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COMPARATIVE EFFECTS OF 3,5-DIMETHYL-3′-ISOPROPYL-L-THYRONINE (DIMIT) AND 3,5-DIIODO-3′-ISOPROPYLTHYROACETIC ACID ($IpTA_2$) ON BODY WEIGHT GAIN AND LIPID METABOLISM IN GENETICALLY OBESE ZUCKER RATS

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Abstract—3,5-Dimethyl-3′-isopropyl-L-thyronine (DIMIT) and 3,5-diiodo-3′-isopropylthyroacetic acid ($IpTA_2$), two thyroid hormone analogs, have been tested in genetically obese Zucker rats and their lean littermates, in comparison with thyroxine (T_4) and triiodothyronine (T_3) for their thyromimetic activities on body weight gain and lipid levels in serum and liver. The compounds were administered for 9 weeks by orogastric tube to 6- to 8-week-old animals. While body weight gain remained practically unchanged in the lean rats, it decreased significantly in the obese individuals, especially with $IpTA_2$. The serum lipid concentrations were also decreased in the obese rats in comparison with their lean littermates, especially with DIMIT. The connection observed between the structure of DIMIT and $IpTA_2$ on one hand and their effects on the other is in good agreement with previous studies. Our results confirm that the iodine substituents are not necessary for thyromimetic activity and demonstrate that the isopropyl substituent in 3′ plays an important role in the serum lipid-lowering effect of the thyroid hormone analogs tested.

Genetically obese Zucker rats are characterized by hyperphagia, increased efficiency in assimilating food, hypertriglyceridemia and excessive lipid deposition [1–4]. Other metabolic abnormalities are hyperinsulinemia [5, 6] and reduced levels of plasma glucagon [7].

The endocrine changes in genetically obese rats include hypothyroidism. The protein-bound iodine (PBI), the uptake of radioactive iodine and the circulating thyroid hormones are decreased [8, 9]. The radioactive thyroxine (T_4) half-time, the peripheral synthesis of 3,5,3′-triiodo-L-thyronine (T_3) from T_4 deiodination and the activity of phosphorylative oxidation in mitochondria are also decreased in obese rats in comparison with lean rats [10].

Engelken and Eaton [11] found that administration of T_4 to obese rats induces a decrease in body weight gain and a concomitant reduction in plasma cholesterol concentration. Levin *et al.* [12] reported that addition of thyroid powder to the food of obese rats causes a decrease in the tissue lipid levels. It has been demonstrated that treatment with 3,5,3′-triiodothyroacetic acid (TRIAC), a metabolite of T_3, does not significantly affect the serum lipid levels in obese rats although it decreases their body weight gain [9].

Among the thyroid hormone analogs, 3,5-dimethyl-3′-isopropyl-L-thyronine (DIMIT) was found to be the most potent nonhalogenated thyromimetic compound [13–19]. 3,5-Diiodo-3′-isopropylthyroacetic ($IpTA_2$) is another thyroid analog [13, 20] which has been less studied than DIMIT so far, and little is known about its biological effects.

The purpose of the present investigation is to compare the effects of DIMIT and $IpTA_2$ with those of T_4 and T_3 on the lipid metabolism in genetically obese Zucker rats. Thus, we examined their influences on body weight gain and serum or hepatic lipid concentration. In order to gather information on the mechanisms by which the thyromimetic compounds act, the present study also considers the mitochondrial oxidation of acylcarnitines in obese and lean rats. In a preliminary study, it was found that the mitochondrial oxidation of acylcarnitines is decreased in thyroidectomized rats and that T_3 administration restores it [21]. These data suggest that the abnormal lipid metabolism in obese Zucker rats may be related to a hypothyroidal-induced decrease in the mitochondrial oxidation of fatty acids. Therefore, the study was focused on the metabolism of acylcarnitines in isolated hepatic mitochondria of genetically obese and lean Zucker rats.

MATERIALS AND METHODS

Genetically obese female rats (fa/fa), 6–8 weeks old, and their lean littermates (Fa/–) were purchased

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from C.S.E.A.L.-C.N.R.S. (Orléans, France). The animals were housed individually and allowed free access to food (powdered chow, UAR, France) and water.

