroid hormone concentrations in plasma. To discriminate between effects of diabetes per se and the effect of the accompanying loss of body weight, we studied diabetic rats with and without insulin therapy and rats on a diet of 30 or 70% reduced daily food intake.

[^{125}I]T_4 and [^{131}I]T_3 were simultaneously infused until isotopic equilibrium was achieved. In this way, we determined the tissue concentrations of T_4 and T_3 and calculated T_4 and T_3 secretion by the thyroid.

RESEARCH DESIGN AND METHODS

Groups of six euthyroid male Wistar rats were used in this study. At the start of the experiments, the rats weighed 297 ± 3 g. Two groups were used as control rats, two groups were diabetic (DM and insulin-treated DM [DMI]), and two groups underwent modified fasting (MF1 and MF2). The DM and DMI rats were made diabetic by one injection of streptozocin (60 mg/kg body wt i.v.), and one group (DMI) received insulin (0.5 U/day per rat i.v.;

Actrapid, Novo, Copenhagen) at a dosage sufficient to maintain a diabetic state without ketosis. MF1 received 70% of the daily food intake and MF2 30% of the daily food intake. The other two groups were controls.

The rats were individually housed in metabolic cages at 23°C with alternating 12-h light-dark cycles. The rats were fed a semisynthetic American Institute of Nutrition diet (20). (The composition of the diet was 20% casein, 10% vegetable oil, 10% cellulose, 55% glucose, and 5% vitamins, minerals, and trace elements.) The powder was mixed with water containing 10 mg/L KI to form a homogeneous paste.

The continuous intravenous infusions of saline with or without the labeled iodothyronines were administered at a constant rate (10 ml/day) via a cannula that was inserted into the right jugular vein and extended to the right atrium (21). The rats were unrestrained and ate and drank normally. Drinking water was available ad libitum. For MF1 and MF2, the mixture of minerals, trace elements, and vitamins was increased to an amount equal to the intake for control rats. All rats survived, and at the end of the experiment, the mean ± SE increase in body weight per day was controls, 3.7 ± 0.6 g; MF1, 0.3 ± 0.2g; MF2, −4.2 ± 0.6 g; controls, 3.7 ± 0.4 g; DMI, −2.0 ± 0.5 g; and DM, −4.3 ± 0.6 g.

Surgery (insertion of cannula) was conducted on day −4. On day 0, DM and DMI rats were made diabetic by an injection of streptozocin (60 mg/kg body wt i.v.), and MF1 and MF2 rats were put on their reduced–food intake diets. Insulin treatment of DMI rats was started on day 1 by the addition of 0.5 U/day insulin to the infusion fluid. On day 2, [^{125}I]T_4 (20 μCi/day per rat) was added to the infusion fluid (all groups). On day 6, [^{131}I]T_3 (25 μCi/day per rat) was added to the infusion fluid (all groups). On day 14, the rats were bled, perfused, and killed with ether anesthesia.

Radioactive T_4 and T_3 infusions and tissue homogenates were prepared, and thyroid hormone concentrations were analyzed and calculated as described earlier (15,16). After decay of the ^{131}I initially present in the samples, the concentrations of stable T_3, reverse triiodothyronine (rT_3), and T_4 in plasma were assessed by radioimmunoassay (RIA) with ^{131}I-labeled T_3, rT_3, and T_4 as tracers. TSH, growth hormone (GH), and prolactin were measured by the specific RIAs developed for the rat by the National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes of Health, Bethesda, MD). Reference preparation RP-2 was used as TSH, GH, and prolactin standard. Plasma glucose was measured by an automated glucose oxidase method (Beckman, Palo Alto, CA).

Statistical analysis was performed with Student's *t* test. Results are means ± SE. Multiple regression analysis was carried out to assess the increases in body weight and T_4 and T_3 levels in several tissues by the NCSS statistical package. The values for control, MF1, and MF2 rats were analyzed separately from those for control, DMI, and DM rats. If the regression lines were not significantly different, the line through control, MF1, MF2, DMI, and DM is given.

RESULTS

All rats received continuous infusions with [^{125}I]T_4 and [^{131}I]T_3 until the radioactivities in urine and feces each reached a constant level, and the daily total excretion of ^{125}I and ^{131}I equaled the daily input for at least 2 days. At that time, ^{125}I and ^{131}I activity accounted for 60–69% (urine) and 31–40% (fecal) of the total radioactivity excreted daily; there were no differences between the groups. The rats were assumed to be in isotopic equilibrium regarding the major pools of T_4, T_3, and their metabolites.

