ABSORPTION OF THYROTROPIN-RELEASING HORMONE AFTER ORAL ADMINISTRATION OF TRH TARTRATE MONOHYDRATE IN THE RAT, DOG AND HUMAN

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Quantitative blood levels of thyrotropin-releasing hormone (TRH) were determined by a sensitive and specific radioimmunoassay after oral administration or intravenous injection of thyrotropin-releasing hormone tartrate monohydrate (TRH-T) in the rat, dog and human. A pharmacokinetic analysis after intravenous injection of the drug revealed biphasic elimination of the whole blood concentration following a two-compartment open model with a half-life in α-phase of 2.6 min and β-phase of 4.6 min in the rat (dose: 500 µg/kg); a half-life in α-phase of 3.2 min and β-phase of 18.1 min in the beagle-dog (dose: 146 µg/dog); a half-life in α-phase of 4.0 min and β-phase of 20.4 min in the human (dose: 730 µg/human).

The absolute bioavailability of TRH after oral administration of TRH-T solution in 24 h fasting rats were 1.5, 0.4, and 0.2% at 29.2, 146, and 730 mg/kg dosing levels, respectively (e.g. 20, 100, 500 mg/kg of TRH) compared with i.v. injection (dose: 500 µg/kg). In beagle-dogs, they were 12.6, 9.8, 5.6, and 3.5% at 292, 146, 29.2, and 146 mg/dog dosing levels, respectively (e.g. 2, 10, 20, and 100 mg/dog of TRH) compared with i.v. injection (dose: 146 µg/dog). Those of after meal in beagle-dogs were 6.0 and 2.3% at 292 and 29.2 mg/dog dosing levels (e.g. 2, and 20 mg/dog of TRH). Thus, TRH absorption showed apparent saturation and was decreased by food ingestion. The absolute bioavailability in the humans, who were administered 11.7 mg TRH-T (2.92 mg/tablet × four, e.g. 8 mg of TRH) two hours after meal, was 2.0% on the average, and thyroid stimulating hormone levels were significantly increased by oral administration of TRH-T tablets.

**Keywords**—thyrotropin-releasing hormone; thyrotropin-releasing hormone tartrate; radioimmunoassay; oral administration; availability; saturation; thyroid stimulating hormone

INTRODUCTION

In a previous paper,1) we investigated a specific radioimmunoassay for the measurement of thyrotropin-releasing hormone (TRH) in buffer and whole blood, which was sensitive enough to detect 20 pg of TRH.

The administration of TRH in clinical studies has been almost always by intravenous injection,2,3) while some investigators have reported that TRH enhanced thyroid stimulating hormone release when administered orally in mice and also man.4–6) These results suggested that TRH was absorbed from the gastrointestinal tract. If TRH is effective for the patients even by the oral administration, it is very convenient for them.

In the present paper, the uptake of TRH was directly proved by determining the blood concentration using the newly developed radioimmunoassay. In addition, the fundamental pharmacokinetic parameters of TRH were assessed
and the absolute bioavailability of the drug after oral administration was determined in the rat, beagle-dog and human.

MATERIALS AND METHODS

Animals — Experimental animals used in this study were male Sprague-Dawley (JCL: SD, SPF) rats weighing 300—360 g, and male beagle-dogs weighing 9.5—10 kg.

Subjects — Five subjects, two females and three males ranging in age from 18 to 66 from whom we had obtained informed consent participated in this study, were inpatients of Neurosurgical Department at Kyoto University Hospital, with normal TRH and thyroid stimulating hormone (TSH) levels.

Materials — TRH-T (L-pyroglutamyl-L-histidyl-L-prolinamide-L-tartrate monohydrate) used was manufactured by Takeda Chemical Ind. 125I-TRH (specific activity: 140 μCi/μg), anti-TRH serum, goat anti-rabbit γ-globulin serum, and normal rabbit serum were described previously.1) Also, anti-TRH serum3) which was kindly supplied by Dr. N. Nihei in Hamamatsu University School of Medicine was used in the absorption study in the human. TSH kit was purchased from Daiichi Radioisotope Lab. All other materials and solvents were of analytical reagent grade and used without further purification. The TRH-T tablet used for the human studies was 6.5 mm in diameter, and contained 2.92 mg of TRH-T (equivalent 2 mg of TRH).

