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# UPTAKE, METABOLISM AND ACTION OF TRIIODOTHYRONINE IN CALF-THYROID SLICES *

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$T_3$ and $T_4$ at $10^{-6}$ M caused a significant inhibition on [$^3$H]uridine incorporation into RNA in calf-thyroid slices. This effect was not altered by addition of $10^{-3}$ M PTU or MMI. The metabolism of $^{125}$I-$T_3$ was studied under the same conditions. There was a very slight dehalogenation after 60 min (less than 5%) which was inhibited by PTU.

The time course of the uptake of labeled $T_3$ showed a temperature dependence, and this uptake was not altered by $10^{-6}$ M KI, I-$T_4$, DIT or MIT, thus indicating specificity. The early phase of labeled $T_3$ entrance into the cell was inhibited by the addition of cold $T_3$ in a dose-dependent manner from $10^{-9}$ to $10^{-5}$ M. Slices previously stimulated by cAMP or cGMP showed a significant increase in the uptake of labeled $T_3$. ATPase activity or ATP, protein or RNA synthesis does not seem to play a role in this process.

The relationship between substitutions in the thyronine molecule and its biological action on RNA synthesis was also studied, and some preliminary conclusions were drawn.

These studies demonstrate that $T_3$ has a direct action on the thyroid.

*Key words:* thyroid, triiodothyronine, RNA synthesis, autoregulation.

Iodine affects different thyroid parameters both in humans and in animals, but its exact mechanism of action is not completely understood (Wolff, 1976). Because the inhibitory action of iodine is relieved by perchlorate, methylmercaptoimidazole and PTU (Burke, 1970; Van Sande and Dumont, 1973; Pisarev and Aiello, 1976;

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*Abbreviations:* cAMP, cyclic adenosine 3',5'-monophosphate; cGMP, cyclic 3',5'-guanosine monophosphate; PTU, propylthiouracil; MMI, methylmercaptoimidazole; BEA, *n*-butanol : ethanol : ammonium hydroxide; BAW, *n*-butanol : acetic acid : water; *T/M*, thyroid/medium ratio for labeled $T_3$; Triac, triiodothyroacetic acid; Tetrac, tetraiodothyroacetic acid; $T_2$, 3,3'-diiodothyronine; DIMIT: 3,5'-dimethyl-3'-isopropylthyronine; DISBT, 3,5'-dimethyl-3'-sec-butylthyronine; LID, low iodine diet.

Rapoport et al., 1976; Sherwin and Tong, 1976) it has been proposed that an intracellular and organic iodo compound is the intermediate of its action. Previous studies showed that $T_3$ and $T_4$ have a direct inhibitory action on thyroid slices (Pisarev et al., 1976; Kleiman de Pisarev et al., 1978). Moreover, iodothyronines are more potent inhibitors, on an equimolar basis, than KI. These findings led us to propose that iodothyronines may play a role in thyroid autoregulation (the short-loop feedback mechanism).

The present studies were performed to answer the following questions. (a) Does $T_3$ enter into the thyroid cell? (b) Is $T_3$ dehalogenated to a significant extent, under the experimental conditions where it inhibits protein and RNA synthesis? (c) Do $T_3$ and $T_4$ have a biological effect in the presence of MMI and PTU? The influence of certain substitutions in the iodothyronine molecule on the inhibitory action was also analyzed.

## MATERIALS AND METHODS

Bovine thyroid was obtained at a local slaughterhouse and transported to the laboratory in iced saline. Slices were made on a Stadie–Riggs microtome. They were rinsed during 15 min in the incubation medium to remove the colloid released by the slicing procedure.

### *[$^3$H]Uridine incorporation into RNA*

The slices were incubated in quadriplicate, in 5 ml of Krebs–Ringer-bicarbonate (KRB) buffer (pH 7.4) containing 8 mM glucose, under 95% $O_2$ and 5% $CO_2$ at 37°C. Each experiment was repeated 3–5 times on different days. The various test substances were present during both the incubation and the labeling procedure. After 30–40 min incubation, the slices were labeled with [5-$^3$H]uridine (spec. act. 30 Ci/mM, New England Nuclear, U.S.A.), at 2 $\mu$Ci/ml during 60 min. The slices were then extensively washed in cold saline, blotted on filter paper and homogenized in 1 ml of distilled water in an all-glass Potter–Elvehjem type tissue homogenizer. RNA was extracted according to the method of Munro and Fleck (1966), and its specific activity was calculated after the radioactivity had been counted in Bray's scintillation solution.