T_4 and T_3 were purchased from Sigma Chemical Co. (St Louis, MO). DIMIT and $IpTA_2$ were prepared, and their purity verified as described by Jorgensen *et al.* [13] and Bolgert and Jorgensen [22].

Doses of T_4, T_3, DIMIT and $IpTA_2$ were selected according to their thyromimetic activities [20, 23]. The daily doses, in nmoles/100 g BW, were 13.00 for T_4, 1.50 and 4.50 for T_3, 32.00 for DIMIT, 16.25 and 32.50 for $IpTA_2$, corresponding to 10.00, 1.00, 3.00, 11.00, 8.75 and 17.50 μg/100 g, respectively. The compounds were solubilized with 0.2 N NaOH in 0.9% NaCl (pH 8.5) and administered by orogastric tube to the rats for 3 weeks. The controls were given vehicle. Body weight gain and food intake were determined daily throughout the experimental period.

The animals were killed by carotid section 24 hr after the last dose of drug. The blood was collected and the serum separated. The livers were removed immediately after bleeding and stored at −40° for the subsequent assays. The total lipids were measured in the serum by a colorimetric method as described by Zöllner and Kirsch [24]. The total cholesterol was determined by the Lieberman–Burchard reaction after extraction with 5 ml of dimethoxymethane-methanol (4:1, v/v). The triglycerides were assayed by an enzymatic method using glycerokinase and lacticodehydrogenase (test combination triglycerides, Boehringer Mannheim GmbH Diagnostica) according to Kreutz [25]. The phospholipids were measured colorimetrically according to Zilversmit and Davis [26]. The free fatty acids (FFA) were assayed by a colorimetric method as described by Duncombe [27] (test combination FFA, Boehringer Mannheim GmbH Diagnostica). Each liver was weighed and the lipids extracted by the Bach *et al.* method [4]. The total lipids, cholesterol, triglycerides and phospholipids were assayed in the extract by the same methods as those described for the serum.

Liver mitochondria were isolated according to Beattie [28]. The protein concentrations were determined by a method based on the biuret reaction [29]. The purity of the mitochondrial suspensions was determined by quantifying the specific marker enzymes [30]. Measurements of mitochondrial respiration and phosphorylative oxidation were carried out at 25° in a GME oxygraph equipped with a vibrating platinum electrode according to Chance and Williams [31]. The mitochondrial suspension (2 mg proteins) was added to 1.6 ml of buffer prepared as follows: 12 mM NaF, 13 mM K_2HPO_4, 3 mM KH_2PO_4, 6 mM $MgCl_2$, 56 mM KCl and 26 mM NaCl (pH 7.4). Acylcarnitines (32 μM) with fatty acids from C8 to C18 were used as substrates. They were prepared by Dr. Deltour (State University of Liège, Belgium) according to Ziegler *et al.* [32] and kindly given to us. The oxygen consumption rates, in nmoles $O_2 \cdot min^{-1} \cdot mg^{-1}$ protein, were recorded in the presence of 150 μM ADP (state 3) and after its depletion (state 4).

RESULTS

The effects, expressed as body weight gain, of the thyromimetic compounds on the obese rats and their lean littermates are reported in Fig. 1. In the lean