Radioimmunoassay — Radioimmunoassay of TRH was performed by the procedure described previously.1) Five to thirty times volume of methanol (MeOH) compared with the volume of blood sample was used for a TRH degrading enzyme inhibitor and an extracting solvent in all assays. To investigate the existence of any other immunoreactive substances than TRH in blood after intravenous injection or oral administration of TRH, the thin-layer chromatography (TLC) experiments were examined. A stepwise procedure was described previously.1) Two developing solvent systems were chosen. (system 1; CHCl3 : MeOH : NH4OH = 6 : 4 : 1, and system 2; BuOH : EtOH : H2O = 1 : 1 : 1) The silica layer between Rf 0.45 and 0.55 (system 1) or Rf 0.32 and 0.38 (system 2) was scraped; Rf values of TRH were 0.50 and 0.35, respectively. Radioimmunoassay of TSH was performed according to the procedure described in the direction in the TSH kit.

Rat Experiments — Rats were fasted 24 h prior to the oral and intravenous administration with free access to water. Various doses of TRH-T solution were administered orally or intravenously to groups of 3—5 rats each. One hundred micro liters of whole blood samples treated with heparin were taken periodically from the tail vein and poured into a disposable test tube containing 3 ml of MeOH; after extracting and evaporating, the radioimmunoassay of TRH was performed. The time-course of TRH blood levels was fitted to a two-compartment open model by a least squares regression analysis.

Dog Experiments — Beagle-dogs were fasted 24 h prior to the oral and intravenous administration with free access to water. Various doses of TRH-T solution were administered orally or intravenously to groups of 5 dogs each. An 1.5 ml of a heparinized venous blood sample from an ante-cubital vein was quickly poured into 7 ml of MeOH. After these samples were extracted and dried, the radioimmunoassay of TRH was performed on them. The time-course of TRH blood levels after intravenous injection was fitted to a two-compartment open model by a least squares regression analysis.

Human Experiments — Four TRH-T tablets (each containing 2.92 mg of TRH-T; e.q. 2 mg of TRH) were administered to the subjects orally or 730 μg of TRH-T saline solution was injected intravenously two hours after lunch. A 2.5 ml of a venous whole blood sample from an ante-cubital vein was quickly poured periodically into a disposable test tube containing 7 ml of MeOH to inactivate the TRH degrading enzyme. After three extractions with 7 ml of MeOH (total 21 ml) and evaporations with a stream of dried N2 gas, the residue was dissolved into distilled water and the radioimmunoassay of TRH was per-
Absorption of TRH

FIG. 1. The Identity between the Direct Measurement of TRH in Blood and the Measurement of TRH in Blood after TLC Treatment by Radioimmunoassay in Rats

a: TLC solvent system 1, (CHCl₃: MeOH: NH₄OH = 6:4:1)
\[ \gamma = 0.995, y = 1.02x + 4.07 \]
b: TLC solvent system 2, (BuOH: EtOH: H₂O = 1:1:1)
\[ \gamma = 0.999, y = 0.99x + 2.75 \]
○: after i.v. injection (dose: 500 µg/kg of TRH-T).
●: after oral administration (dose: 146 mg/kg of TRH-T).
The curves were drawn by the least squares regression analysis.


a: TLC solvent system 1, \[ \gamma = 0.997, y = 0.96x + 3.62 \]
b: TLC solvent system 2, \[ \gamma = 0.996, y = 0.96x + 1.69 \]
○: after i.v. injection (dose: 146 µg/dog of TRH-T).
●: after oral administration (dose: 29.2 mg/dog of TRH-T).
The curves were drawn by the least squares regression analysis.
FIG. 3. The Identity between the Direct Measurement of TRH in Blood and the Measurement of TRH in
Blood after TLC Treatment by Radioimmunoassay in Humans

a: TLC solvent system 1, $\gamma = 0.998, y = 0.90x + 0.13$

b: TLC solvent system 2, $\gamma = 0.998, y = 0.88x + 0.09$

○: after i.v. injection (dose: 730 μg/human of TRH-T).
●: after oral administration (dose: 11.7mg/human of TRH-T).
The curves were drawn by the least squares regression analysis.

