REDUCED NUCLEAR TRIIODOTHYRONINE RECEPTORS IN STARVATION-INDUCED HYPOTHYROIDISM*

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SUMMARY

Starvation of male rats during 48 hours causes a marked reduction of serum thyroxine, serum triiodothyronine, and liver nuclear triiodothyronine content. Liver nuclear receptors capacity for binding of triiodothyronine was reduced, in contrast to thyro-previc hypothyroidism in which binding capacity is normal. DNA-dependent RNA polymerase activities were reduced. In contrast to typical hypothyroidism, serum thyrotropin was low. This form of pituitary non-responsive hypothyroidism may represent a selective response to caloric and/or amino acid deprivation.

INTRODUCTION

Acute starvation is known to reduce serum T_3 in man and rats (1 - 3). This effect is explained at least in part by a reduction in peripheral conversion of thyroxine (T_4) to 3, 5, 3'-triiodothyronine (T_3), and possibly increased formation of 3, 3', 5'-triiodothyronine (reverse T_3) (3). Alteration in serum hormone levels may modulate cell receptor capacity. For example, reduction of serum insulin levels induced by starvation of obese individuals leads to increased membrane insulin receptor capacity (4). High serum prolactin levels lead to augmented prolactin receptor capacity (5). It thus becomes of interest to determine whether starvation induced reduction of serum T_3 is associated with altered nuclear T_3 receptor capacity.

To date little is known about the physiology of nuclear T_3 receptors. We have shown that T_3 binding capacity is not altered by hypothyroidism or

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T_3 BINDING CAPACITY AND T_3 LEVELS

Expt.	Hours of Fasting	T_3 Binding Capacity x 10^{-15}M/100 ug DNA		T_3	
		Nuclei	Total	Serum ng/ml	Liver Nuclei ng/g Tissue Equivalent
A	0	20.2 ± 2.1	63.1 ± 11	-	-
	12	15.8 ± 2.3	51.9 ± 2.7	-	-
	24	14.8 ± 1.0 *	52.4 ± 3.1	-	-
	48	16.5 ± 1.3 *	50.1 ± 2.4 *	-	-
B	0	59.7	-	-	-
	14	41	-	-	-
	20	42.1	-	-	-
C	0	40.4 ± 3.4	54.3 ± 4.1	.79 ± .03	1.40 ± .43
	12	34.5 ± 9.8	46.4 ± 9.4	.69 ± .03 *	.84 ± .05
	24	38.8 ±12	55.9 ± 11	.64 ± .11 *	.77 ± .14 *
	48	24.1 ± 8.1 *	38.4 ± 10.2 *	.51 ± .10 *	.78 ± .23 *
D	0	46.2 ±10.3	60.1 ± 3.5	.65 ± .16	1.15 ± .54
	24	25.8 ± 2.3 *	52 ± 2.9 *	.51 ± .14	.61 ± .12
	48	24 ± 2.7 *	50.8 ± 6.1	.40 ± .11	.45 ± .24

Four experiments are presented. Data are means ± standard deviations.

In Experiment A, n = 3 in each group, and all assays were done on individual animals in triplicate.

In Experiment B, three livers were pooled for each group. Assays were done on each pool in triplicate.

In Experiment C, n = 6 in each group, and all assays were done on individual animals in triplicate.

In Experiment D, n = 3 with each group consisting of a pool of two livers. All pools were individually assayed in triplicate.

* Different from 0 hour control with $P < .05$.

TABLE 2

DNA DEPENDENT RNA POLYMERASE ACTIVITY: FRACTION CTP BOUND/mg DNA

Hours of Fasting	Total Polymerase	Polymerase I
Experiment B:		
0	.186 ± .001	.038 ± .002
14	.118 ± .003 *	.025 ± .003 *
20	.115 ± .001 *	.019 ± .002 *
Experiment C:		
0	.14 ± .02	.021 ± .005
12	.12 ± .02	.013 ± .001 *
24	.09 ± .01 *	.010 ± .001 *
48	.09 ± .01 *	.010 ± .001 *

* Different from 0 hour control with $P < .05$.

Experiments are as described in Table 1.

acute exposure to exogenous T_3 (6). We have reported low nuclear binding capacity in neonatal male rats; capacity rises to adult levels by age 30 - 50 days (7). Estrogen, glucocorticoids, and testosterone had no effect on T_3 binding capacity (7).