### *Uptake of $^{125}$I-$T_3$ by thyroid slices*

Beef-thyroid slices (10–40 mg wet weight), free from fat and connective tissue, were incubated at 37°C during 30 min in KRB containing the different test substances. A tracer dose (around 800 000 cpm) of $^{125}$I-$T_3$ (spec. act. 144 $\mu$Ci/$\mu$g, New England Nuclear) was then added and the incubations were continued for different times up to 60 min. The slices were then thoroughly washed with cold saline, blotted on filter paper and weighed, and their radioactivity was counted in a Packard auto-gamma spectrometer. The radioactivity of the incubation media was

also counted. The T/M ratio for $T_3$ was calculated according to the equation

$$T/M = \frac{\text{thyroid radioactivity (cpm/mg wet weight)}}{\text{medium radioactivity (cpm/ml)}}$$

*Metabolism of labeled $T_3$*

To study the metabolism of $T_3$ inside the thyroid cell, slices were incubated in 5 ml of KRB during 60 min with $^{125}$I-$T_3$ (about $1.5 \times 10^6$ cpm). The purity of each preparation of labeled hormone was checked by paper chromatography before each experiment. At the end of the incubation the slices were thoroughly washed, blotted on filter paper and homogenized in 0.5 ml of 1 mM PTU. Aliquots of the homogenate and of the incubation medium were then subjected to paper chromatography together with standards of iodothyronines, iodide and iodotyrosines to help in the identification of the labeled compounds. 3 solvent systems were used: (a) ascending paper chromatography in *n*-butanol : ethanol : 0.5 N ammonium hydroxide (5 : 1 : 2; v/v); (b) ascending paper chromatography in *n*-butanol : acetic acid : water (138 : 5 : 6; v/v); and (c) descending paper chromatography in hexane : tertiary amyl alcohol : 2 N ammonium hydroxide (1 : 5 : 6; v/v) according to Bellabarba et al. (1968), all with Whatman No. 1 paper. The running time was around 20 h in all cases. Iodide spots were identified with 0.5% palladium chloride, and iodoaminoacids were located with 0.5% ninhydrin in acetone. The paper was cut into strips and the radioactivity was counted. The distribution of radioactivity was calculated as percentage of the total counts in each strip. Because the separation of the spots of $T_3$ and $T_4$ was poor in the BEA and BAW systems, their radioactivities were estimated together. In the system with hexane : tertiary amyl alcohol : ammonium hydroxide, MIT and DIT could not be adequately separated and therefore their radioactivities were estimated together. The protein content in the samples was determined according to Lowry et al. (1951).

The various iodo compounds used in the present studies were kindly donated by: Glaxo Laboratories (Argentina); Smith-Kline Laboratories (U.S.A.); Dr. Vivian Cody, Medical Foundation of Buffalo (U.S.A.); and Dr. Gerald N. Burrow, Toronto General Hospital (Canada). Actinomycin D was generously provided by Merck, Sharp and Dohme Laboratories, NJ (U.S.A.). $T_3$ and $T_4$ were purchased from Sigma Chemical Co., MO (U.S.A.), while all the other drugs were reagent-grade. *n*-Butanol was distilled in our laboratory. Statistical analysis was performed according to Student's *t* test.