FIG. 4. Blood Levels of TRH after i.v. Injection of
TRH-T in the Rat

Dose: ○0.2 mg/kg, ○ 0.5 mg/kg, ● 5 mg/kg, ○25 mg/kg.

Each point represents the mean and vertical bar indicates S.E. (n=3).
The curves were drawn by optimum parameters calculated by the least squares regression analysis.

formed. The time-course of TRH blood levels after intravenous injection was fitted to a two-
compartment open model by a least squares regression analysis. In addition, a 2.5 ml of
heparinized venous blood sample was collected from an ante-cubital vein at each period, and
centrifuged at 3000 rpm as quickly as possible; 1 ml of serum was obtained and the radioim-
munoassay of TSH was performed.

RESULTS AND DISCUSSION

To investigate the existence of any other immunoreactive substances than TRH in blood
after intravenous or oral administration of TRH, the direct measurement of TRH in blood by
radioimmunoassay and the measurement of TRH by radioimmunoassay after TLC treatment were
compared. The results are presented in Fig. 1 (rats) Fig. 2 (beagle-dogs), and Fig. 3 (humans). It
was found from these results that there were almost no other immunoreactive substances than
TRH in blood after intravenous injection or oral administration of TRH.
TABLE I. Least Squares Estimates of Parameters$^a)$ of Two-Compartment Open Model for Blood TRH Concentration Curve after i.v. Injection of TRH-T in the Rat

<table>
<thead>
<tr>
<th>Parameter$^a)$ estimated</th>
<th>0.2</th>
<th>0.5</th>
<th>5.0</th>
<th>25.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$ (µg/ml)</td>
<td>0.17</td>
<td>1.20</td>
<td>4.50</td>
<td>256.0</td>
</tr>
<tr>
<td>$B$ (µg/ml)</td>
<td>0.13</td>
<td>0.95</td>
<td>3.50</td>
<td>54.0</td>
</tr>
<tr>
<td>$\alpha$ (h$^{-1}$)</td>
<td>26.5</td>
<td>25.8</td>
<td>27.7</td>
<td>16.2</td>
</tr>
<tr>
<td>$\beta$ (h$^{-1}$)</td>
<td>6.0</td>
<td>9.0</td>
<td>6.4</td>
<td>2.2</td>
</tr>
<tr>
<td>$K_{12}$ (h$^{-1}$)</td>
<td>6.9</td>
<td>4.2</td>
<td>7.1</td>
<td>6.2</td>
</tr>
<tr>
<td>$K_{21}$ (h$^{-1}$)</td>
<td>14.9</td>
<td>16.4</td>
<td>15.7</td>
<td>4.6</td>
</tr>
<tr>
<td>$K_{el}$ (h$^{-1}$)</td>
<td>10.7</td>
<td>14.1</td>
<td>11.3</td>
<td>7.6</td>
</tr>
<tr>
<td>$V_1$ (ml)</td>
<td>610</td>
<td>250</td>
<td>625</td>
<td>80</td>
</tr>
<tr>
<td>Half life (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\alpha$-Phase</td>
<td>2.7</td>
<td>2.6</td>
<td>3.1</td>
<td>3.3</td>
</tr>
<tr>
<td>$\beta$-Phase</td>
<td>6.9</td>
<td>4.6</td>
<td>6.5</td>
<td>19.2</td>
</tr>
</tbody>
</table>

*a) Parameters are shown as TRH.

b) Model is given in the chart below.

Chart for two-compartment open model

\[
C_1 \xrightarrow{K_{12}} C_{II} \xleftarrow{K_{21}} C_1 \xrightarrow{K_{el}} C_1 = Ae^{-\alpha t} + Be^{-\beta t}
\]

$C_1$: concentration in central compartment

$i$: time

TABLE II. AUC and Absolute Bioavailability after Oral Administration of TRH-T Solution in the Rat (24 h Fasting)

<table>
<thead>
<tr>
<th>TRH-T Dose (mg/kg)</th>
<th>$n$</th>
<th>$AUC(0-2)$ (ng/h/ml)</th>
<th>Absolute$^a)$ bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.2</td>
<td>4</td>
<td>132.2 ± 25.3</td>
<td>1.48</td>
</tr>
<tr>
<td>146</td>
<td>4</td>
<td>175.8 ± 13.0</td>
<td>0.39</td>
</tr>
<tr>
<td>365</td>
<td>4</td>
<td>263.6 ± 20.8</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Each value of AUC represents the mean ± S.E.