In MF1 and MF2 rats, plasma T_4 decreased and plasma rT_3, plasma T_3, and plasma TSH did not change (Table 1). The plasma clearance rate (PCR) for T_4 did not change, but that for T_3 was reduced. Both the production rate for T_4 (PRT_4) and the plasma appearance rate for T_3 ($PART_3$) were lower. The latter was caused by a decreased peripheral production of T_3 during MF1 and even more so during MF2, whereas thyroid PRT3 did not change. T_4 concentrations in most MF1 and MF2 rat tissues were decreased more or less in parallel with the plasma T_4 concentration (Table 1; Fig. 1). In MF2 rats, the decrease was greater than in MF1 rats. The T_4 tissue-plasma gradient was not changed, except for the liver and heart only during severe fasting (liver: control 0.525 ± 0.024, MF2 0.364 ± 0.020 [$P < 0.0005$]; heart: control 0.094 ± 0.006; MF2 0.063 ± 0.003 [$P < 0.005$]).

Total tissue T_3 decreased significantly only in liver (Fig. 1). The percentage of local conversion (percentage locally produced T_3 from T_4 in relation to total T_3) changed drastically in liver (control 34 ± 1, MF1 26 ± 5, MF2 6 ± 1). The decrease in total T_3 in the liver was caused by the decrease in locally produced T_3 and the decrease in the amount of plasma-derived T_3. T_3 concentrations did not change in cerebellum, brown adipose tissue, muscle, and heart. In brain, the amount of locally produced T_3 was decreased, opposite to the pituitary where locally produced T_3 was increased during modified fasting. The distribution of plasma-derived T_3 over the tissues and plasma, expressed as [^{131}I]T_3 tissue-plasma gradient, changed only in liver (control 9.05 ± 0.31, MF1 7.06 ± 0.42, MF2 6.34 ± 0.35·[$P < 0.01$]). In the other tissues, there were no significant changes (data not shown).

Diabetes mellitus was confirmed during the experiment by glucosuria and at the end of the study by high plasma glucose levels. DM but not DMI rats were slightly ketotic (+ to ++, ketostix, Ames, Elkhart, IN) throughout the experiment. DM and DMI rats had decreased plasma T_4 and T_3 concentrations (Table 2). The plasma rT_3 concentration was increased in DM but not in DMI rats. Plasma TSH was decreased but only significantly in DM rats. The PCR for T_4 was significantly increased, whereas that for T_3 was decreased. PRT_4 and $PART_3$ were both drastically lower in DM and DMI rats. The thyroid PRT_3 was not significantly reduced, whereas the peripheral T_3 production was markedly lower in DM and DMI rats. T_4 concentrations were decreased in most tissues during DM and DMI more or less in parallel with plasma T_4 (Fig. 2). No differences were found for the T_4 tissue-plasma gradients (data not shown). The total T_3 concentration in most

TABLE 1
Effect of fasting on plasma T_3, T_4, rT_3, TSH, and glucose levels; plasma clearance rates for T_3 and T_4; production rates for T_4; plasma appearance rate for T_3; and T_3 production by the thyroid and peripheral conversion

		Modified fast (MF)	
	Control	MF1 (30% food reduction)	MF2 (70% food reduction)
T_4 (nM)	56 ± 3	41 ± 2*	35 ± 2*
T_3 (nM)	0.70 ± 0.02	0.71 ± 0.03	0.71 ± 0.0
rT_3 (nM)	0.13 ± 0.01	0.15 ± 0.01	0.15 ± 0.01
TSH (ng/ml)	0.9 ± 0.2	0.7 ± 0.2	0.4 ± 0.1
Glucose (mM)	8.2 ± 0.2	7.8 ± 0.4	7.6 ± 0.3
Plasma clearance rate ($ml \cdot h^{-1} \cdot 100\ g^{-1}$ body wt)			
T_4	0.69 ± 0.06	0.75 ± 0.03	0.55 ± 0.03†
T_3	22.5 ± 1.2	16.8 ± 0.8‡	16.2 ± 1.0‡
Production rate of T_4 ($pmol \cdot h^{-1} \cdot 100\ g^{-1}$ body wt)	37.6 ± 1.8	30.9 ± 2.0§	19.0 ± 2.4*†
Plasma appearance rate T3 ($pmol \cdot h^{-1} \cdot 100\ g^{-1}$ body wt)	15.7 ± 0.9	11.9 ± 0.9‡	11.4 ± 0.9‡
Thyroid production T_3 ($pmol \cdot h^{-1} \cdot 100\ g^{-1}$ body wt)	5.3 ± 0.8	4.4 ± 0.8	6.3 ± 0.7
Peripheral production of T_3 from T_4 ($pmol \cdot h^{-1} \cdot 100\ g^{-1}$ body wt)	10.5 ± 0.6	7.5 ± 0.5*	5.1 ± 0.5*‖