## RESULTS

As shown in Table 1, thyroxine at $10^{-5}$ M caused a significant decrease in [$^3$H]-uridine incorporation into RNA, and this action was not altered by the addition of MMI at $10^{-3}$ M to the incubation mixture (Expt. A). Moreover, the inhibitory

Table 1
Inhibitory action of $T_3$ and $T_4$ on RNA synthesis in the presence of MMI or PTU

| Expt. | Treatment | RNA (cpm/μg) | Inhib. (%) | p |
|---|---|---|---|---|
| A | Control | 90.6 ± 28.6 | – | – |
| | MMI $10^{-3}$ M | 73.0 ± 7.2 | – | n.s. |
| | $T_4$ $10^{-5}$ M | 30.4 ± 13.8 | 67 | 0.01 |
| | $T_4$ plus MMI | 23.6 ± 4.5 | 74 | 0.005 |
| B | Control, PTU solv. | 96.8 ± 13.3 | – | – |
| | Control, iodothyron. solv. | 96.7 ± 17.8 | – | – |
| | PTU $10^{-3}$ M | 97.9 ± 18.7 | – | – |
| | $T_3$ $10^{-6}$ M | 26.3 ± 1.7 | 73 | 0.001 |
| | $T_4$ $10^{-6}$ M | 53.9 ± 14.4 | 45 | 0.005 |
| | $T_3$ plus PTU | 34.1 ± 9.1 | 65 | 0.0005 |
| | $T_4$ plus PTU | 48.9 ± 2.2 | 50 | 0.0005 |

Each value is the average from 4 slices ± 1 S.D.

action of $10^{-6}$ M $T_3$ or $T_4$ on RNA labeling was not affected by $10^{-3}$ M PTU (Expt. B).

The possible metabolization of labeled $T_3$ was studied under the same experimental conditions in which $T_3$ inhibits the incorporation of [$^3$H]uridine into RNA. As can be seen in Table 2, after 60 min of incubation only a small proportion of the hormone had been dehalogenated and this process was inhibited by the addition of $10^{-3}$ M PTU.

With the knowledge that labeled $T_3$ remains unaltered during incubations of up to 60 min, its entrance into the thyroid cell was then studied. Fig. 1 shows the time-course curve of the uptake of $^{125}$I-$T_3$ into thyroid slices. When the incubations were performed at 37°C where was a rapid rise in the T/M ratio, which reached a plateau after 20 min, the values remaining steady for up to 60–120 min of incubation. When the slices were incubated at 0°C the uptake curve was similar in shape, but the T/M ratio showed values that were 25–30% of those observed at 37°C. Addition of cold $T_3$ to the incubation mixture caused a decrease in labeled $T_3$ uptake. Fig. 2 shows that $T_3$ in concentrations from $10^{-9}$ to $10^{-5}$ M caused a progressive decrease in the T/M ratio measured after a 1-min pulse. Similar amounts of 1-$T_4$ failed to alter the rate of $T_3$ entrance into the cell. As can be seen in Table 3, neither KI, 1-$T_4$, MIT nor DIT at $10^{-6}$ M caused a significant alteration in the T/M ratio. Ouabain showed only a marginal and non-significant effect, similar to that of puromycin and dinitrophenol (DNP). Cycloheximide and actinomycin D caused an unexpected increase in the T/M ratio. These results were observed in 6 different experiments and with concentrations of actinomycin D of 10 and 2 μg/ml. When the action of cyclic nucleotides was analyzed, both cyclic AMP and cyclic GMP at

Table 2
Metabolism of $^{125}$I-$T_3$ by calf thyroid

% Distribution of products by paper chromatography

| | BEA | | | | BAW | | | | Hexane : tert.-amyl alcohol : ammonium | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Tissue | | Medium $T_3^*$ | | Tissue | | Medium $T_3^*$ | | Tissue | | $T_3^*$ |
| | Control | PTU | | | Control | PTU | | | Control | PTU | |
| MIT | 2.1 ± 0.6 | 1.0 ± 0.3 | 1.1 | 0.4 | 0.9 ± 0.0 | 1.0 ± 0.1 | 1.6 | 0.9 | 2.1 ± 0.3 | 2.4 ± 1.5 | 0.2 |
| DIT | 1.7 ± 0.5 | 0.3 ± 0.1 | 0.4 | 0.3 | 3.5 ± 0.4 | 2.9 ± 0.3 | 2.2 | 3.0 | | | |
| $T_3$ | | | | | | | | | 90.2 ± 1.1 | 91.8 ± 1.9 | 95.1 |
| | 90.1 ± 1.3 | 95.5 ± 1.0 | 95.1 | 95.7 | 91.9 ± 1.1 | 94.0 ± 0.4 | 94.3 | 94.2 | | | |
| $T_4$ | | | | | | | | | 3.7 ± 1.1 | 2.7 ± 0.2 | 3.5 |
| Iodide | 4.6 ± 1.0 | 2.2 ± 0.5 | 3.0 | 2.9 | 2.7 ± 0.7 | 1.5 ± 0.2 | 1.7 | 1.6 | 4.0 ± 0.3 | 3.0 ± 0.3 | 1.2 |
| Produced | 2.5 ± 0.4 | 1.0 ± 0.3 | 0.4 | 0.6 | 1.1 ± 0.5 | 0.7 ± 0.3 | 0.3 | 0.3 | – | – | |

