Cyclic Nucleotide Phosphodiesterases and Thyroid Hormones*

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SUMMARY

Evidence is presented that modulation of the maximum velocity of a particulate low $K_m$ cyclic adenosine 3':5'-monophosphate (cyclic AMP) phosphodiesterase by thyroid hormones is one mechanism for the regulation of the responsiveness of rat epididymal adipocytes to lipolytic agents such as epinephrine and glucagon. Fat cells of propylthiouracil-induced hypothyroid rats are unresponsive to lipolytic agents and the $V_{max}$ of particulate low $K_m$ cyclic AMP phosphodiesterase of these cells is elevated above normal. In vivo treatment of hypothyroid rats with triiodothyronine restores to control values both the lipolytic response of the fat cells to epinephrine and the $V_{max}$ of the particulate bound low $K_m$ cyclic AMP phosphodiesterase. No similar correlation is found with the soluble high $K_m$ cyclic AMP phosphodiesterase. The phosphodiesterases of fat cells from normal and hypothyroid rats respond identically in vitro to propylthiouracil, triiodothyronine, methylisobutylxanthine, or theophylline, although the particulate low $K_m$ cyclic AMP phosphodiesterase is inhibited to a greater extent than soluble cyclic guanosine 3':5'-monophosphate phosphodiesterase activity.

Protein kinase of fat cells from hypothyroid rats can be stimulated by cyclic AMP to the same total activity as observed in fat cells of normal rats. However, less of the protein kinase in fat cells from hypothyroid rats was in the cyclic AMP-independent form. This shift in the equilibrium of protein kinase forms is consistent with an increased activity of low $K_m$ cyclic AMP phosphodiesterase and probably results from a lowering of the lipolytically significant pool of cyclic AMP.

Several effects of catecholamines are dependent on thyroid status (1). Dependency on thyroid hormone of catecholamine-stimulated lipolysis in epididymal adipocytes has been correlated with cyclic nucleotide metabolism (2–4). Our previous studies suggested modulation of the low $K_m$ particulate bound cyclic

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† The abbreviations used are: cyclic AMP, cAMP, adenosine 3':5'-monophosphate; cyclic GMP, guanosine 3':5'-monophosphate; dibutyryl cyclic AMP, N4,O9'-dibutyladenosine 3':5'-monophosphate.
In accordance with previous findings (4), lipolysis of fat cells from propylthiouracil-treated rats was not stimulated by epinephrine (Fig. 1) or by glucagon. Dibutyl cyclic AMP did stimulate lipolysis in these cells but not as effectively as in fat cells from normal rats. Treatment of hypothyroid rats with triiodothyronine restored to normal lipolytic responses of fat cells to either epinephrine or exogenous dibutyryl cyclic AMP. Fat cells from the hyperthyroid rats used in these studies exhibited relatively normal responses. However, in agreement with previous reports (2, 10–12), fat cells from rats made hyperthyroid with 25 μg of triiodothyronine per 100 g body weight, consistently exhibited greater responses to epinephrine than did fat cells of control rats (data not shown).

The specific activities of the cyclic nucleotide phosphodiesterases using either 20 μM cyclic GMP or 0.5 μM cyclic AMP as substrate are significantly greater in the fat cells of hypothyroid rats than in cells from control rats (Table I). This was true for control rats of the same age or of the same weight as hypothyroid rats. There were no significant differences between the two control groups. The mean specific activities of the cyclic GMP phosphodiesterase and apparent low K<sub>c</sub> cyclic AMP phosphodiesterase from the fat cells of hyperthyroid rats were lower than those of fat cells from control rats, although these differences were not statistically significant.

After treatment of hyperthyroid rats with triiodothyronine, the specific activities of the apparent low K<sub>c</sub> cyclic AMP phosphodiesterase of both the supernatant (56 ± 8 pmol/min/mg of protein, N = 3) and particulate fractions (242 ± 34 pmol/min/mg of protein, N = 4) were no longer greater than controls (data in Table I). The specific activity of the cyclic GMP phosphodiesterase of the supernatant fraction from these triiodothyronine-treated hyperthyroid rats was also restored to normal values (842 ± 69 pmol/min/mg of protein, N = 3).

When phosphodiesterase was measured with the luciferin-luciferase assay to enable more accurate determinations at high substrate concentrations (200 μM cyclic AMP), there were no statistically significant differences in the activities of phosphodiesterase in the supernatant fractions of fat cells from any of the four groups of rats. However, when measuring phosphodiesterase with the radioactive assay using 100 μM cyclic AMP, the specific activities of the supernatant fractions of fat cells from hypothyroid and triiodothyronine-treated hypothyroid rats were both found to be slightly greater than either control or hyperthyroid rats, the latter two groups having the same values.