Values are means ± SE n = 6 rats/group. T_4, thyroxine; T_3, triiodothyronine; rT_3, reverse triiodothyronine; TSH, thyrotropin. Plasma T_3, T_4, rT_3, and TSH levels were measured by radioimmunoassay.
*$P < 0.001$, ‡$P < 0.05$, §$P < 0.005$, MF1 and MF2 vs. control.
†$P < 0.005$, ‖$P < 0.05$, MF1 vs. MF2.

tissues decreased drastically during DM but less in DMI rats. During DM, the percentage of locally converted T_3 in DM rats was enhanced in brain (control 58 ± 2, DM 71 ± 4) and cerebellum (control 49 ± 2, DM 61 ± 4); however, the percentage of locally converted T_3 was depressed in DM and DMI rat liver (control 34 ± 2, DM 11 ± 3, DMI 9 ± 2). Plasma-derived T_3 decreased significantly in all DM and DMI rat tissues, except in the pituitary. The tissue-plasma gradient for [^{131}I]T_3 was lower in the tissues of DM and DMI rats. However, these values were only significantly different from control values for the liver (control 9.1 ± 0.3, DMI 6.5 ± 0.4, DM 5.1 ± 0.3, $P < 0.05$), kidney (control 12.3 ± 0.6, DM 9.3 ± 0.8, $P < 0.005$), and cerebellum (control 1.6 ± 0.1, DM 1.2 ± 0.1, $P < 0.05$).

The TSH and prolactin contents expressed as amount of hormone per whole gland and per milligram of tissue wet weight were not significantly different. Only the values for GH during DM differed from those for controls (538 ± 65 vs. 286 ± 63 μg/gland; 67.7 ± 5.0 vs. 46.7 ± 4.7 μg/mg pituitary, control vs. DM, respectively).

Normally, rats gain 3–4 g wt/day. MF1 rats did not gain weight, and DMI, DM, and MF2 rats lost weight. When each rat's change in body weight in grams per day is plotted against each rat's PRT_4 for all groups (Tables 1 and 2), there is a striking relationship (Fig. 3). This also applied for the plasma T_4 concentration ($y = 42.7 + 3.4x$; $r = 0.84$). A difference in the relationship was found for $PART_3$ between DMI and DM rats and MF1 and MF2 rats. No relationship between the change in body weight and thyroidal T_3 secretion was found (Fig. 3). Only in DM and DMI rats was there a relationship with the plasma T_3 concentration ($y = 0.591 + 0.026x$, $r = 0.72$).

In tissues too, the changes in T_4 concentration in MF1, MF2, DM, and DMI rats correlated with the change in body weight. The similarity between the regression lines obtained for control, MF1, and MF2 groups and those for control, DMI, and DM groups was striking. For this reason only, the regression lines for the combined groups are given (liver $y = 22.7 + 2.2x$, $r = 0.90$; kidney $y = 14.6 + 0.9x$, $r = 0.75$; brain $y = 1.88 + 0.18x$, $r = 0.78$; heart $y = 3.81 + 0.37x$, $r = 0.87$). Correlations between total tissue T_3 and the change in body weight were found for control, DMI, and DM groups but were different for control, MF1, and MF2 groups in some tissues (kidney, heart, skeletal muscle, and brown adipose tissue). No difference in regression lines was present for liver ($y = 6.6 + 0.7x$, $r = 0.87$), brain ($y = 2.03 + 0.07x$, $r = 0.53$), cerebellum ($y = 2.00 + 0.06x$, $r = 0.53$), and pituitary ($y = 5.2 + 0.01x$). In the liver, in both DMI and DM and MF1 and MF2 groups, the amounts of locally produced T_3 from T_4 and plasma-derived T_3 correlated with changes in body weight.

