Effects of intrathyroidal metabolism of thyroxine on thyroid hormone secretion: increased degradation of thyroxine in mouse thyroids stimulated chronically with thyrotophin

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Abstract. Mice were infused continuously with graded doses of bovine TSH (bTSH) and changes in plasma concentrations of bTSH and T₄ were measured. Then mice infused with 100 mU TSH per day were sacrificed on days 0, 1, 3 and 5 and their thyroids were excised to determine in vitro secretion of T₄, T₃ and rT₃ during 3 h of incubation. At the end of the incubation, thyroidal contents of T₄, T₃ and rT₃ were also determined after pronase digestion. Plasma bTSH levels were increased on day 1 to a level of 110 µU/ml and remained unchanged thereafter. Plasma T₄ concentrations increased approximately 2-fold on day 1, but decreased to initial levels on days 3 and 5. Changes in T₄ secretion in vitro paralleled those in plasma T₄ concentrations; T₄ secretion increased 2-fold on day 1, and decreased to the pre-TSH levels on days 3 and 5. In contrast, T₃ secretion increased throughout the experimental period. The T₃/T₄ ratio in thyroidal secretion in vitro was the same as that in thyroidal contents on days 0 and 1 of TSH infusion, but the former was significantly greater than the latter on days 3 and 5. PTU (5.9 × 10⁻⁵ M), a known inhibitor of T₄ deiodination, added to the incubation media did not affect T₄ secretion on days 0 and 1, but increased T₄ secretion on days 3 and 5 to the level of day 1, but did not affect T₃ secretion. In the presence of PTU, the T₃/T₄ ratio in thyroidal secretion did not differ from that in thyroidal contents throughout the experimental period.

Secretion of rT₃ was increased on days 3 and 5 and PTU augmented this increase. Thyroidal content of rT₃ was much increased on days 3 and 5. In contrast, methimazole (10⁻³ M), which does not inhibit in vitro T₄ deiodination, added to the incubation media did not affect T₄, T₃ and rT₃ secretion in vitro. When [¹²₅I]T₄ was added to the media and incubated with mouse thyroid, no labelled products of T₄-deiodination were observed to appear in the media even in mice infused with TSH for 5 days. These results suggest that intrathyroidal metabolism of T₄ has physiological significance in controlling thyroid hormone secretion at least in TSH-stimulated thyroids.

Thyroid hormone metabolism has been extensively studied by many investigators in various extrathyroidal tissues (Oppenheimer & Surks 1971; Middlesworth 1974; Chopra et al. 1978). Deiodination of T₄ in thyroid glands was also reported using thyroid lobes of rats (Haibach 1971; Green 1978) and cultured human thyroid cells (Bidey et al. 1976). Recently, 5'- or 5-deiodinating activity was observed in the particulate fraction of thyroids of rats (Erickson et al. 1981, 1982) and man (Ishii et al. 1981, 1982), and these activities were increased in TSH-stimulated thyroids in rats and in thyroids in patients with Graves' disease. However, there is little evidence that intrathyroidal metabolism of thyroid hormones plays a significant role in regulating their secretion in vivo. The present experiments were carried out to investigate whether such intrathyroidal metabolism affects hormone secretion in thyroids of mice stimulated chronically with TSH.
Material and Methods

Experiments were performed in male DDY mice (30–40 g body weight) fed with a regular diet. Bovine TSH (bTSH) was from Sigma Chemical Co., St. Louis, Mo, USA and pronase (10^6 tyrosine units/g) was from Kaken Science Co., Tokyo, Japan. Other reagents were purchased from commercial sources.

Continuous infusion of bTSH

A tail vein of the mouse was cannulated with a polyethylene tube (0.3 mm inner diameter) connected at the other end through a tuberculin needle to a 1 ml syringe mounted on an infusion pump (Showa Science Co., Tokyo, Japan). Saline was infused for more than 2 h to allow the mouse to become accustomed to these new conditions. With a fresh syringe, bTSH in saline containing 0.1% bovine serum albumin (BSA) was infused continuously at a rate of 1 ml/day for 1 to 5 days. Syringes were changed every 24 h.