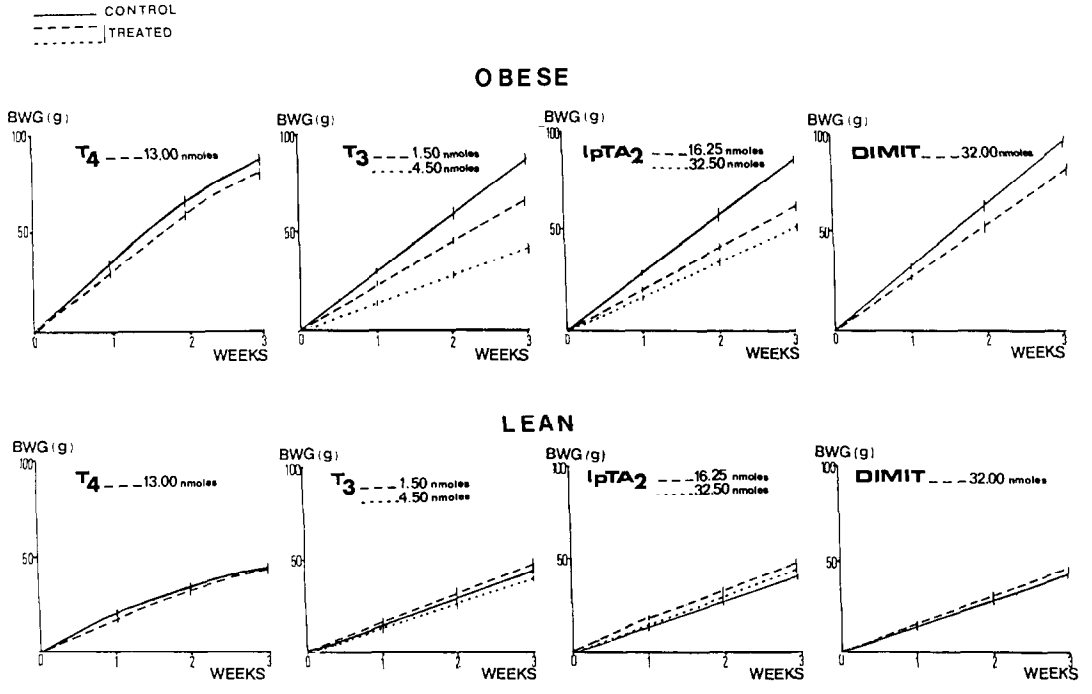

Fig. 1. Effects of T_4, T_3, $IpTA_2$ and DIMIT on the body weight gain (BWG) in genetically obese and lean Zucker rats. Cf. Methods for experimental conditions.

Table 1. Effects of T_4, T_3, $IpTA_2$ and DIMIT on the serum lipid levels in lean (Fa/–) Zucker rats

Compound (nmoles)	Treatment	TL (g/l)	CH (g/l)	TG (g/l)	PL (g/l)	FFA (mM)
T_4	Control	2.77 ± 0.38 (8)	0.94 ± 0.12 (8)	0.41 ± 0.10 (8)	1.26 ± 0.12 (8)	1.03 ± 0.19 (8)
(13.00)	Treated	3.04 ± 0.35 (8)	1.06 ± 0.14 (8)	0.40 ± 0.05 (8)	1.56 ± 0.12 (8)	1.10 ± 0.12 (8)
T_3	Control	3.88 ± 0.22 (8)	1.07 ± 0.13 (8)	0.31 ± 0.13 (8)	1.63 ± 0.15 (8)	1.17 ± 0.05 (8)
(1.50)	Treated	3.69 ± 0.17 (7)	1.06 ± 0.07 (7)	0.38 ± 0.02 (7)	1.42 ± 0.14 (7)	1.06 ± 0.04 (7)
T_3	Control	3.22 ± 0.25 (5)	0.96 ± 0.13 (5)	0.38 ± 0.03 (5)	1.42 ± 0.14 (5)	1.02 ± 0.04 (5)
(4.50)	Treated	2.11 ± 0.05 (6)‡	0.66 ± 0.05 (6)*	0.34 ± 0.03 (6)	1.16 ± 0.05 (6)	0.98 ± 0.10 (6)
$IpTA_2$	Control	3.88 ± 0.22 (8)	1.07 ± 0.13 (8)	0.31 ± 0.03 (8)	1.63 ± 0.15 (8)	1.17 ± 0.05 (8)
(16.25)	Treated	4.03 ± 0.37 (8)	1.07 ± 0.11 (8)	0.31 ± 0.02 (8)	1.68 ± 0.10 (8)	1.31 ± 0.05 (8)
$IpTA_2$	Control	2.77 ± 0.38 (8)	0.94 ± 0.12 (8)	0.41 ± 0.10 (8)	1.26 ± 0.13 (8)	1.03 ± 0.19 (8)
(32.50)	Treated	2.61 ± 0.12 (8)	0.80 ± 0.08 (8)	0.46 ± 0.05 (8)	1.18 ± 0.09 (8)	1.06 ± 0.11 (8)
DIMIT	Control	3.22 ± 0.25 (5)	0.96 ± 0.13 (5)	0.38 ± 0.03 (5)	1.42 ± 0.14 (5)	1.02 ± 0.04 (5)
(32.00)	Treated	2.32 ± 0.06 (6)†	0.66 ± 0.03 (6)*	0.30 ± 0.01 (6)*	1.09 ± 0.04 (6)*	1.04 ± 0.06 (6)