DISCUSSION

Diabetes mellitus and modified fasting are both associated with a deficiency of thyroid hormones. Whether this is caused by changes in peripheral production and/or thyroidal production is not clearly understood. Earlier studies indicated that diabetes mellitus affects the thyroid gland by causing a decrease in iodide uptake and the formation and alterations in the distribution of iodoamino acids in the gland (3,22). Our study shows a clear decrease in thyroid hormone production by the thyroid during both diabetes mellitus and modified fasting. This decrease is due mainly to the marked decrease in T_4 production; T_3 secretion is only slightly reduced. Calcu-

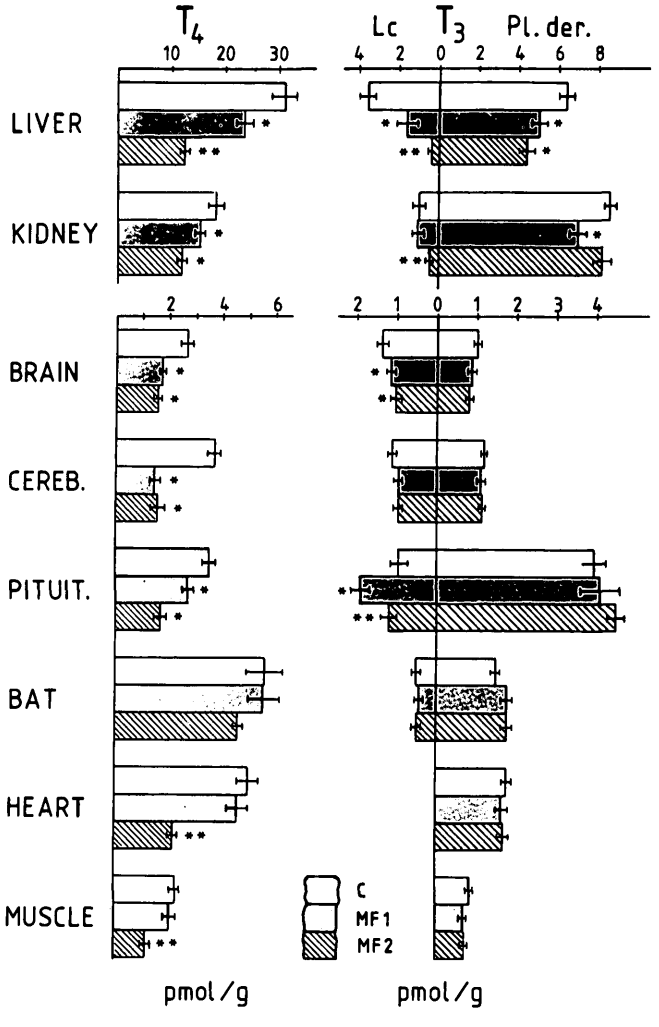

FIG. 1. Influence of modified fasting on tissue concentrations of thyroxine (T_4) and triiodothyronine (T_3). The latter consists of T_3 locally produced from T_4 (LcT_3) and T_3 derived from plasma (Pl.der.). BAT, brown adipose tissue; C, controls; MF1, rats receiving 70% of daily food intake; MF2, rats receiving 30% of daily food intake. Values are means ± SE (n = 6 rats/group). * $P < 0.05$ vs. control. ** $P < 0.05$ vs. control and MF1.

lation of the ratio of secreted T_3 to T_4 shows a change from 0.16 to 0.29. This increase together with the effects on iodine metabolism shown by Pericas and Jolin (22), suggests that, during diabetes mellitus, the changes in thyroidal thyroid hormone production are due to a decreased iodide uptake that leads to intracellular iodine deficiency. Because this is also seen during modified fasting, we attribute this phenomenon during diabetes mellitus to an intracellular energy shortage.

Despite a significant reduction in T_4 concentrations in the pituitary, intrapituitary TSH concentrations did not change. We attribute this to the unchanged total T_3 values. The increased amount of locally converted T_3 from T_4, also seen in the enhanced T_3-T_4 ratio, can cause the normal or even decreased TSH levels. Plasma TSH was decreased in DM and DMI rats but not during modified fasting. This lack of reaction to the lower plasma thyroid hormone levels could also be attributed to a decreased TSH secretion due to an inhibition of TSH-releasing hormone synthesis and/or release (3,7,23,24). The decrease in pituitary GH content can be attributed to a reduced ability to synthesize and release GH and altered hypothalamic-hypophyseal responses of GH-releasing hormone and/or somatostatin secretion (3,25).