In each Expt., 4 slices were incubated in KRB, with an without PTU $10^{-3}$ M. Aliquots of the tissue homogenates, the incubation medium and the labeled $T_3$($T_3^*$) used were analyzed by paper chromatography with 3 different solvent systems. Each value is the average from 4 samples ± 1 S.D.

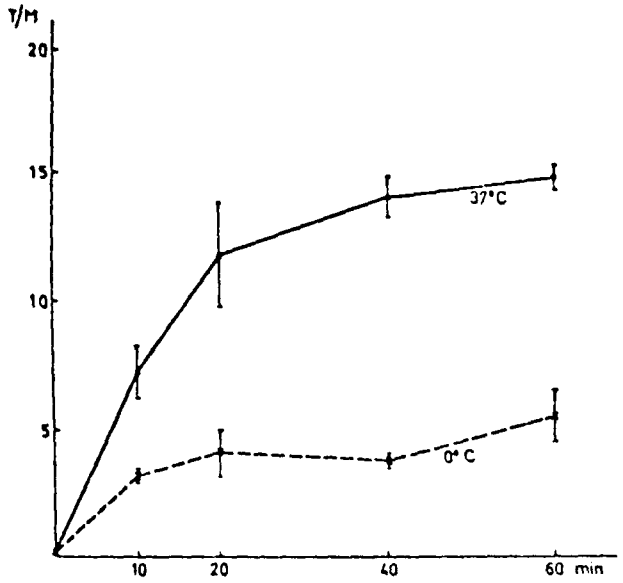


Fig. 1. Time course of the uptake of $^{125}$I-$T_3$ by thyroid slices. Each value is the average from 4 slices ±1 S.D. The slices were incubated during the indicated times at 37 and at 0°C.

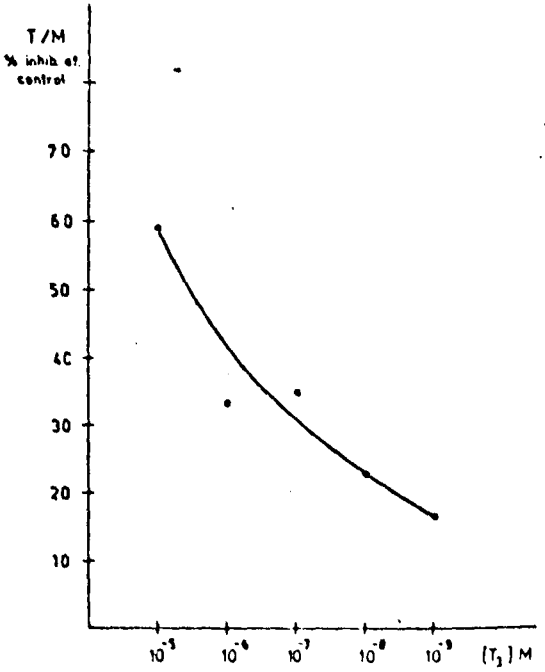


Fig. 2. Action of unlabeled $T_3$ on $^{125}$I-$T_3$ uptake by thyroid slices. The slices were incubated with the cold hormone at the concentrations indicated for 30 min, and then pulse labeled for 1 min. The values are the average from 4 slices and are expressed as percentage of the controls, which were taken as 100%.

