Effects of tetraiodothyronine and triiodothyronine on hamster cheek pouch microcirculation

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Colantuoni, A., P. L. Marchiafava, D. Lapi, F. S. Forini, and G. Iervasi. Effects of tetraiodothyronine and triiodothyronine on hamster cheek pouch microcirculation. Am J Physiol Heart Circ Physiol 288: H1931–H1936, 2005.—The aim of the present study was to assess the effects of topically applied triiodothyronine (T3) and thyroxine (T4) on the arterioles of hamster cheek pouch microcirculation in vivo. Microvessels were visualized using a fluorescent microscopy technique. Topical application of T3 (3.08, 30.8, 61.5, 307, 615, and 6,150 nM/l) consistently induced dose-dependent dilatation of arterioles within 2.0 ± 0.5 min of administration. The application of T4 (150, 257, 514, and 5,140 nM/l) caused different dose-dependent effects: dilatation at the three lower doses within 16 ± 2 min and rhythmic diameter changes at the highest dose. Aging of hamsters did not alter the arteriolar responses to T3 and T4. T3-induced dilatation was countered by the inhibition of nitric oxide synthase with N\textsuperscript{G}-nitro-L-arginine-methyl ester or N\textsuperscript{G}-nitro-L-arginine. Iopanoic acid (IPA), which inhibits types I and II 5\textsuperscript{-}deiodinase, abolished the dilatation elicited by 514 nM T4 but did not affect T3-induced dilatation. 6-Propyl-2-thiouracil (PTU), which inhibits type I 5\textsuperscript{-}deiodinase only, did not affect the dilatation induced by T4. IPA and PTU did not impair arteriolar dilatation induced by acetylcholine or sodium nitroprusside. These results indicate that T3 induces arteriolar dilation, likely through nitric oxide release. The local conversion of T4 to T3 appears to be crucial for the dilatation induced by T3.

microcirculation; vasodilation; arterioles; nitric oxide; N\textsuperscript{G}-nitro-L-arginine methyl ester; N\textsuperscript{G}-nitro-L-arginine; iopanoic acid; 6-propyl-2-thiouracil; thyroid hormones

THE THYROID GLAND synthesizes and releases the thyroid hormones (THs) mainly as tetraiodothyronine (thyroxine, T4) (15). Most of the biologically active triiodothyronine (T3) derives from the conversion of T4 by 5\textsuperscript{-}monodeiodination (types I and II 5\textsuperscript{-}deiodinase) in peripheral tissues (17, 19). Type I 5\textsuperscript{-}deiodinase has a primary role in maintaining circulating T3 levels, whereas type II 5\textsuperscript{-}deiodinase regulates the intracellular concentration of T3 (12, 18). The direct effects of the THs are triggered by their binding to nuclear receptors (3). Recently, T3 binding sites of T3. This effect was independent of cAMP and nitric oxide (NO) formation (14). Indeed, primary cultures of vascular endothelial cells exposed to T3 show no NO production, indicating that T3 interacts directly with VSM to cause relaxation. However, it has been reported in rat skeletal muscle resistance arteries (diameter: ~100 μm) that T3 is more effective than T4 in inducing vasodilation (13). This dilatation appears to have both endothelium-dependent and -independent components, because T3 dilatation was attenuated by N\textsuperscript{G}-nitro-L-arginine, indomethacin, and glibenclamide.

By contrast, in rat mesenteric resistance vessels, Zwaveling and colleagues (29) have observed that T4 is more potent than T3 in inducing vascular relaxation. This effect was impaired by N\textsuperscript{G}-nitro-L-arginine methyl ester (l-NAME); moreover, vascular relaxation was observed at supraphysiological concentrations (100 times the basal level), the authors concluded that the direct effects of the THs are not relevant for the in vivo situation. Recently, direct effects of the THs have been described in rat coronary arteries within a few seconds of administration, suggesting a nongenomic mechanism of action of the hormone (23). All data indicate that the peripheral vasculature may represent a physiological target for the THs. By contrast, the THs have not yet been proved to affect in vivo microcirculation.