In vitro thyroid hormone secretion

After infusion of TSH, mice were bled and killed by a cervical dislocation, and tracheae with adhering thyroids were excised. These were incubated each in a separate test tube (12 × 75 mm) in 0.25 ml of Krebs-Ringer bicarbonate buffer containing 0.2% BSA and 0.1% glucose. Following pre-incubation in a shaking water bath at 37°C under 95% O_2-5% CO_2 for 30 min, the tissue was transferred to fresh media, incubated for 3 h and then the thyroid lobes were removed from the trachea, weighed and frozen for determination of thyroidal hormone contents. The media were collected for analysis of T_4, T_3 and rT_3. In experiments studying effects of antithyroid drugs on thyroid hormone secretion in vitro, propylthiouracil (PTU, 5.9 × 10^{-5} M = 10 µg/ml) or methimazole (MMI, 10^{-3} M) was added to the incubation media.

Thyroid hormone contents

The thyroid homogenates were digested with pronase according to the method of Inoue & Taurog (1967) in rats. Briefly, each thyroid was homogenized in a glass homogenizer in 0.5 ml of cold Tris buffered saline (0.03 M Tris-HCl-0.11 M NaCl, pH 8.5) containing 0.02 M MMI. The homogenate was centrifuged at 1000 × g for 15 min at 4°C. A quarter ml of the buffer containing pronase (1.75 mg/tube) and then a drop of toluene was added to the supernate (0.25 ml). After anaerobic digestion at 37°C for 18 h, the iodothyronines were extracted with methanol:2 N ammonia (99:1). For measurements of T_4, T_3 and rT_3, the extract was evaporated to dryness and the residue was re-dissolved with 0.1 M sodium phosphate buffer (pH 7.4) containing 0.1% BSA. In mice, our previous study (Chiu et al. 1983) showed that homogenates of the thyroid pre-labelled with ^125I were digested satisfactorily with pronase.

Measurements

Plasma bTSH concentrations in bTSH-infused mice were measured by RIA developed in this laboratory. Purified bTSH and anti-bTSH antisera were kindly supplied by Dr. Rees Smith, Cardiff, UK. T_4 and T_3 in plasma, incubation media and pronase-digests were measured by specific RIAs (Gamma Coat T_4 and T_3, Clinical Assays, Cambridge, Mass, USA). Reverse T_3 was measured with RIA kits (Dainabot Radioisotope Lab., Matsudo, Chiba, Japan). In these RIAs, cross-reactivities of the antisera with other iodothyronines were as follows; 4.8% with T_3 and 1.0% with rT_3 for T_4 RIA, 0.21% with T_4 and < 0.01% with rT_3 for T_3 RIA, and 0.009% with T_4 and < 0.0001% with T_3 for rT_3 RIA, respectively. In vitro thyroidal secretion and thyroidal content of each iodothyronine were expressed as pmoles/mouse.

Degradation of[^125I]T_4 added to the incubation media

[^3,5^-125I]T_4 (80 µCi/ml; 698 µCi/µg) was obtained from Dainabot Radioisotope Lab. (Matsudo, Chiba, Japan) in 50% propylene glycol and purified by dialysis according to the method of Schussler & Plager (1967) with a modification by adding 1% BSA instead of human serum. The labelled T_4 was added to the media (0.1 µCi/tube) and incubated with mouse thyroids under the same conditions as described above.

Thin layer chromatography

After the incubation, iodoamino acids in the media were extracted with 2 vol of methanol:2 N ammonia (99:1) containing 10^{-4} M of unlabelled T_4, T_3 and rT_3 as carriers. The extract was concentrated by evaporation and an aliquot was applied to a silica gel plate for thin layer chromatography (Eastman Kodak Co., Rochester, NY, USA) and chromatographed by an ascending system in ethyl acetate:methanol:2 N ammonia (5:2:3) solvent (West et al. 1965). Inorganic iodide, T_4, T_3 and rT_3 could be separated satisfactorily in this system. The areas of the chromatogram corresponding to the bands on its radioautogram or to the bands of iodothyronine markers stained by diazotized sulphanilic acid were excised and counted by an automatic γ-counter. The degradation of[^125I]T_4 during incubation was determined by subtracting the value in tissue free incubation.

Statistical analysis

The significance of difference was determined by Student's t-test.