Table 3
Influence of Various Compounds on $^{125}$I-$T_3$ Uptake by the Thyroid Cell

| Treatment | Concentration | $T_3^*$ Uptake (%) |
|---|---|---|
| Control | | 100 |
| KI | $10^{-6}$ M | 92 |
| I-$T_4$ | $10^{-6}$ M | 112 |
| MIT | $10^{-6}$ M | 91 |
| DIT | $10^{-6}$ M | 84 |
| Ouabain | $10^{-3}$ M | 85 |
| Actinomycin D | 10 μg/ml | 160 |
| | 2 μg/ml | 167 |
| Dinitrophenol | $10^{-3}$ M | 97 |
| Cycloheximide | 100 μg/ml | 138 |
| Puromycin | 100 μg/ml | 88 |
| Cyclic AMP | $10^{-3}$ M | 158 |
| Cyclic GMP | $10^{-3}$ M | 133 |

Beef-thyroid slices were incubated in quadriplicate in KRB containing the various substances. After 30 min a tracer dose of labeled $T_3$ was added and the uptake measured after 1 min. The *T/M* ratio was calculated as described under Materials and Methods. Results are expressed by taking the controls as 100% and are representative of 4–6 different Expts.

Table 4
Action of Thyroid Hormone Analogs on Thyroid RNA synthesis

| Compound | % Inhibition of RNA (cpm/μg) |
|---|---|
| l-3,3',5-Triiodothyronine | 59 |
| l-Thyroxine | 44 |
| l-Tetrachlorothyronine | 54 |
| l-3,3',5-Trichlorothyronine | 37 |
| l-3,3',5-Triiodothyroacetic acid | 60 |
| l-Tetraiodothyroacetic acid | 47 |
| l-3,3',5-Triiodothyroformic acid | 0 |
| l-Tetraiodothyroformic acid | 23 |
| l-Tetraiodothyropropionic acid | 65 |
| l-3,3'-Diiodothyronine | 0 |
| l-3'-Isopropyl-3,5-diiodothyronine | 0 |
| l-3'-Isopropyl-3,5',5-triiodothyronine | 50 |
| l-3,5'-Dimethyl-3'-isopropyl thyronine | 61 |
| l-3,5'-Dimethyl-3'-sec-butyl thyronine | 13 |

The percentage inhibition of RNA synthesis was calculated from the average inhibition observed in 8 different Expts. In each Expt. 4 slices were incubated with the various compounds at a final concentration of $10^{-5}$ M.

$10^{-3}$ M caused a significant increase in the entrance of labeled $T_3$. Similar results were obtained when the T/M ratio was measured after a 10-min pulse.

The action on RNA synthesis of some thyroid-hormone analogs was studied. As shown in Table 4, besides $T_3$ and $T_4$, tetrachlorothyronine, trichlorothyronine, Triac, Tetrac, triiodothyropropionic acid, tetraiodothyropropionic acid, isopropyl-$T_3$ and DIMIT caused a significant and equivalent inhibition of RNA labeling. On the other hand, DISBT had a slight but non-significant action, similar to that of triiodothyroformic acid, tetraiodothyroformic acid, diiodothyronine and isopropyl-diiodothyronine.

## DISCUSSION

The present studies indicate that $T_3$ enters into the thyroid cell and that it is concentrated in a progressive manner. This process is temperature-dependent. The T/M ratio for $T_3$ rose from values of around 1.8–2.0 at 1 min to 13.6 after 40–60 min of incubation. Green (1978) has also shown that $T_3$ and $T_4$ can be concentrated by the rat thyroid. The kinetics of the entrance of labelled $T_3$ into the cell has a rapid phase of about 10–20 min, followed by a plateau. The entrance of labeled $T_3$ can be progressively decreased by the addition of increasing amounts of cold $T_3$, at concentrations as low as $10^{-9}$ M. The mechanism involved in the entrance of the hormone into the thyroid seems to be highly specific because the T/M ratio was not altered by incubation with KI, thyroxine, DIT or MIT. This process does not seem to be dependent on ATP generation, or on synthesis of protein or RNA. Moreover, an ouabain-sensitive ATPase does not seem to be involved either.

The results obtained with actinomycin D and cycloheximide are rather unexpected. The "stimulatory" action of actinomycin D was observed consistently with 2 different concentrations of this compound and in 6 separate experiments. The most likely explanation would be that these results are due to some non-specific effect. However, the possibility that these 2 compounds impair the synthesis of some protein which exerts a negative action on $T_3$ entrance cannot be dismissed, and further studies will be necessary to clarify this point.