*a) Absolute bioavailability = $AUC_{(p,o.)} \times$ dose ratio / $AUC_{(i.v., dose 0.5 mg/kg)} \times 100$

The whole blood levels of TRH in the rat at various times after intravenous administration of 100 µl of TRH-T solution at four dose levels, 0.2, 0.5, 5 and 25 mg/kg (e.g. 0.14, 0.34, 3.42, and 17.1 mg/kg of TRH) are shown in Fig. 4. The pharmacokinetic parameters were calculated by the least squares regression analysis and presented in Table I. TRH disappeared from the blood very rapidly in the $\alpha$-phase and somewhat slowly in the $\beta$-
phase. The elimination rate constant \((K_e)\) of TRH from the blood was smaller in the highest dose of TRH-T (25 mg/kg) than in the lower doses (0.2, 0.5, 5 mg/kg). This might be due to the saturation of urinary excretion or TRH degrading enzyme activity in the blood.\(^{14,15}\) Though, in the dose of less than 5 mg/kg, the linear relation between the dose and \(AUC\) \((0 \to \infty)\) was observed. The whole blood levels of TRH in the rat at various times after oral administration of 0.2 ml of TRH-T saline solution at three dose levels, 29.2, 146, and 365 mg/kg (e.g., 20, 100, and 250 mg/kg of TRH) were determined. The area under the blood concentration curve \((AUC)\) calculated by the trapezoidal rule is shown in Table II, and the absolute bioavailability was calculated against the \(AUC\) obtained in intravenous injection (dose: 500 \(\mu g/kg\)). The absolute bioavailability was significantly influenced by dose. Increasing the dose from 29.2 to 365 mg/kg (12.5 times) increased the \(AUC\) by only approximately two times. Consequently the absolute bioavailability decreased from 1.5 to 0.2% when the dose increased from 29.2 to 365 mg/kg. Thus, TRH absorption from the gastrointestinal tract showed apparent saturation in the rat.

### TABLE III. Least Squares Estimates of Parameters \(^{b)}\) of Two-Compartment Open Model for Blood TRH Concentration Curve after i.v. Injection of TRH-T in the Beagle-dog

| Parameter \(^{a)}\) estimated | Dose (\(\mu g/dog\)) |
|---|---|---|
| \(A\) (ng/ml) | 17.0 | 56.5 | 144.4 |
| \(B\) (ng/ml) | 39.0 | 53.7 | 186.8 |
| \(\alpha\) (h\(^{-1}\)) | 12.7 | 11.2 | 18.2 |
| \(\beta\) (h\(^{-1}\)) | 2.3 | 1.8 | 1.4 |
| \(K_{12}\) (h\(^{-1}\)) | 6.38 | 3.46 | 2.40 |
| \(K_{21}\) (h\(^{-1}\)) | 10.87 | 6.38 | 9.56 |
| \(K_{el}\) (h\(^{-1}\)) | 2.34 | 3.16 | 3.06 |
| \(V_1\) (ml) | 2.61 | 3.31 | 2.20 |
| Half life (min) | | | |
| \(\alpha\)-Phase | 10.5 | 7.9 | 8.3 |
| \(\beta\)-Phase | 18.1 | 23.1 | 29.7 |

\(^{a)}\) Parameters are shown as TRH.

\(^{b)}\) Model is given in the chart as shown in Table I.
The whole blood levels of TRH in the beagle-dog at various times after intravenous injection of 1 ml of TRH-T saline solution at three dose levels, 146, 365, and 730 μg/dog (e.q. 100, 250, and 500 μg/dog of TRH, respectively) are shown in Fig. 5. The pharmacokinetic parameters calculated by the least squares regression analysis are presented in Table III. The elimination patterns also showed two-compartment open model, but the half-life in the α-phase and β-phase were longer than those of the rat. This might be due to a species difference in TRH degrading enzyme activity. The linear relation between the dose and $AUC(0\rightarrow\infty)$ was also observed in the beagle-dog.