Results

Effects of bTSH infusion on plasma bTSH and T_4 concentrations

In the first series of experiments, mice were infused with graded doses (0–500 mU/day) of bTSH...
Effects of TSH infusion on in vitro T₄ and T₃ secretion

At the end of the 5-day infusion period, T₄ and T₃ secretion rates in vitro were determined (Fig. 2). T₄ secreted from thyroid lobes into the media was unchanged by infusion of TSH (20–500 mU/day) for 5 days, but T₃ secretion was increased with a dose of TSH 50 mU or more per day.

In the second series of experiments, mice were infused with 100 mU/day of TSH and sacrificed on days 0, 1, 3 and 5 of infusion to determine possible changes in rates of T₄ and T₃ secretion in vitro (Fig. 3, open columns). T₄ secretion was twice normal on day 1 but decreased to pre-TSH levels on days 3 and 5. On the other hand, T₃ secretion was 3 times normal on day 1 and remained high thereafter.

Fig. 1.
Plasma bTSH and T₄ concentrations in mice during a 5-day infusion of bTSH. Mice were infused with graded doses of bTSH for 5 days and were bled on days 0, 1, 3 and 5 of infusion. ND, plasma bTSH concentrations were not detectable (<10 μU/ml). Results shown are the means ± SE of values for 6 mice. One determination was made for each mouse.

for 5 days. The animals were bled on days 0, 1, 3 and 5 and plasma bTSH and T₄ concentrations were measured (Fig. 1). Plasma bTSH was detectable on day 1 in mice infused with 50 mU or more of TSH per day. In the mice which received 500 mU/day of TSH, plasma bTSH concentrations were remarkably higher than normal on day 1 (650 μU/ml) and then decreased gradually thereafter, while in those infused with 50 and 100 mU/day of TSH, plasma levels remained constant after day 1 (30 and 110 μU/ml). Plasma T₄ concentrations in mice infused with TSH more than 50 mU/day were significantly higher than normal on day 1, but decreased to normal control levels by day 5 in spite of high levels of plasma TSH.

Fig. 2.
Effects of graded doses of TSH infusion for 5 days on T₄ and T₃ secretion in vitro in mice. After the 5-day infusion of TSH, secretion of T₄ and T₃ in vitro was determined. Results shown are the means ± SE of values for 6 mice. One determination was made for each mouse. **P < 0.01 vs control (0 mU/day).
Effects of PTU on in vitro T_4 and T_3 secretion in TSH-infused mice

PTU added to the incubation media of thyroids of mice infused with 100 mU TSH per day did not affect T_4 secretion on days 0 and 1, but increased on days 3 and 5 to the level of day 1 (Fig. 3, shaded columns), thus preventing the decrease (from the high level of day 1) in T_4 secretion seen on days 3 and 5 in the absence of PTU. T_3 secretion was, however, not affected by PTU throughout the experimental period.

**Fig. 3.**

T_4 and T_3 secretion in vitro with and without PTU in the media. Mice were infused with 100 mU/day of TSH for 5 days. Thyroids were excised on days 0, 1, 3 and 5, and T_4 and T_3 secretion in vitro was determined with or without 5.9 x 10^-6 m PTU in the incubation media. Results shown are the means ± se of values for 5 mice. One determination was made for each mouse. **P < 0.01 between incubations with and without PTU. **P < 0.01; *P < 0.05 vs control (day 0).

**Effects of TSH infusion on thyroidal content of T_4 and T_3**

Changes in thyroidal content of T_4 and T_3 during TSH infusion are shown in Fig. 4. Thyroidal T_4 was decreased during TSH infusion, but T_3 was increased significantly only on day 5. PTU added to the incubation media had no effect on thyroidal hormone content at the end of the incubation period and data pertaining to the two groups (± PTU) were combined. Weights of thyroids were not changed on day 1 of TSH infusion, but increased about 2-fold on days 3 and 5.