Although the calculated regression lines were not always significantly different, the values for total tissue T_3 were always lower in the DM group than in the MF2 group. Because the [^{131}I]T_3 tissue-plasma ratios for most organs were also lower during DM, we concluded that the uptake of T_3 from plasma was affected. Treatment with insulin (DMI) led to higher values, indicating that this phenomenon is insulin dependent and tissue specific. A similar insulin sensitivity has been demonstrated in vitro for T_3 uptake but not for T_4 in rat skeletal muscle (26).

Diabetes mellitus and modified fasting markedly affect the liver in a strikingly similar fashion, indicating that T_4 and T_3 metabolism in the liver is energy dependent and not specifically insulin dependent. In both situations, local conversion of T_3 from T_4 decreased, as found in other studies (6,8,17), comparable to a tissue hypothy-

TABLE 2
Effects of diabetes on plasma T_3, T_4, rT_3, TSH, and glucose levels; plasma clearance rates for T_3 and T_4; production rates for T_4; plasma appearance rate for T_3; and T_3 production by the thyroid and peripheral conversion

	Control	Insulin-treated diabetic	Diabetic
T_4 (nM)	56 ± 6	36 ± 4*	22 ± 6*
T_3 (nM)	0.70 ± 0.02	0.50 ± 0.05†	0.50 ± 0.07†
rT_3 (nM)	0.13 ± 0.01	0.14 ± 0.01	0.37 ± 0.10†‡
TSH (ng/ml)	1.1 ± 0.3	0.6 ± 0.2	0.0 ± 0.1*
Glucose (mM)	8.0 ± 0.2	19.7 ± 3.4†	29.5 ± 1.6‡§
Plasma clearance rate (ml · h^{-1} · 100 g^{-1} body wt)			
T_4	0.59 ± 0.02	0.71 ± 0.03	0.98 ± 0.13†
T_3	22.3 ± 1.2	19.9 ± 0.4†	14.8 ± 1.4*‖
Production rate of T_4 (pmol · h^{-1} · 100 g^{-1} body wt)	32.7 ± 1.8	25.1 ± 2.4*	19.0 ± 2.8*
Plasma appearance rate T_3 (pmol · h^{-1} · 100 g body wt^{-1})	15.8 ± 0.7	9.9 ± 1.0*	7.0 ± 0.6‡§
Thyroid production of T_3 (pmol · h^{-1} · 100 g body wt^{-1})	6.0 ± 0.8	5.1 ± 0.8	4.7 ± 0.7
Peripheral production of T_3 from T_4 (pmol · h^{-1} · 100 g body wt^{-1})	8.9 ± 0.6	4.8 ± 0.4§	2.3 ± 0.4§‖

Values are means ± SE for n = 6 rats/group. T_4, thyroxine; T_3, triiodothyronine; rT_3, reverse triiodothyronine; TSH, thyrotropin. Rats were made diabetic with streptozocin. Plasma T_3, T_4, rT_3, and TSH were measured with radioimmunoassay.
*$P < 0.005$, †$P < 0.05$, §$P < 0.001$, insulin-treated diabetic and diabetic vs. control.
‡$P < 0.05$, ‖$P < 0.005$, diabetic vs. insulin-treated diabetic.