TL: total lipids; CH: total cholesterol; TG: triglycerides; PL: phospholipids; FFA: free fatty acids.
Treatments given for 3 weeks, cf. Methods for conditions.
No. of rats in brackets.
Results presented as means ± S.E.M.
Comparison by Student's test with control rats; * < 0.05; † < 0.01; ‡ < 0.001.

animals, all the compounds had practically no effect on the character whereas in the obese rats, except for T_4, they decreased it: 20% ($\alpha < 0.001$) and 50% ($\alpha < 0.001$) with 1.50 and 4.50 nmoles of T_3, respectively, 22% ($\alpha < 0.01$) and 40% ($\alpha < 0.001$) with 16.25 and 32.50 nmoles of $IpTA_2$, respectively and 15% ($\alpha < 0.01$) with 32.00 nmoles of DIMIT. These losses in body weight gain were not associated with any significant decrease in food intake.

The results on the serum lipid levels are reported in Tables 1 and 2. As compared to the lean rats (Table 1), the obese individuals (Table 2) had consistently high levels of lipids; this confirms other results [1–4, 9].

The lean rats were much less sensitive to the different treatments than their obese littermates. Only T_3 and DIMIT affected the serum lipids in the lean rats. The higher dose of T_3 (4.50 nmoles) induced a significant decrease both in the total lipid (34%, $\alpha < 0.001$) and in the cholesterol (30%, $\alpha < 0.05$) levels. DIMIT (32.00 nmoles) also reduced significantly both the total lipid (28%, $\alpha < 0.01$) and the cholesterol (31%, $\alpha < 0.05$) levels. In addition, DIMIT decreased the concentration of the triglycerides (21%, $\alpha < 0.05$) and phospholipids (23%, $\alpha < 0.05$).

In contrast, in the obese rats, all the compounds except for T_4 and the smaller dose of T_3, affected most of the serum lipids. T_3 (4.50 nmoles) reduced the serum concentration of the total lipids (44%, $\alpha < 0.001$), cholesterol (30%, $\alpha < 0.01$), triglycerides (43%, $\alpha < 0.001$) and phospholipids (23%, $\alpha < 0.01$). At 16.25 nmoles, $IpTA_2$ induced a decrease in the cholesterol level (24%, $\alpha < 0.05$) and, at 32.50 nmoles, in the total lipid (20%, $\alpha < 0.05$), cholesterol (17%, $\alpha < 0.05$) and triglycerides (34%, $\alpha < 0.05$) levels. DIMIT (32.00 nmoles) was the most active compound: it

Table 2. Effects of T_4, T_3, $IpTA_2$ and DIMIT on the serum lipid levels in genetically obese (fa/fa) Zucker rats

Compound (nmoles)	Treatment	TL (g/l)	CH (g/l)	TG (g/l)	PL (g/l)	FFA (mM)
T_4	Control	5.95 ± 0.31 (8)	1.42 ± 0.23 (8)	2.10 ± 0.17 (8)	2.12 ± 0.15 (8)	1.76 ± 0.11 (8)
(13.00)	Treated	5.61 ± 0.78 (8)	1.28 ± 0.19 (8)	1.91 ± 0.24 (8)	1.89 ± 0.21 (8)	1.82 ± 0.11 (8)
T_3	Control	6.31 ± 0.23 (7)	1.56 ± 0.21 (7)	1.34 ± 0.08 (7)	1.83 ± 0.12 (7)	2.05 ± 0.08 (7)
(1.50)	Treated	6.14 ± 0.57 (8)	1.33 ± 0.07 (8)	1.64 ± 0.28 (8)	1.66 ± 0.10 (8)	2.12 ± 0.12 (8)
T_3	Control	5.86 ± 0.12 (5)	1.27 ± 0.10 (5)	1.58 ± 0.06 (5)	2.11 ± 0.09 (5)	1.50 ± 0.05 (5)
(4.50)	Treated	3.27 ± 0.12 (6)‡	0.89 ± 0.05 (6)†	0.90 ± 0.11 (6)‡	1.63 ± 0.08 (6)†	1.50 ± 0.07 (6)
$IpTA_2$	Control	6.31 ± 0.23 (7)	1.56 ± 0.21 (7)	1.34 ± 0.08 (7)	1.83 ± 0.12 (7)	2.05 ± 0.08 (7)
(16.25)	Treated	5.62 ± 0.50 (8)	1.18 ± 0.11 (8)*	1.38 ± 0.28 (8)	1.71 ± 0.15 (8)	1.80 ± 0.13 (8)
$IpTA_2$	Control	5.95 ± 0.31 (8)	1.42 ± 0.23 (8)	2.10 ± 0.17 (8)	2.12 ± 0.25 (8)	1.76 ± 0.11 (8)
(32.50)	Treated	4.78 ± 0.48 (8)*	1.18 ± 0.08 (8)*	1.38 ± 0.17 (8)*	1.94 ± 0.17 (8)	1.71 ± 0.14 (8)
DIMIT	Control	5.86 ± 0.12 (5)	1.27 ± 0.10 (5)	1.58 ± 0.06 (5)	2.11 ± 0.09 (5)	1.50 ± 0.05 (5)
(32.00)	Treated	3.59 ± 0.22 (6)‡	0.76 ± 0.05 (6)‡	0.96 ± 0.11 (6)‡	1.95 ± 0.10 (6)	1.35 ± 0.09 (6)