The whole blood levels of TRH in the beagle-dog at various times after oral administration of 50 ml of TRH-T solution at four dose levels, 2.92, 14.6, 29.2, and 146 mg/dog (e.q. 2, 10, 20, and 100 mg/dog of TRH, respectively) are shown in Fig. 6. The $AUC$ obtained by the trapezoidal rule and the relative bioavailability calculated against the $AUC$ obtained in the intravenous injection (dose: 730 μg/dog), are shown in Table IV. The absolute bioavailability was significantly influenced by dose as it was in the rat. Increasing the dose from 2.92 to 146 mg/dog (50 times) increased the $AUC$ by only approximately 10 times, and consequently the absolute bioavailability decreased from 12.6 to 3.5%. Thus, TRH absorption from the gastrointestinal tract showed apparent saturation in the beagle-dog as it was in the rat.

Fig. 7 shows the mean whole blood levels of TRH after oral administration of TRH-T at two dose levels of 2.92 and 29.2 mg/dog (e.q. 2, and 20 mg/dog of TRH) immediately after meal or in the fasting state. The whole blood levels after food ingestion were approximately half of those in the fasting state. The absolute bioavailability in the

![Figure 6. Blood Levels of TRH after Oral Administration of TRH-T Solution in the Beagle-dog (after 24 h Fasting)](image)

**TABLE IV. AUC and Absolute Bioavailability after Oral Administration of TRH-T Solution in the Beagle-dog (24 h Fasting)**

<table>
<thead>
<tr>
<th>TRH-T Dose (mg/kg)</th>
<th>$n$</th>
<th>$AUC(0\rightarrow6)$ (ng h/ml)</th>
<th>Absolute$^a$ bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.92</td>
<td>5</td>
<td>$54.6\pm8.8$</td>
<td>12.6</td>
</tr>
<tr>
<td>14.6</td>
<td>5</td>
<td>$211.6\pm4.0$</td>
<td>9.8</td>
</tr>
<tr>
<td>29.2</td>
<td>5</td>
<td>$241.4\pm16.4$</td>
<td>5.6</td>
</tr>
<tr>
<td>146</td>
<td>5</td>
<td>$765.8\pm94.0$</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Each value of $AUC$ represents the mean±S.E.

$^a$ Absolute bioavailability = $\frac{AUC(p.o.) \times \text{dose ratio}}{AUC(i.v., \text{dose 730 μg/dog}) \times 100}$
fasting state were 12.6 and 5.6% (dose 292 and 29.2 mg/dog), while those after food ingestion were 6.0 and 2.3%, respectively. These results indicate that the bioavailability of TRH-T is decreased markedly by food ingestion. Oligopeptides are reported to be absorbed from the gastrointestinal by some specific mechanisms, and absorption sites are limited in the small intestine. The uptake of some oligopeptides is reported to be inhibited by other oligopeptides, and this is due to the competition between these peptides at the absorption site. The absorption of some β-lactam antibiotics is inhibited by oligopeptides. In our studies, the absorption of TRH, a kind of oligopeptides, was observed to be reduced by food ingestion. This might be due to some oligopeptides which originated from food. However, this will be the subject of further studies.

The blood levels of TRH in the human at various times after intravenous injection of 1 ml of TRH-T solution (TRH-T 730 μg, e.q. 500 μg of TRH) are shown in Fig. 8. The pharmacokinetic parameters were calculated by the least squares regression analysis and presented in Table V. The elimination patterns also showed two-compartment open model and the value of a $t_{1/2}$ in the β-phase was almost the same order as that of the beagle-dog and slower than that of the rat. This phenomenon agrees with the degradation rate of TRH in vitro in rat, beagle-dog, and human blood (Fig. 9). The whole blood levels of TRH after oral administration of 11.7 mg of TRH-T (e.q. 8 mg of TRH; four tablets, each containing 2.92 mg of TRH-T) are shown in Fig. 7.