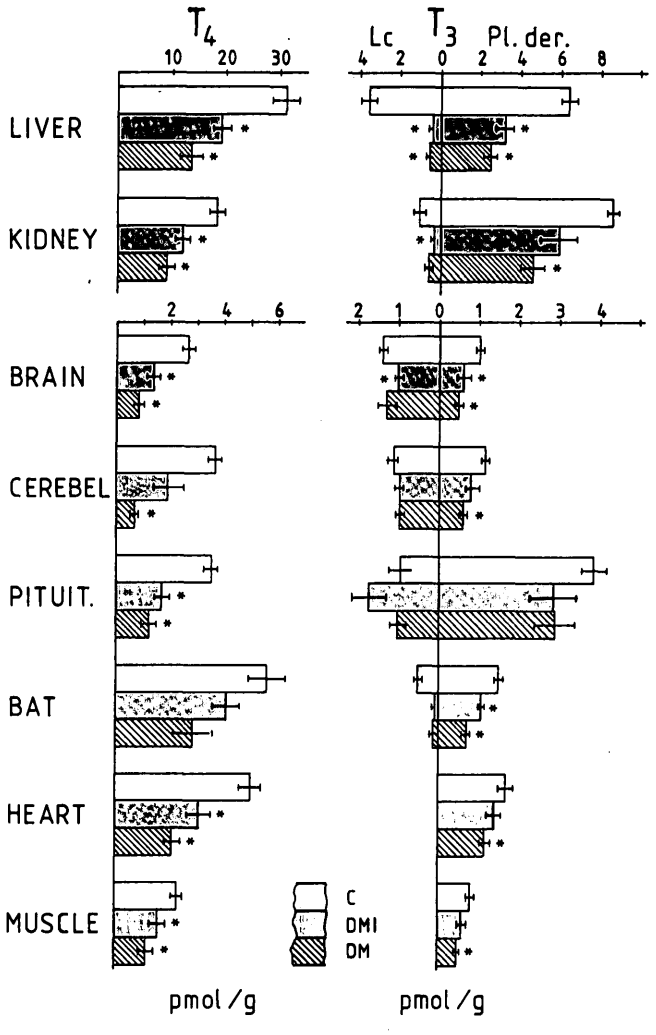

FIG. 2. Influence of diabetes mellitus on tissue concentrations of thyroxine (T_4) and triiodothyronine (T_3). The latter consists of T_3 locally produced from T_4 (LcT_3) and T_3 derived from plasma (pl.der). BAT, brown adipose tissue; C, controls; DMI, diabetic plus insulin rats; DM, diabetic rats. Values are means ± SE (n = 6 rats/group). $P < 0.05$ vs. control. ** $P < 0.05$ vs. control and DMI.

roid state (17). This, together with the lowered uptake of T_3 from plasma, resulted in a lower total T_3 concentration in the liver. Studies of hepatocytes revealed that T_3 transport is an energy-dependent process (27); food, especially glucose, seems to restore this phenomenon, as indicated by the results for MF1 and DMI rats in this study. This is in accordance with an in vitro study by Gavin et al. (11) who showed that T_3 neogenesis was reduced in hepatocytes from rats that had fasted for 48 h, and that both insulin and glucose reversed the process.

Untreated diabetes lowers T_4 and T_3 concentrations in all tissues. This is accompanied by shifts in local conversions in the brain, cerebellum, and liver that closely resemble those found during hypothyroidism (17). From these findings, we conclude that untreated diabetes mellitus causes tissue hypothyroidism. However, this can be validated only by measuring relevant biological end points in the different tissues because an essential step between the intracellular and nuclear T_3 concentrations and biological end points is the number of T_3 receptors and occupancy. We found three different responses of tissue T_3 in relation to changes in body weight: *1*) discrepancy between diabetes mellitus and modified fasting (kidney, muscle, heart, and brown adipose tissue), *2*) no difference between diabetes and fasting and with only a slight or no decrease in T_3 (brain, cerebellum, pituitary), and *3*) no difference between diabetes and fasting and a strong decrease in tissue T_3 (liver). We attribute these different responses to insulin sensitivity and energy dependency. It may be that the effect of the first group is mainly caused by insulin sensitivity, the effect of the second group by insulin insensitivity and/or slight energy dependency, whereas the effect in the liver would be mainly energy dependency. We speculate that the regulatory variations in glucose transport (GLUT4) follow the intracellular T_3 concentrations that we found in the relevant tissues, which means that this regulation