Prior stimulation of the thyroid cells with cAMP or cGMP caused a significant increase in the uptake of labeled $T_3$. These results confirm once more than these 2 cyclic nucleotides may have parallel and stimulatory effects on the thyroid (Pisarev and Kleiman de Pisarev, 1977).

The metabolism of labeled $T_3$ was analyzed with 3 different solvent systems. Because the original $^{125}$I-$T_3$ used was about 95–96% pure, dehalogenation of the hormone under our incubation conditions was almost negligible. However, a small amount of iodide was produced, and this process was significantly inhibited by incubation with PTU at $10^{-3}$ M. Therefore we may conclude that the calf thyroid has a rather inactive iodothyronine($T_3$)-dehalogenating system, similar to the iodo-

thyronine metabolic pathway found in sheep and dog thyroid (Roche et al., 1952; Tong et al., 1962). On the contrary, a very active iodothyronine-dehalogenating system was found in the rat thyroid by Haibach (1971) and Green (1978). Therefore, although a small proportion of labeled $T_3$ was dehalogenated, the amount of iodide produced is unlikely to have a role in the inhibitory action of $T_3$ on protein and RNA synthesis, because iodide is no longer inhibitory at $10^{-7}$ M, while $T_3$ and $T_4$ were used at concentrations of $10^{-6}$ M (Pisarev et al., 1976; Kleiman de Pisarev et al., 1978; and the present data).

The inhibitory action of iodine on the thyroid affects other parameters besides synthesis of protein and RNA (Sherwin and Tong, 1975; Pisarev et al., 1976). Cyclic AMP formation is also decreased by iodine (Van Sande and Dumont, 1973; Rapoport et al., 1975; Yu et al., 1976; Sherwin, 1978), and the effect of iodine on the thyroid is mediated by an intracellular and organic iodo compound (Burke, 1970; Van Sande and Dumont, 1973; Pisarev and Aiello, 1976; Pisarev et al., 1976; Rapoport et al., 1976; Sherwin and Tong, 1976). Moreover, $T_3$ and $T_4$ have a direct inhibitory action on the thyroid (Pisarev et al., 1976; Friedman et al., 1977). However, because iodothyronine dehalogenase is important in the rat thyroid (Haibach, 1971; Green, 1978) a conversion of the iodide produced from this process into some other iodo compound could not be excluded. The present studies provide the first strong evidence to support the notion that, under conditions where RNA and protein synthesis are inhibited by $T_3$ and $T_4$, no significant dehalogenation occurs. Moreover, the demonstration that these compounds can still strongly inhibit RNA synthesis in the presence of $10^{-3}$ M PTU or MMI supports this view.

The relationship between structure and biological action of various compounds was analyzed. Although the number of compounds is limited, some conclusions can be drawn. Iodine can be replaced by chlorine in the thyronine molecule without change in its inhibitory potency. Similar results are obtained when the α-amino group is replaced by an acetic or propionic chain. However, when a formic chain is placed in that position there is a sharp decrease in its inhibitory action. It is likely that, among other factors, the length of the chain bears a relation to its biological activity. There was a close parallelism between our results with a system "in vitro", and those obtained by Money et al. (1959) when the inhibitory action on $^{131}I$ uptake was studied in the rat in vivo. Diiodothyronine and its isopropyl derivative were devoid of action, while addition of an isopropyl chain to $T_3$ failed to alter its inhibitory effect. In agreement with the results in vivo reported by Comite et al. (1978) with the goiter-preventing assay in the rat, we also found that DIMIT is a very potent inhibitor of RNA synthesis, whereas the effect of DISBT was rather negligible.

In summary, we have confirmed our previous results showing that $T_3$ and $T_4$, have a direct effect on the thyroid in vitro, independent of pituitary TSH, and that $T_3$ enters into the thyroid cell and is not significantly metabolized under conditions where it inhibits protein and RNA synthesis. Moreover, the action of $T_3$ and $T_4$ occurred even when iodide organification was blocked. Although these findings

strongly support the hypothesis that iodothyronines may play a role in thyroid autoregulation, further studies will be necessary before we can reach a conclusion on this important topic.

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