The present study was designed to assess the effects of T3 and T4 on the arterioles of hamster cheek pouch microcirculation, a widely used experimental model (7, 6). We hypothesize that T3 might induce its predominant vasodilatory effect through NO release. Moreover, T3 dilatory effect might be related to local conversion of T4 into T3. Therefore, we evaluated the arteriolar responses to T3 and T4 administration after inhibition of NO synthase (NOS) by l-NAME or N\textsuperscript{G}-nitro-L-arginine (l-NNa). Furthermore, we topically applied the hormones on the cheek pouch after inhibition of types I and II 5\textsuperscript{-}deiodinase by iopanoic acid (IPA) or inhibition of type I 5\textsuperscript{-}deiodinase by 6-propyl-2-thiouracil (PTU) (12).

METHODS

Male Syrian hamsters weighing 80–100 g (Charles River) were randomly assigned to 10 groups. Control hamsters (n = 10) received
topically the vehicles or DMSO and were compared with the animals from the other nine groups that received topically T3 or T4 alone or preceded by other substances, as described below. Group A (n = 50) received topically T3 (at the doses of 3.0, 30.8, 61.5, 307, 615, and 6,150 nM/L delivered for 2 min) or T4 (150, 257, 514, and 5,140 nM/L delivered for 2 min). T3 and T4 were dissolved in a solution containing methanol-ammonia (99:1); 1 μg/μl of T3 and T4 from this stock solution was finally added to Ringer solution to obtain the appropriate concentration with adjusted pH. Group B (n = 8) was administered 1 mM topical L-NAME 15 min before receiving T3, 615 nM/L delivered for 2 min. Group C (n = 5) was administered 1 mM topical L-NNA 15 min before receiving T3, 615 nM/L delivered for 2 min. Group D (n = 5) was administered 1 mM topical L-NAMe 15 min before receiving T4, 5,140 nM/L delivered for 2 min. Group E (n = 5) was administered 1 mM topical L-NNA 15 min before receiving T4, 5,140 nM/L delivered for 2 min. Group F (n = 5) was given topically 1 mM L-arginine and 1 mM topical D-NAME, an isomer of NAME (n = 3), 15 min before receiving T3, 615 nM/L delivered for 2 min. Group G (n = 5) was given topically 1 mM L-arginine and 1 mM L-NNA 15 min before receiving T3, 615 nM/L delivered for 2 min. Group H was administered 0.4 mM topical IPA 15 min before receiving T3, 615 nM/L delivered for 2 min (n = 5), or T4, 514 nM/L delivered for 2 min (n = 5), or T4, 5,140 nM/L delivered for 2 min (n = 5); 0.3 ml of DMSO was added to the solution of IPA. Group I (n = 5) received topically 2 mM PTU 20 min before T4, 514 nM/L delivered for 2 min. Group J (n = 30) was given topically 1 μM ACh (n = 5) or 1 μM sodium nitroprusside (NT) (n = 5), or 0.4 mM IPA 15 min before ACh (n = 5) or NT (n = 5), or 2 mM PTU 20 min before ACh (n = 5) or NT (n = 5). Each dose of the THs was used in only one animal. The drugs were obtained from Sigma (St. Louis, MO).

A reverse-phase HPLC technique was used for purification and separation of iodothyronines to assess contaminant T4 or T3. Briefly, chromatography was performed by a 10-cm HPLC column (Leitz KG1). The area of interest was televised with a Dage MTI 300 computer.

RESULTS

The arterioles in each preparation were classified according to a centrifugal ordering scheme from the largest (A1) to the smallest (A4) arterioles. In each animal, two A2, two A3, and two A4 arterioles were studied under baseline conditions and after application of the THs alone or preceded by the drugs. These substances were applied switching from one to another reservoir filled with the drugs for 2 min. The time to maximum dilation and the time to baseline diameter recovery were evaluated starting from the end of drug application. The video images of the microvascular networks were recorded for 20 min during baseline observation and for up to 45 min after drug administration. To reduce the effects of epi-illumination on microvessels, the recordings were performed for 20 s/min under baseline conditions and for 30 s/min when the observation lasted more than 10 min after drug administration. At the end of the observation, dilation to topical ACh (1 × 10⁻⁶ M) and constriction to phenylephrine (PE) (5 × 10⁻⁶ M) were randomly assessed to explore vessel reactivity.