TL: total lipids; CH: total cholesterol; TG: triglycerids; PL: phospholipids; FFA: free fatty acids.
Treatments given for 3 weeks, cf. Methods for conditions.
No. of rats in brackets.
Results presented as means ± S.E.M.
Comparison by Student's *t*-test with control rats; * < 0.05; † < 0.01; ‡ < 0.001

Table 3. Effects of T_4, T_3, $IpTA_2$ and DIMIT on the hepatic lipid levels in lean (Fa/–) Zucker rats

Compound (nmoles)	Treatment	Fa/–			
		TL (mg/g)	CH (mg/g)	TG (mg/g)	PL (mg/g)
T_4	Control	65 ± 7 (8)	4.08 ± 0.16 (8)	7.48 ± 0.95 (8)	39.0 ± 3.1 (8)
(13.00)	Treated	74 ± 9 (8)	3.98 ± 0.12 (8)	7.50 ± 1.16 (8)	43.4 ± 1.4 (8)
T_3	Control	68 ± 1 (8)	4.04 ± 0.07 (8)		30.2 ± 4.5 (8)
(1.50)	Treated	69 ± 2 (7)	4.07 ± 0.08 (7)		37.8 ± 0.5 (7)
T_3	Control	63 ± 3 (5)	4.04 ± 0.12 (5)	8.83 ± 0.64 (5)	36.8 ± 1.6 (5)
(4.50)	Treated	72 ± 4 (6)	3.81 ± 0.04 (6)	8.16 ± 0.67 (6)	40.9 ± 0.8 (6)
$IpTA_2$	Control	68 ± 1 (8)	4.04 ± 0.07 (8)		30.2 ± 4.5 (8)
(16.25)	Treated	67 ± 2 (8)	4.09 ± 0.07 (8)		37.6 ± 0.6 (8)
$IpTA_2$	Control	65 ± 7 (8)	4.08 ± 0.16 (8)	7.48 ± 0.95 (8)	39.0 ± 3.1 (8)
(32.50)	Treated	66 ± 7 (8)	4.15 ± 0.19 (8)	7.01 ± 0.83 (8)	37.4 ± 1.2 (8)
DIMIT	Control	63 ± 3 (5)	4.04 ± 0.12 (5)	8.83 ± 0.64 (5)	35.8 ± 1.6 (5)
(32.00)	Treated	59 ± 7 (6)	3.90 ± 0.06 (6)	7.33 ± 0.64 (6)	40.3 ± 0.7 (6)

TL: total lipids; CH: total cholesterol; TG: triglycerides; PL: phospholipids.
Treatments given for 3 weeks, cf. Methods for conditions.
No. of rats in brackets.
Results presented as means ± S.E.M.

induced a striking reduction in the serum concentration of the total lipids (39%, $\alpha < 0.001$), cholesterol (40%, $\alpha < 0.001$) and triglycerides (39%, $\alpha < 0.001$). The FFA were not significantly affected by the different treatments.