METHODS

Male Charles River Farm rats of 150 - 220 g body weight were studied while having Purina rat chow continuously available, or while fasted for 12 - 48 hours. Animals were housed on screen floor cages, and were given tap water ad lib.

At the desired interval animals were sacrificed by stunning or by exsanguination through cardiac puncture under light ether anesthesia. Serum was analyzed for T_3 (8), T_4 (9), TSH (10), and total serum proteins. T_3 binding capacity of liver nuclei, binding affinity of receptors for T_3, nuclear $^3T_3$ content, and liver nuclear DNA-dependent RNA polymerase (total and Polymerase I) were determined as previously described (11, 12).

Protein was assayed by the method of Lowry et al. (13) and DNA by the method of Munro and Fleck (14). Statistical comparisons were made using a Student "t" test for unpaired data. Means, standard deviations, and statistical significance are given in all tables.

TABLE 3

HORMONE AND PROTEIN LEVELS

Hours of Fasting	SERUM T_4 (μg/100 ml)	SERUM Total Protein (g/100 ml)	SERUM TSH (ng/ml)	Pituitary TSH μg/gland
0	4.0 ± 0.8	6.1 ± 0.3	80 ± 47	1155 ± 75
24	3.7 ± 0.5	5.9 ± 0.2	27 ± 16 **	1116 ± 56
48	2.8 ± 0.6 *	5.8 ± 0.6	< 20 **	961 ± 64

* $P < 0.05$

** $P < 0.005$

Data are from Experiment D

RESULTS

T_3 Receptor Capacity (Table 1) --

In four separate experiments, starvation was associated with reduction in mean binding capacity. The mean level was reduced by 12 - 14 hours (but not statistically significant) in three studies in which observations were made at this time period. After 48 hours T_3 binding capacity in nuclei was reduced by 18 - 48%, and the reduction was statistically significant in all experiments. The reduction occurred both in the receptors present in the nuclei at the end of *in vitro* incubation and in total receptor capacity, including receptor released to the incubation medium during the *in vitro* assay. (Indicated in Table 1 as "total" receptor.)

Nuclear Polymerase Activity (Table 2) --

Both total polymerase and Polymerase I activity diminished after 12 hours of starvation and were significantly reduced by 35% (total) and 52% (Polymerase I) after 48 hours.

Liver and Serum Hormone Levels (Tables 1, 3) --

T_3 content of liver nuclei fell within 12 hours and was depressed by

45 - 61% at 48 hours. Serum T_3 was likewise lower at 12 hours, reaching a depression of 49 - 60% by 48 hours. The decrease in liver T_3 exceeded the decrease in serum T_3, and both exceeded the decrease in T_3 receptor capacity.

Serum T_4 and TSH dropped dramatically during 48 hours of starvation. T_4 declined by 31% and TSH more than 75% at 48 hours. Serum proteins were not altered.

DISCUSSION

Our studies confirm the previously reported depression in serum T_3 with starvation in man and in the rat, and depression of serum T_4 observed during fasting in rats (2). We show that this is associated with a significant lowering of nuclear T_3 content and nuclear T_3 receptor capacity. Nuclear DNA dependent RNA of polymerase activity is also sharply reduced. In striking contrast to the usual response in hypothyroidism, serum TSH is reduced rather than elevated.

Physiologic primacy among these variables remains to be determined. Animals lost 16 to 20% of body weight during a 48 hour fast, but serum proteins were minimally altered. Serum TSH fell despite the presence of considerable TSH reserves in the pituitary (Table 3). T_4 fell much faster than could be explained by a cessation of intrathyroidal hormone synthesis. Most likely, then, the changes observed represent a selective physiologic response to acute caloric and amino acid deficiency.

The decrease in T_3 receptors probably represents an independent effect of starvation, rather than a response to lowering of serum T_3, since the T_3 receptors capacity is normal in hypothyroid animals, despite even lower serum T_4 and T_3 levels. DNA dependent RNA polymerase is reduced in hypothyroid animals (12). While it is obviously of great interest that receptor content and polymerase function both decline, our data do not prove a cause and effect relationship between these parameters during starvation.

A tenable hypothesis is that the changes observed represent a group of selective physiologic responses designed to induce a state of "pituitary non-

responsive hypothyroidism" and to protect tissues from the catabolic effects of T_3 and T_4 during acute caloric and amino acid deficiency. While this is a teleologic hypothesis, it is possible to directly test the possible value of this form of hypothyroidism in the fasting animal.

Extension of this hypothesis to man may be logical, and may be related to the diminished caloric expenditures observed during human fasting.

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