All values are means ± SD. An SPSS statistical package was used for analysis of statistical significance. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Parametric (paired and unpaired Student’s t-test, ANOVA, and Scheffe’s post hoc test) and nonparametric tests (Wilcoxon test, Friedman test, Mann-Whitney U-test, and Kruskal-Wallis test) were applied where appropriate. Statistical significance was set at P < 0.05.

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Fig. 1. Dose-dependent arteriolar (A2, A3, and A4) relaxation induced by triiodothyronine (T3). Percent changes were evaluated by the ratio of maximum diameters before and after T3. All diameter variations were statistically significant, *P < 0.01. Each entry = 10 arterioles studied in 5 animals.
group vs. AG group: A2, 23.5 ± 1.5 μm; A3, 13.7 ± 1.4 μm; and A4, 7.7 ± 0.8 μm). Pilot studies indicated that the lowest effective doses inducing vasodilation were 3.08 nM (T3) and 150 nM (T4) because lower concentrations of the hormones (1.54, 1.84, 2.15, 2.46 nM T3 and 50, 75, 100, 125 nM T4) caused no vessel response. We used different doses in the range 3.08–6,150 nM for T3 and 150–5,140 nM for T4. We report in Fig. 1 and in Table 1 the arteriolar responses to the lowest effective and higher doses that are comprised in the report in Fig. 1 and in Table 1 the arteriolar responses to the lowest effective and higher doses that are comprised in the plasmatic ranges of hamster THs (15, 20).

T3 induced a dose-dependent dilation of all arterioles. The percent changes of A2, A3, and A4 arteriole diameter after T3 topical administration (semilog plot) are reported in Fig. 1. Vessel diameter increased significantly (P < 0.01) with all doses. Time to maximum dilation was 2.0 ± 0.5, 1.8 ± 0.6, 1.8 ± 0.5, 4.5 ± 1.0, 5.5 ± 0.7, and 2.5 ± 0.8 min for the corresponding dose of T3, respectively. 3.08, 30.8, 61.5, 307, 615, and 6,150 nM/L. Effect duration was also dose dependent and lasted 5.0 ± 1.0, 18.0 ± 2.5, 22.0 ± 3.0, 28.0 ± 3.0, 33.0 ± 1.0, and 36.0 ± 1.0 min according to the dose, as above reported.

T4 also caused dose-dependent responses (Table 1). The lowest dose-induced arteriolar dilation, 16.0 ± 2.0 min from administration, lasting 4.5 ± 1.0 min; a typical response is reported in Fig. 2. Arteriolar dilation was also observed for the doses 257 and 514 nM within 15.0 ± 1.0 and 14.0 ± 0.8 min of injection, respectively. Maximum of dilation was detected just at the beginning and lasted 16.0 ± 2.0 and 20.0 ± 3.0 min, respectively. The highest dose of T4 caused rhythmic diameter changes within 5.0 ± 1.0 min of application that lasted up to 20.0 ± 2.0 min from administration.

Inhibition of NOS by L-NAME or L-NNA prevented the vasodilatory action of T3 (Table 2). L-Arginine but not D-arginine was able to reverse the effects of both inhibitors (Table 2), whereas D-NNA did not influence the dilation induced by T3 (data not shown). L-NNAME did not affect the rhythmic changes in diameter induced by the highest dose of T4.

IPA, which inhibits both type I and type II 5'-deiodinase, the enzyme that transforms the prohormone T4 into biologically active T3, did not interfere with the dilation elicited by T3 (Table 3). By contrast, it abolished the effect induced by the diluting dose of T4 (514 nM). IPA did not interfere with the effects of the highest dose of T4 (5,140 nM) that were characterized by rhythmic changes in diameter.