**FIG. 7. Blood Levels of TRH after Oral Administration of TRH-T Solution in the Beagle-dog after 24 h Fasting or after Meal.**
- O Dose: 29.2 mg/dog; after 24 h fasting,
- ● Dose: 29.2 mg/dog; after meal,
- ○ Dose: 2.92 mg/dog; after 24 h fasting,
- □ Dose: 2.92 mg/dog; after meal.
Each point represents the mean and vertical bar indicates S.E. (n=5).

**FIG. 8. Blood Levels of TRH after i.v. Injection of TRH-T in the Human**
- Dose: 730 μg/human.
- Each point represents the mean and vertical bar indicates S.E. (n=5).
- The curves were drawn by optimum parameters calculated by the least squares regression analysis.
TABLE V. Least Squares Estimates of Parameters of Two-Compartment Open Model for Blood TRH Concentration Curve after i.v. Injection of TRH-T in the Human

<table>
<thead>
<tr>
<th>Parameter °</th>
<th>Dose estimated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ng/ml)</td>
<td>43.32</td>
</tr>
<tr>
<td>B (ng/ml)</td>
<td>5.31</td>
</tr>
<tr>
<td>α (h⁻¹)</td>
<td>10.44</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>2.04</td>
</tr>
<tr>
<td>K₁₂ (h⁻¹)</td>
<td>2.28</td>
</tr>
<tr>
<td>K₂₁ (h⁻¹)</td>
<td>2.94</td>
</tr>
<tr>
<td>Kₑ₁ (h⁻¹)</td>
<td>7.26</td>
</tr>
<tr>
<td>V₁ (ml)</td>
<td>15.0</td>
</tr>
<tr>
<td>Half life (min)</td>
<td>α-phase</td>
</tr>
<tr>
<td></td>
<td>β-phase</td>
</tr>
</tbody>
</table>

°) Parameters are shown as TRH.

b) Model is given in the chart as shown in Table I.

Fig. 10. The blood levels of TRH were increased after 0.5–1 h and peak levels of TRH were attained 3–4 h after the administration of TRH-T tablets; then the blood levels were decreased. The AUC was 2.13 ng h/ml when 11.7 mg of TRH-T was administered (calculated by the trapezoidal rule from 0–6 h data), and the absolute bioavailability was calculated against the AUC obtained in the intravenous injection (dose: TRH-T 730 µg); it was about 20%. This value would be almost identical to that of the beagle-dog following administration after meal.

TSH serum levels after oral administration of TRH-T tablets were also studied. The TSH kit can detect TSH serum levels as small as 0.5 µU. This sensitivity was good enough to analyze the endogenous TSH serum levels. The endogenous TSH serum level of the healthy man is about 2–10 µU.® The serum levels are shown in Fig. 11. The serum levels were significantly increased and peak levels were attained 2–3 h after administration of TRH-T tablets. Increased TSH levels (Δ TSH) were 7 µU on the average. Utiger

FIG. 9. Disappearance of TRH during Incubation with Blood at 37°C in Vitro

○ beagle-dog whole blood (spiked 14.6 ng TRH in 1 ml blood).
● human whole blood (spiked 14.6 ng TRH in 1 ml blood).
〇 rat whole blood (spiked 14.6 ng TRH in 1 ml blood).

FIG. 10. Blood Levels of TRH after Oral Administration of TRH-T Tablets in the Human

Dose: 11.7 mg/human.

Each point represents the mean and vertical bar indicates S.E. (n= 5).

The significant difference to the initial value is expressed with a) p<0.05 and b) p<0.01.
FIG. 11. **Plasma Levels of TSH after Oral Administration of TRH-T Tablets in the Human Dose: 11.7 mg/human.**

Each point represents the mean and vertical bar indicates S.E. (n= 5).

The significant difference to the initial value is expressed with a) p<0.05 and b) p<0.01.

reported that Δ TSH was about 7 μU after oral administration of 10 mg TRH solution, and our results were almost identical with his data.

Although some investigators suggested the uptake of TRH from the gastrointestinal tract by determining TSH levels after oral administration of TRH, there have been no reports that proved the uptake of TRH by determining the TRH blood or plasma levels. In our studies, the TRH blood levels after oral administration were determined by a sensitive radioimmunoassay, and the uptake of TRH from gastrointestinal tract was directly proved for the first time.

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Absorption of TRH