**Fig. 4.**

T_4 and T_3 contents in thyroids. Mice were infused with 100 mU/day of TSH for 5 days and were sacrificed on days 0, 1, 3 and 5 of infusion. At the end of the incubation for measurements of thyroid hormone secretion in vitro, thyroidal contents of T_4 and T_3 were determined after pronase digestion. Results shown are the means ± se of values for 10 mice. One determination was made for each mouse. **P < 0.01; *P < 0.05 vs control (day 0).
Effects of PTU on T₃/T₄ ratio in in vitro secretion from thyroids of TSH-infused mice

Molar T₃/T₄ ratios in thyroidal secretion in the presence or absence of PTU and in thyroid glands were compared (Fig. 5). The data were taken from Figs. 3 and 4. T₃/T₄ in thyroids of mice infused with 100 mU TSH per day increased gradually from 0.1 to 0.2 during 5 days of TSH infusion. T₃/T₄ in thyroidal secretion was the same as that in thyroids on days 0 and 1 of infusion, but the former was significantly greater than the latter on days 3 and 5. In the presence of PTU in the incubation media, T₃/T₄ ratios in thyroidal secretion and in thyroids were the same throughout the experimental period.

Effects of TSH infusion on in vitro rT₃ secretion and on thyroidal rT₃

Reverse T₃ secretion in vitro was increased significantly on day 5 and PTU augmented rT₃ secretion on days 3 and 5 of infusion of 100 mU TSH per day (Fig. 6). Thyroidal rT₃ was increased 3-fold on day 3 and 6-fold on day 5.

Effects of MMI on in vitro hormone secretion from thyroids of TSH-infused mice

MMI (10⁻³ M) added to the incubation media had no significant effects on secretion of T₄, T₃ and rT₃ in vitro during 5 day infusion of TSH (Table 1).

Degradation of [¹²⁵I]T₄ added to the incubation media
The fate of [¹²⁵I]T₄ added to the incubation media

Fig. 6.
Reverse T₃ secretion in vitro with or without PTU in the media and rT₃ contents in thyroids during TSH infusion in mice. Mice were infused with 100 mU/day of TSH for 5 days. Thyroids were excised on days 0, 1, 3 and 5. Reverse T₃ secretion was determined with or without 5.9 x 10⁻⁵ M PTU in the media. After the incubation, rT₃ was determined in pronase hydrolysates of thyroids. Results shown are the means ± SE of values for 5 (secretion) or 10 (contents) mice. One determination was made for each mouse. * P < 0.05 between incubations with and without PTU. ** P < 0.01 vs control (day 0).
was incubation. By methanol values Mice infusion of 0, 1, 3 and 5 of infusion with or without 10^{-3} M MMI in the incubation media. Results shown are the means ± SE of values for 5 mice. One determination was made for each mouse. ** P < 0.01; * P < 0.05 vs control (day 0).

was studied (Table 2). Radioactivity was taken up in part by thyroid lobes (5–7%) at the end of the incubation. More than 95% of the radioactivity in methanol extracts of the media was detected as T4. By subtracting values in tissue free incubation, no radiolabelled products of deiodination of T4 (in-organic iodide, T3 and rT3) were observed in the media even after incubation with thyroids of TSH-infused mice, while, in experiment done in tandem, in vitro T4 secretion in mice infused with TSH for 5 days was increased by PTU in the same way as shown in Fig. 3.

### Table 1.
Effects of MMI in the media on T4, T3 and rT3 secretion in vitro in mice infused with TSH in vivo.

<table>
<thead>
<tr>
<th>Days of infusion</th>
<th>T4 secretion (pmoles/mouse)</th>
<th>T3 secretion (pmoles/mouse)</th>
<th>rT3 secretion (pmoles/mouse)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMI (−)</td>
<td>MMI (+)</td>
<td>MMI (−)</td>
</tr>
<tr>
<td>0</td>
<td>4.31 ± 0.32</td>
<td>4.73 ± 0.58</td>
<td>0.45 ± 0.05</td>
</tr>
<tr>
<td>1</td>
<td>10.58 ± 2.24*</td>
<td>7.42 ± 0.53*</td>
<td>1.40 ± 0.28**</td>
</tr>
<tr>
<td>3</td>
<td>4.15 ± 0.19</td>
<td>4.91 ± 0.69</td>
<td>1.81 ± 0.17**</td>
</tr>
<tr>
<td>5</td>
<td>4.31 ± 0.27</td>
<td>3.85 ± 0.05</td>
<td>1.34 ± 0.22**</td>
</tr>
</tbody>
</table>

Mice were infused with 100 mU/day of TSH and T4, T3 and rT3 secretion from excised thyroids was determined on days 0, 1, 3 and 5 of infusion with or without 10^{-3} M MMI in the incubation media. Results shown are the means ± SE of values for 5 mice. One determination was made for each mouse. ** P < 0.01; * P < 0.05 vs control (day 0).