Topical application of PTU, the specific inhibitor of type I 5'-deiodinase, 20 min before 514 nM T4 did not affect the

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**Table 1. Averages of maximum diameters of A2, A3, and A4 arterioles under baseline conditions and after application of T4**

<table>
<thead>
<tr>
<th>Diameter, μm</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline + Vehicle</td>
<td>22.5±0.9</td>
<td>13.4±0.9</td>
<td>7.5±0.6</td>
</tr>
<tr>
<td>Baseline + T4 (150 nM)</td>
<td>22.6±1.0</td>
<td>13.5±0.8</td>
<td>7.4±0.7</td>
</tr>
<tr>
<td>Baseline + T4 (257 nM)</td>
<td>22.7±0.9</td>
<td>12.9±0.8</td>
<td>7.6±0.7</td>
</tr>
<tr>
<td>Baseline + T4 (514 nM)</td>
<td>23.8±1.0*</td>
<td>13.9±0.9*</td>
<td>8.8±0.7*</td>
</tr>
<tr>
<td>Baseline + T4 (5,140 nM)</td>
<td>25.0±1.0*</td>
<td>14.2±0.9*</td>
<td>9.5±0.8*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 5 hamsters. T4, tetraiodothyronine. *P < 0.01 vs. baseline.

**Table 2. Averages of maximum diameters of A2, A3 and A4 arterioles under baseline conditions, after l-NNAME or l-NNA, and after T3 application**

<table>
<thead>
<tr>
<th>Diameter, μm</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline + Vehicle</td>
<td>22.2±1.0</td>
<td>12.7±0.9</td>
<td>7.9±0.7</td>
</tr>
<tr>
<td>Baseline + T3 (615 nM)</td>
<td>22.6±1.0</td>
<td>12.5±0.8</td>
<td>8.0±0.6</td>
</tr>
<tr>
<td>Baseline + l-NNAME</td>
<td>21.7±1.1</td>
<td>12.9±1.0</td>
<td>8.0±0.6</td>
</tr>
<tr>
<td>Baseline + T3 (514 nM)</td>
<td>21.0±1.2</td>
<td>12.4±1.1</td>
<td>7.4±0.6</td>
</tr>
<tr>
<td>Baseline + l-NNA</td>
<td>21.1±1.1*</td>
<td>12.5±1.0*</td>
<td>7.5±0.7*</td>
</tr>
<tr>
<td>Baseline + T3 (5,140 nM)</td>
<td>21.8±0.9</td>
<td>12.8±0.7</td>
<td>7.8±0.7</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 5 hamsters. l-NNAME, N°-nitro-l-arginine methyl ester; l-NNA, N°-nitro-l-arginine; T3, triiodothyronine. *P < 0.01 vs. group A, hamsters treated with T3; comparisons were made between l-NNAME plus T3-treated hamsters (group B) and T3-treated animals (group A), between l-NNA plus T3-treated hamsters (group C) and T3-treated animals (group A).
dilation induced by the hormone (Table 3). The increase in arteriolar diameter was observed within 16.0 ± 2.0 min of T₄ administration.

In each animal, at the end of the experimental protocol, the vessels retained vascular tone because the arterioles dilated to ACh (A2: +13.0 ± 1.5% of baseline; A3: +19.0 ± 2.0%; and A4: +25.0 ± 1.9%) and constricted after PE (A2: −12.0 ± 1.2% of baseline; A3: −15.0 ± 1.9%; and A4: −19.0 ± 1.8%).

Topical application of IPA, PTU, the vehicles, and DMSO did not modify arteriolar diameter. Topically applied IPA or PTU did not interfere with arteriolar dilation induced by ACh or NT (Fig. 3). The arteriolar responses to THs did not appear to be related to the age of animals. In AG hamsters the arteriolar diameter changed significantly after application of 615 nM T₃ (A2: 25.1 ± 1.2 μm vs. 22.3 ± 1.3 μm; A3: 17.8 ± 1.1 μm vs. 13.1 ± 1.0 μm; A4: 10.2 ± 1.0 μm vs. 7.2 ± 0.9 μm; P < 0.01; n = 5 animals) and 514 nM T₄ (A2: 25.6 ± 1.1 μm vs. 23.8 ± 1.2 μm; A3: 18.1 ± 1.0 μm vs. 14.0 ± 0.9 μm; A4: 10.6 ± 1.0 μm vs. 7.8 ± 0.8 μm; P < 0.01; n = 5 animals).