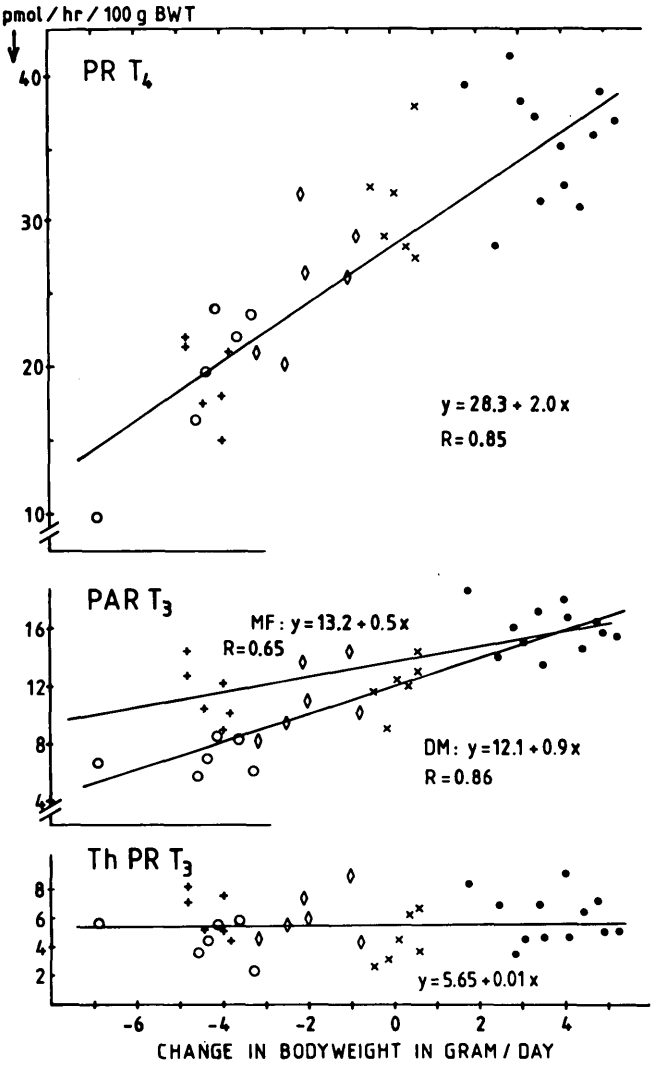

FIG. 3. Individual production rate for thyroxine (T_4) (PRT_4), plasma appearance rate for triiodothyronine (T_3) ($PART_3$), and thyroidal T_3 production ($ThPRT_3$) in diabetes mellitus (DM) and modified fasting (MF) are plotted against individual change in body weight. Regression lines for PRT_4 and $ThPRT_3$ did not differ during MF and DM, thus 1 line was drawn. Two regression lines were drawn for $PART_3$. ●, control rats; ×, MF group 1 (70% daily food intake); ◇, insulin-treated DM; +, MF group 2 (30% daily food intake); ○, DM rats.

occurs due to the tissue T_3 level rather than the plasma T_3 concentration.

In conclusion, diabetes mellitus affects the thyroid hormone economy by interfering with thyroidal and peripheral production, leading to a tissue hypothyroid state. The changes in T_4 production and tissue T_4 concentration, similar to those seen during modified fasting, are due to the same phenomenon: intracellular energy shortage. Note that these changes correlated with the changes in body weight. In contrast, the changes in T_3 production, total tissue T_3 being present in diabetes mellitus and often absent in modified fasting, seem to be insulin dependent and tissue specific.

ACKNOWLEDGMENTS

We thank Chris van der Bent for excellent technical assistance, P.J. Vink and H. Lelieveld for mechanical maintenance of the continuous infusion setup, and Dr. J. Hermans for advice on statistical analysis. Reagents used for the rat TSH, GH, and prolactin assays were kindly provided by the Rat Pituitary Hormone Distribution Program (National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health).

Part of this study was presented at the 18th Annual Meeting of the European Thyroid Association (Copenhagen) 26–30 June 1989, and at the 10th International Thyroid Conference (The Hague, Netherlands) 4–8 February 1991.