### Table 2.
Degradation of [125I]T4 added to the incubation media.

<table>
<thead>
<tr>
<th></th>
<th>PTU in the media</th>
<th>Radioactivity in the media (%)</th>
<th>Radioactivity in thyroids (%)</th>
<th>T4 in extracts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue free¹</td>
<td>(−)</td>
<td>(100)</td>
<td>−</td>
<td>93.7</td>
</tr>
<tr>
<td>Saline-infused²</td>
<td>(−)</td>
<td>80.6</td>
<td>5.6</td>
<td>95.2</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>80.1</td>
<td>5.4</td>
<td>95.3</td>
</tr>
<tr>
<td>TSH-infused³</td>
<td>(−)</td>
<td>76.9</td>
<td>7.1</td>
<td>96.2</td>
</tr>
<tr>
<td></td>
<td>(+)</td>
<td>75.3</td>
<td>6.8</td>
<td>95.4</td>
</tr>
</tbody>
</table>

Mouse thyroids were incubated in vitro for 3 h with [125I]T4 with or without PTU (5.9 × 10^{-5} m) in the media. After incubation, iodoamino acids in the media were extracted with methanol-2 N ammonia and analyzed by thin layer chromatography (see Material and Methods). About 6% loss of label in going from media to methanol-extracts was observed in all groups including 'tissue free'. Data are the means of duplicate determinations.

¹ Labelled T4 was incubated without mouse thyroids.
² Mice were infused with saline for 5 days as normal control.
³ Mice were infused with 100 mU TSH per day for 5 days.
⁴ Per cent radioactivity in the media at the end of the incubation.
⁵ Per cent radioactivity in the thyroid lobes at the end of the incubation. Residual radioactivity was found in surrounding tissues.
⁶ Per cent radioactivity of band of T4 on the thin layer chromatogram.

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Discussion

Chiu et al. (1983) have previously reported that plasma T₄ concentrations increased only transiently in mice even if a large injected dose of TSH was repeated. In the present study, this effect was also observed in TSH-infused mice. Several explanations are possible. First, infused TSH may be inactivated by production of the antibody against bTSH. However, plasma bTSH concentrations measured by RIA were elevated and remained so during 5 days of infusion of the highest levels of infused TSH. Second, the decrease in the transiently high plasma T₄ may be attributable to an actual decreased thyroidal secretion of the hormone. Third, increase in clearance of T₄ in extrathyroidal tissues is another possibility. The clearance rate of T₄ in blood is increased in patients with thyrotoxicosis (Sterling & Chodos 1956) and in thyrotoxic rats (Cullen et al. 1973).

The present study examined the second possibility by measuring in vitro secretion of T₄ after TSH stimulation. In mice infused chronically with TSH, increase in in vitro thyroidal secretion of T₄ was transient. In vitro release of thyroid hormones from excised thyroids may not reflect in vivo secretion. However, the changes in thyroidal secretion of T₄ measured here in vitro are consistent with those found in plasma levels of the hormone. As for T₃, plasma concentration of the hormone determined at the time of sacrifice was significantly higher than the initial level after 5 day infusion of TSH as was in vitro T₃ secretion (data are not shown). Moreover, it has recently been demonstrated that TSH added to the incubation media increased both free intrathyroidal and released thyroid hormones proportionally (Kubota et al. 1982). These results suggest that the changes in thyroid hormone secretion measured in vitro reflect similar changes in in vivo secretion rates indicating that the decrease in thyroidal secretion of T₄ is one of the causes for the decrease in plasma T₄ concentration.

Although refractoriness to stimulation by TSH of thyroid hormone synthesis and secretion has been described (Field et al. 1979), our previous report showed that refractoriness to TSH is not the cause of the decrease after the initial rise in plasma T₄ concentrations (Chiu et al. 1983). Furthermore, the present study shows that T₃ secretion in vitro was continuously increased by infusion of TSH for 5 days.