Table 3. Averages of maximum diameters of A2, A3, and A4 arterioles under baseline conditions and after application of IPA and T₃, or IPA and T₄, or PTU and T₄

<table>
<thead>
<tr>
<th>Condition</th>
<th>A2</th>
<th>A3</th>
<th>A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22.5 ± 0.9</td>
<td>13.0 ± 1.0</td>
<td>7.9 ± 0.8</td>
</tr>
<tr>
<td>+ Vehicle</td>
<td>22.6 ± 1.1</td>
<td>12.9 ± 0.8</td>
<td>7.8 ± 0.9</td>
</tr>
<tr>
<td>Baseline</td>
<td>23.1 ± 1.2</td>
<td>12.7 ± 1.0</td>
<td>7.7 ± 0.6</td>
</tr>
<tr>
<td>+ IPA + T₃ (615 nM)</td>
<td>28.4 ± 1.3*</td>
<td>16.7 ± 1.0*</td>
<td>10.7 ± 0.7*</td>
</tr>
<tr>
<td>Baseline</td>
<td>23.0 ± 1.0</td>
<td>12.6 ± 0.8</td>
<td>7.8 ± 0.7</td>
</tr>
<tr>
<td>+ IPA + T₄ (514 nM)</td>
<td>22.5 ± 1.2</td>
<td>12.4 ± 0.8</td>
<td>7.5 ± 0.7</td>
</tr>
<tr>
<td>Baseline</td>
<td>22.8 ± 1.0</td>
<td>13.1 ± 1.0</td>
<td>7.9 ± 0.5</td>
</tr>
<tr>
<td>+ IPA + T₄ (5.140 nM)</td>
<td>(Vasomotion)</td>
<td>(Vasomotion)</td>
<td>(Vasomotion)</td>
</tr>
<tr>
<td>Baseline</td>
<td>22.9 ± 1.1</td>
<td>12.5 ± 0.9</td>
<td>7.7 ± 0.8</td>
</tr>
<tr>
<td>+ Vehicle</td>
<td>23.0 ± 0.9</td>
<td>12.6 ± 1.0</td>
<td>7.6 ± 0.7</td>
</tr>
<tr>
<td>Baseline</td>
<td>22.6 ± 1.0</td>
<td>12.9 ± 0.9</td>
<td>7.8 ± 0.7</td>
</tr>
<tr>
<td>+ PTU + T₄ (514 nM)</td>
<td>28.0 ± 1.0*</td>
<td>17.3 ± 1.0*</td>
<td>10.7 ± 0.8*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 5 hamsters. IPA, iopanoic acid; PTU, 6-propyl-2-thiouracil. *P < 0.01 vs. baseline.

DISCUSSION

Administration of the THs induced microvascular responses in the in vivo model of hamster cheek pouch micrcirculation used in this study. T₃ caused a dose-dependent dilation of the arterioles within few minutes of its application. Such quick response suggests a nongenomic mechanism of action triggered by the hormone. In addition, arteriolar relaxation was abolished by NOS inhibition, indicating a correlation between T₃-induced dilation and NOS activation. Therefore, these results support our suggestion that NO is the main factor in T₃-induced arteriolar dilation.

The present findings are in agreement with previous observations of a nongenomic mechanism of action of T₃ and T₄ (23), even though the vessels investigated in that work were different. The data indicating that NO mediates T₃-induced arteriolar dilation are partially supported by the observations that T₄-induced dilation is attenuated by NOS inhibition in rat skeletal muscle resistance arterioles (13). However, previous results indicate that vascular endothelial cells exposed to T₃ do not release nitrate nor show increased cGMP content (14).

These discrepancies with our results may be ascribed to differences in the experimental procedure, namely between the study of primary cultures of rat aortic endothelial or VSM cells and the present in vivo model of micrcirculation. It is reasonable to suppose that in vitro conditions do not allow one to observe the integrated response of the peripheral microcircu-
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lation. It is worth noting that a previous research (1) showed that skin muscle arterioles respond differently to NOs inhibition, pointing to different properties of endothelial and VSM cells in different sized arterioles.