REFERENCES

1. Wartofsky L, Burman KD: Alterations in thyroid function in patients with systemic illness: "the euthyroid sick syndrome." *Endocr Rev* 3:164–217, 1982
2. Pittman CS, Suda AK, Chambers JB, McDaniel HG, Ray GY, Preston BK: Abnormalities of thyroid hormone turnover in patients with diabetes mellitus before and after insulin therapy. *J Clin Endocrinol Metab* 48:854–60, 1979
3. Jolin T, Gonzalez C: Thyroid iodine metabolism in streptozotocin-diabetic rats. *Acta Endocrinol* 88:506–16, 1978
4. Ortiz-Caro J, Gonzalez C, Jolin T: Diurnal variations of plasma growth hormone, thyrotropin, thyroxine, and triiodothyronine in streptozotocin-diabetic and food-restricted rats. *Endocrinology* 115:2227–32, 1984
5. Balsam A, Ingbar SH: The influence of fasting, diabetes and several pharmacological agents on the pathways of thyroxine metabolism in rat liver. *J Clin Invest* 62:415–24, 1978
6. Gavin LA, McMahon FA, Moeller M: The mechanism of impaired T_3 production from T_4 in diabetics. *Diabetes* 30:694–99, 1981
7. Pastor MR, Jolin T: Peripheral metabolism and secretion rate of thyrotropin in streptozotocin-diabetic rats. *Endocrinology* 112: 1454–59, 1983
8. Jennings AS: Regulation of hepatic triiodothyronine production in the streptozotocin-induced diabetic rat. *Am J Physiol* 247:E526–33, 1984
9. Ferguson DC, Hoenig M, Jennings AS: Triiodothyronine production by the perfused rat kidney is reduced by diabetes mellitus but not by fasting. *Endocrinology* 117:64–70, 1985
10. Gavin LA, Cavalieri RR: Iodothyronine deiodination in the brain of diabetic rats: influence of thyroid status. *J Endocrinol Invest* 9:127–33, 1986
11. Gavin LA, Cavalieri RR, Moeller M: Glucose and insulin reverse the effects of fasting on 3,5,3′-triiodothyronine neogenesis in primary cultures of rat hepatocytes. *Endocrinology* 122:858–64, 1987
12. Weinstein SP, Watts J, Haber RS: Thyroid hormone increases muscle/fat glucose transporter gene expression in rat skeletal muscle. *Endocrinology* 129:455–64, 1991
13. Weinstein SP, Watts J, Graves PN, Haber RS: Stimulation of glucose transport by thyroid hormone in ARL 15 cells: increased abundance of glucose transporter protein and messenger ribonucleic acid. *Endocrinology* 126:1421–29, 1990
14. Höppner W, Kausch C, Matthaei S: Effect of thyroid hormone on glucose transporter systems (Glut-1 and Glut-4) in isolated rat adipocytes (Abstract). *Ann Endocrinol* 52:35, 1991
15. Schröder-van der Elst JP, van der Heide D: Effects of 5,5′-diphenylhydantoin on thyroxine and 3,5,3′-triiodothyronine concentrations in several tissues of the rat. *Endocrinology* 126:186–91, 1990
16. Schröder-van der Elst JP, van der Heide D: T4, T3 and rT3 concentrations in several tissues of the rat: effects of amiodarone and desethylamiodarone on thyroid hormone metabolism. *Endocrinology* 127:1656–64, 1990
17. Van Doorn J, van der Heide D, Roelfsema F: Sources and quantity of 3,5,3′-triiodothyronine in several tissues of the rat. *J Clin Invest* 72:1778–92, 1983
18. Van Doorn J, van der Heide D, Roelfsema F: The influence of partial food deprivation on the quantity and source of triiodothyronine in several tissues of athyreotic thyroxine-maintained rats. *Endocrinology* 115:705–11, 1984
19. Van Doorn J, van der Heide D, Roelfsema F: The contribution of local thyroxine monodeiodination to intracellular 3,5,3′-triiodothyronine in several tissues of hyperthyroid rats at isotopic equilibrium. *Endocrinology* 115:174–82, 1984
20. Ad hoc Committee on Standards for Nutritional Studies: Report of the American Institute of Nutrition. *J Nutr* 7:1340–48, 1977
21. Roelfsema F, van der Heide D, Smeenk D: Circadian rhythms of urinary electrolyte excretion in freely moving rats. *Life Sci* 27:2303–309, 1980
22. Pericas I, Jolin T: The effect of streptozotocin-induced diabetes on the pituitary-thyroid axis in goitrogen-treated rats. *Acta Endocrinol* 86:128–37, 1977
23. Gonzalez C, Montoya E, Jolin T: Effect of streptozotocin diabetes on the hypothalamic-pituitary-thyroid axis in the rat. *Endocrinology* 107:2099–103, 1980
24. O'Brian JT, Bybee DE, Burman KD, Osburne RC, Melba RK, Wartofsky L, Georges LP: Thyroid homeostasis in states of relative caloric deprivation. *Metabolism* 29:721–26, 1980
25. Olchovsky D, Bruno JF, Wood TL, Gelato MC, Leidy JW Jr, Gilbert JM Jr, Berelowitz M: Altered pituitary growth hormone (GH) regulation in streptozotocin-diabetic rats: a combined defect of hypothalamic somatostatin and GH-releasing factor. *Endocrinology* 126:53–61, 1990
26. Centanni M, Pontecorvi A, Robbins J: Insulin effect on thyroid hormone uptake in rat skeletal muscle. *Metabolism* 37:626–30, 1988
27. Krenning EP, Docter R, Bernard HF, Visser TJ, Hennemann G: Decreased transport of thyroxine (T4), 3,3′,5-triiodothyronine (T3) and 3,3′,5′-triiodothyronine (rT3) into rat hepatocytes in primary culture due to a decrease of cellular ATP content and various drugs. *FEBS Lett* 140:229–33, 1982