T₃ secretion in vitro was higher than normal throughout the 5 day period of TSH infusion in contrast to that of T₄, and the T₃/T₄ ratio in thyroidal secretion was significantly greater than that in the thyroids on days 3 and 5. Since the thyroidal T₃/T₄ ratio is determined principally by the ratio of these amino acids in thyroglobulin, the discrepancy in this ratio in secreted vs thyroidal hormone suggests that either preferential release of T₃ from thyroglobulin and/or selective degradation of T₄ occur in the gland. With regard to the former, heterogeneous metabolism of thyroid iodine pools (Schneider 1964) might lead to preferential hydrolysis of a small pool of T₃-rich thyroglobulin with a higher T₃/T₄ ratio than would be expected on the basis of the average T₃/T₄ determined for total thyroidal thyroglobulin. The results of the experiments suggest that TSH-stimulated deiodination of T₄ to T₃ in the thyroid was at least partly responsible for the high T₃/T₄ ratio in the secreted material.

In the present study, a large increase in thyroidal rT₃ was observed in mice infused with TSH for 3 or 5 days. In control mice, percentage of rT₃ in total thyroidal iodothyronines was very similar to that in dogs determined by RIA (Laurberg 1978a). Taurog et al. (1976) demonstrated that, when compared with T₄, more thyroidal rT₃ was formed in rats with lower iodine intake. It is not clear at present why rT₃ increases in chronically stimulated thyroids in mice, but it might be possible that rT₃ could be increased in chronically stimulated thyroids.

Thus, PTU present in the incubated media in concentrations that inhibit the conversion of T₄ to T₃ in rat liver homogenates (Chopra 1977) and in a particulate fraction of thyroids in rats (Erickson et al. 1981) and man (Ishii et al. 1981) prevented the decrease in T₄ secreted in vitro on days 3 and 5 of the in vivo TSH infusion after the initial rise on day 1 causing a significant increase in secreted T₃/T₄ over the control value on days 3 and 5 and over thyroidal T₃/T₄. MMI which does not inhibit hepatic and thyroidal deiodinations was without effect. Our study with addition of [¹²⁵I]T₄ to the incubation media appears to indicate that deiodination of T₄ re-entered to thyroids from the media described by Green (1978), if any, does not affect secretion rates of thyroid hormones measured in vitro under the present experimental conditions, and that the effect of PTU on in vitro secretion of T₄ on days 3 and 5 of TSH infusion is mainly due
to inhibition of the deiodination of T4 prior to release of the hormone from the gland.

In perfused canine thyroids, PTU in the perfusate decrease secretion of T3 and rT3 without increase in T4 secretion (Laurberg 1978b). However, in our results, the increase in T4 secretion in the presence of PTU was not accompanied by a decrease in T3 and rT3 secretion. TSH-stimulated thyroids were used in our studies, which may explain the difference of the effect of PTU. PTU increased rT3 secretion in vitro on days 3 and 5 of TSH infusion, probably because it inhibited deiodination of rT3 in addition to that of T4. In Graves’ thyroid tissue which is presumed to be chronically stimulated, the sequential deiodinations of T4 enhanced and PTU inhibits all steps of the metabolism (Ishii et al. 1982).

Gerber et al. (1981) demonstrated that when organic binding of iodine was severely depressed by NaClO4, the parital resistance of endocytosis to chronic TSH stimulation in rats was abolished and T4 release was increased. However, our results indicate that both 1 mM MMI and 10 mM NaClO4 (unpublished data) have failed to reproduce the effect of PTU. In rat thyroid homogenates, T4 degradation mediated by thyroid peroxidase was demonstrated (Dawber et al. 1971) and the degradation was blocked by both MMI and PTU. However, a lack of effect of MMI on T4 secretion suggest that the peroxidatic degradation of T4 is unlikely in our system.

Our results suggest that PTU augments T4 secretion from chronically TSH-stimulated thyroids because it is an inhibitor of monodeiodination of iodothyronines. The results indicate further that intrathyroidal metabolism of T4 has physiological significance in controlling thyroid hormone secretion, at least in TSH-stimulated thyroids.

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