Interestingly, the present results demonstrate that the lower doses of T₄ (150 nM) determined dilation of the arterioles after its application. Time to dilation was significantly different for T₄ and T₃. The effect of T₄ was abolished by the inhibition of 5'-deiodinase activity (types I and II) by IPA, because 514 nM T₄ did not cause dilation after IPA. The concentration 5,140 nM T₄ after IPA, however, determined rhythmic changes in arteriolar diameter. We did not test lower doses of T₄ after IPA because the highest dilatory dose of T₄ (514 nM) was ineffective. Therefore, these results support the hypothesis that local conversion of T₄ into T₃ is crucial for dilation induced by THs. Indeed, PTU, an inhibitor of type I 5'-deiodinase, did not interfere with the dilation induced by T₄. We did not try to assess the effects of different doses of T₄ after PTU because there was no change in the vessel response to T₄ after local application of PTU. T₄ may thus cause an increase in arteriolar diameter after type II 5'-deiodinase-mediated local conversion to T₃. This finding argues for the presence of type II 5'-deiodinase in vascular smooth muscle cells, as recently shown in cultured coronary artery and aortic smooth muscle cells (12). This enzyme thus appears to play a physiological role in the regulation of the vascular tone and arteriolar dilation induced by T₃.

Our data indicate that the highest dose of T₄ (5,140 nM) did not cause significant arteriolar dilation but induced rhythmic changes in diameter. Such effect may be related to the inhibition of 5'-deiodinase activity by high T₄ concentrations. The inhibition of 5'-deiodinase by supraphysiological doses of T₄ has been reported previously in smooth muscle cell preparations (12). Moreover, 5'-deiodinase blockade by IPA does not appear to affect the rhythmic changes in diameter caused by 5,140 nM T₄. However, further studies are required to clarify this important issue.

The opposite effects of T₄, dilation at lower doses and vasomotion at higher doses, are in agreement with previous observations, indicating increase in sarcoplasmic reticulum ATPase activity at lower doses and decrease of this activity at higher concentrations of T₄ (20). Therefore, T₄ appears to differently modulate responses of target cells, according to the doses.

It has been reported that pentobarbital anesthesia reduces plasma T₄ level in rats. These effects appear within 60–90 min of pentobarbital administration and have been described only for T₄ (15). In our model, we did not measure serum T₄ and T₃ concentrations. However, the experiments lasted up to 60–120 min according to the protocol, but there were no significant changes in the diameter of control hamster arterioles up to 60–120 min of observation.

In this study, we used hamster upper physiological range doses of T₃ and T₄ (16, 21). However, it is worth noting that lower doses of THs were used by Kemperer and co-workers (13, 14) to reduce the systemic vascular resistance and to increase coronary blood flow in clinical pathophysiological conditions. In our model, the morphological and functional properties of the cheek pouch membrane, where a thick epithelial layer effectively opposes the diffusion of substances, dictated the utilization of relatively high doses of THs to cause vessel response. The same approach has previously been tried using this model with substances such as bradykinin (5).

Altogether, our findings show marked effects of the THs in the in vivo microvasculature that implicate a modulation of the NO system, which has a role in maintaining the microvascular tone.

Our data support previous studies indicating that T₄ affects the NO system because subcutaneous injection of T₄ for 3 days suppressed the contraction of aortic rings induced by norepinephrine (NE); L-NNA, an inhibitor of NOS, enhanced the NE-induced contraction of aortic rings in T₄-treated rats more than in control ones (8).

It is difficult to derive indications on endogenous thyroid hormone function in humans from the present experimental data. However, recent results indicate that in human hypothyroidism there is a reduction in NO availability (26). Moreover, clinical hypothyroidism and hyperthyroidism are accompanied by changes in systolic-diastolic index, indicating variations in arterial compliance (7). Furthermore, clinical hypothyroidism is characterized by an increase in the time to peak flow during postocclusion reactive hyperemia, likely due to decrease in dilatation capacity of arterioles giving origin to the nailfold capillaries (19).

The effects of THs were not influenced by ageing of animals, at least for the single dose used in this study. Furthermore, we did not observe differences in the response of single animals. However, these preliminary results need to be confirmed by experiments carried out on a large number of animals with different doses of THs.

In conclusion, our results indicate that microcirculation is a physiological target for THs. The effects of T₃ on the in vivo microcirculation appear to be mostly mediated by NO through a nongenomic mechanism of action. The effects of T₄ appear to be mediated by local conversion to T₃ when the concentration is in the physiological range. Higher doses of T₄ are able to induce vessel responses characterized by vessel diameter changes with no evident dilation.

REFERENCES