The results on the hepatic concentration of the lipid classes are given in Tables 3 and 4. The levels of the total lipids and triglycerides were higher in the obese rats (Table 4) than in their lean littermates (Table 3), confirming previous observations [4]. In both lean and obese individuals neither of the four compounds significantly affected the hepatic lipids.

The measurements of phosphorylative oxidation in liver mitochondria are reported in Table 5. Whatever the oxidizable substrate, the respiratory rates in states 4 (resting respiration) and 3 (active respiration) were similar in the obese and lean rats.

DISCUSSION

The present results confirm that DIMIT has thyromimetic properties since, like T_3, it decreases the body weight gain and the concentration of most of the serum lipids in obese rats. Similar conclusions could be drawn as regards $IpTA_2$.

Our data demonstrate that the relatively small variations in the thyroid hormone molecule have an impact on the thyromimetic activities similar to that observed in previous bioassays [23]. It should be noted that T_4 had practically no effect in either lean or obese rats although the dose utilized was about three times as high as that of T_3 which was found to be highly active. It is generally accepted that the difference in potency between T_4 and T_3 is due to a difference in the degree of binding to the various transport proteins of the plasma; T_3 is less strongly bound, so that it reaches the peripheral sites of action more readily.

The difference in potency between the thyroid hormones and their analogs is known to depend on the differences in their chemical structures, in particular the replacement of iodine atoms by methyl

Table 4. Effects of T_4, T_3, $IpTA_2$, and DIMIT on the hepatic lipid levels in genetically obese (fa/fa) Zucker rats

Compound (nmoles)	Treatment	TL (mg/g)	CH (mg/g)	TG (mg/g)	PL (mg/g)
T_4	Control	107 ± 19 (8)	3.65 ± 0.19 (8)	14.11 ± 2.43 (8)	40.4 ± 5.4 (8)
(13.00)	Treated	102 ± 35 (8)	3.60 ± 0.21 (8)	12.91 ± 2.61 (8)	42.8 ± 2.8 (8)
T_3	Control	86 ± 5 (7)	3.64 ± 0.10 (7)		39.1 ± 1.5 (7)
(1.50)	Treated	123 ± 18 (8)	3.62 ± 0.11 (8)		39.8 ± 2.8 (8)
T_3	Control	103 ± 15 (5)	4.17 ± 0.42 (5)	32.41 ± 8.12 (5)	39.7 ± 1.8 (5)
(4.50)	Treated	90 ± 8 (6)	3.84 ± 0.39 (6)	35.52 ± 11.41 (6)	42.0 ± 0.9 (6)
$IpTA_2$	Control	86 ± 5 (7)	3.64 ± 0.10 (7)		39.1 ± 1.5 (7)
(16.25)	Treated	76 ± 6 (8)	3.64 ± 0.10 (8)		33.6 ± 1.6 (8)
$IpTA_2$	Control	107 ± 19 (8)	3.65 ± 0.19 (8)	14.10 ± 2.43 (8)	40.4 ± 5.4 (8)
(32.50)	Treated	80 ± 12 (8)	3.80 ± 0.19 (8)	16.02 ± 2.43 (8)	37.4 ± 3.1 (8)
DIMIT	Control	103 ± 15 (5)	4.17 ± 0.42 (5)	32.41 ± 8.12 (5)	39.7 ± 1.8 (5)
(32.00)	Treated	84 ± 1 (6)	3.19 ± 0.20 (6)	15.97 ± 1.83 (6)	40.3 ± 1.1 (6)

TL: total lipids; CH: total cholesterol; TG: tryglycerides; PL: phospholipids.
Treatments given for 3 weeks, cf. Methods for conditions.
No. of rats in brackets.
Results presented as means ± S.E.M.

Table 5. Oxidative phosphorylation of liver mitochondria from genetically obese (fa/fa) and lean (Fa/–) Zucker rats.

	State IV (initial)		State III		State IV (final)		P/O	
Acylcarnitine	fa/fa	Fa/–	fa/fa	Fa/–	fa/fa	Fa/–	fa/fa	Fa/–
C8	6.80 ± 0.72	6.21 ± 0.47	15.3 ± 0.6	17.8 ± 0.8	3.92 ± 0.40	4.42 ± 0.49	1.87 ± 0.10	2.11 ± 0.12
C10	7.17 ± 0.54	7.04 ± 0.68	24.7 ± 1.1	26.5 ± 1.8	4.96 ± 0.60	5.64 ± 1.00	1.96 ± 0.09	2.05 ± 0.11
C12	8.17 ± 0.86	7.96 ± 0.52	28.6 ± 2.2	29.4 ± 0.9	7.67 ± 0.44	7.64 ± 0.50	2.01 ± 0.11	2.05 ± 0.09
C14	6.76 ± 0.66	7.51 ± 0.47	27.1 ± 1.1	24.4 ± 0.3	8.43 ± 0.39	8.78 ± 0.50	1.94 ± 0.09	1.96 ± 0.16
C16	8.41 ± 1.05	8.92 ± 0.38	24.3 ± 2.4	22.7 ± 1.4	8.46 ± 0.39	9.27 ± 0.18	1.97 ± 0.08	1.99 ± 0.17
C18	7.82 ± 1.33	9.13 ± 0.73	23.2 ± 1.8	21.3 ± 0.9	7.41 ± 0.43	9.38 ± 0.80	1.94 ± 0.09	1.98 ± 0.10

Each acylcarnitine (32 μM) had a fatty acid with 8 to 18 carbon atoms.
Results presented as means ± S.E.M. of 5 determinations.
Oxygen consumption rates in states III and IV are expressed in nmoles $O_2 \cdot min^{-1} \cdot mg^{-1}$ of mitochondrial proteins.

or aryl groups [20]. This is well illustrated by the effects of DIMIT as compared to those of T_3. DIMIT is the nonhalogenated analog of T_3 in which the three iodine atoms are replaced by two methyl and one isopropyl groups. DIMIT was shown to exhibit thyroid hormone-like properties, i.e. to cause a slight inhibition of TSH secretion [18, 33, 34] and to restore the propylthiouracil (PTU)-induced depression of the hepatic L-T_3 aminotransferase activity in foetal rats [17]. DIMIT was also found to restore the phosphorylative oxidation in mitochondria [35], the activity of liver mitochondria and brain nuclei in hypothyroidal rats [23] and to stimulate the hepatic monodeiodination of T_4 to T_3 [36]. Besides, DIMIT is known to have a relatively high affinity for the brain nuclei [37]. Even if DIMIT was found to be less active than T_3, this demonstrates that the iodine atoms are not absolutely necessary to the expression of the thyroid hormone activity. The difference in potency between DIMIT and T_3 could be related to the low affinity of DIMIT for the hepatic T_3 receptors [37].

$IpTA_2$ is an analog of TRIAC in which the 3'iodine atom is replaced by an isopropyl group. This analog was found to have powerful morphogenetic properties [38] and to stimulate the brain RNA polymerase activity [23]. In comparison with TRIAC previously studied [9], $IpTA_2$, at a similar dose, was found to be more active than TRIAC on the serum lipid levels. Similar data were previously reported for brain and liver RNA polymerase activity [23]. Thus, it appears that the isopropyl substituent in 3' enhances the effect of acetic thyromimetic analogs on serum lipids. In addition, since this activity of $IpTA_2$ was higher than that of TRIAC, the 3'-isopropyl substituent seems to play a role in the effects of thyromimetic analogs on lipids. This observation, in agreement with the above results found for DIMIT, can explain that DIMIT kept an activity on serum lipids.

It is worth pointing out that the obese rats had an enhanced response to thyroid hormone analogs as compared to the lean rats. This apparent hypersensitivity of the obese individuals to thyromimetic compounds is consistent with the reports on hypothyroidism [8–10]. However, our results show that the hepatic mitochondrial oxidation of the acylcarnitines was not decreased in the obese rats as in hypothyroid rats [21]. These observations suggest that the mitochondrial acylcarnitine transferase activity is probably not involved in the action of the thyroid hormones and their analogs on the lipid metabolism in the obese rats.

In conclusion, the present experiments on obese rats extend previous data indicating that DIMIT and $IpTA_2$ are thyromimetic compounds [23]. Also, they show that obese rats are more sensitive to thyromimetic compounds than their lean littermates. The different potencies of these compounds are highly influenced by the isopropyl substituent in 3'. However, it appears that other factors are involved in creating thyromimetic activities that can be greater than those found with the parent molecules as demonstrated for $IpTA_2$ in comparison with TRIAC.

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