Kinetic analyses according to Lineweaver and Burk (13) were obtained for cyclic AMP phosphodiesterase activities of whole homogenates, supernatants, and particulate fractions of fat cells (Figs. 2, 3, and 4). Table II summarizes all of the extrapolated kinetic parameters obtained. The V<sub>max</sub> of cyclic GMP phosphodiesterase and apparent low K<sub>c</sub> cyclic AMP phosphodiesterase are greater in the fat cells of the hypothyroid rat than in controls, whereas there were no statistical differences in the apparent Michaelis-Menten constants. The maximum velocities of the enzymes from hypothyroid rats were restored to normal values by triiodothyronine administration ("Hypo. + T₃") in Table II. Although the average V<sub>max</sub> of the low K<sub>c</sub> cyclic AMP phosphodiesterase of cells from the hyperthyroid rats was lower than that of control, there were no statistically significant differences

<table>
<thead>
<tr>
<th>Cell Fraction</th>
<th>Substrate</th>
<th>Picomoles/min/mg Protein ± S.E.</th>
<th>&quot;Control&quot;</th>
<th>&quot;Hypothyroid&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole</td>
<td>0.5 μM cAMP</td>
<td>70 ± 8 (4)</td>
<td>118 ± 11 (4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Homogenate</td>
<td>0.5 μM cAMP</td>
<td>281 ± 61 (4)</td>
<td>538 ± 169 (4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>&quot;Supernatant&quot;</td>
<td>0.5 μM cAMP</td>
<td>48 ± 4 (10)</td>
<td>67 ± 4 (10)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 μM cAMP</td>
<td>1200 ± 235 (4)</td>
<td>1844 ± 131 (4)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 μM cGMP</td>
<td>764 ± 111 (8)</td>
<td>1303 ± 178 (8)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>&quot;Particulate&quot;</td>
<td>0.5 μM cAMP</td>
<td>197 ± 21 (10)</td>
<td>323 ± 33 (10)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 μM cGMP</td>
<td>662 ± 290 (6)</td>
<td>1859 ± 360 (6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> - Luciferin-Luciferase assay
<sup>b</sup> - Not sign. diff. than control by group t test, p = 0.05 by paired t test
<sup>c</sup> - p < 0.05 by group t test, p = 0.005 by paired t test
<sup>d</sup> - p = 0.005 by group t test and by paired t test
<sup>e</sup> - N of separate cell preparations

Enzymes measured by radioisotope method except as indicated.

"Supernatant" refers to the fraction remaining on top of the sucrose gradient. "Particulate" refers to the fraction collected at the 0.5–1.2 M sucrose density interface. Statistics calculated by nondirectional Students t-test.

![Fig. 1. Stimulation by epinephrine (EPI) or dibutyryl cyclic AMP (B&AMP) of glycerol production in fat cells from control (C), hypothyroid (PTU), hyperthyroid (T₃), and T₃-treated hypothyroid (PTU + T₃) rats. Values in parentheses refer to the number of separate cell preparations from which data were pooled. Standard errors from each group are indicated.](image)

![Fig. 2. Representative Lineweaver-Burk plot of cyclic AMP phosphodiesterase of whole homogenates from fat cells of control (C), hypothyroid (PTU), hyperthyroid (T₃), and T₃-treated hypothyroid (PTU + T₃) rats (●). Velocity (V) is expressed in nanomoles of cyclic AMP hydrolyzed per min per mg protein.](image)
observed between the enzyme activities of cells from control and hyperthyroid rats.

In some cases, the total \( V_{\text{max}} \) of cyclic AMP phosphodiesterase of the supernatant of cells from the triiodothyronine-treated hypothyroid rats did not return to normal values, but in all cases in which lipolysis was restored, the \( V_{\text{max}} \) values of the low \( K_m \) cyclic AMP phosphodiesterase and cyclic GMP phosphodiesterase were restored to normal.

Phosphodiesterase activity of fat cells from hypothyroid and normal rats responded identically to in vitro incubation with propylthiouracil, triiodothyronine, methylisobutyloxanthine, or theophylline (Fig. 5). At concentrations greater than \( 10^{-4} \) M, propylthiouracil inhibited cyclic AMP phosphodiesterase activity when \( 0.25 \mu M \) cyclic AMP was used as substrate. These data indicate that propylthiouracil itself is not exerting any direct effect on phosphodiesterase that could account for the observed variations in phosphodiesterase activities of the hypothyroid rats. In vitro triiodothyronine in concentrations of \( 10^{-4} \) M or less had no effect on phosphodiesterase activities. At \( 10^{-4} \) M or higher, slight inhibition of both enzymes by triiodothyronine was observed. Since enzyme activities of both normal and hypothyroid rat fat cells were affected similarly, and \( 10^{-4} \) M triiodothyronine is clearly unphysiological, it is unlikely that triiodothyronine administration returns phosphodiesterase activity to normal by a direct effect on the enzyme.

Cyclic AMP phosphodiesterase activity of the particulate fraction responded differently than did the cyclic GMP phosphodiesterase and the supernatant fractions. The highest concentration of theophylline used did not inhibit cyclic GMP phosphodiesterase activity more than 50%, but the low \( K_m \) cyclic AMP phosphodiesterase could be inhibited completely (50% inhibition at \( 10^{-1} \) M). The \( K_I \) for methylisobutyloxanthine to inhibit these enzymes was 10-fold lower than theophylline.

Table II

| Kinetic parameters of cyclic nucleotide phosphodiesterase activities |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| \( V_{\text{max}} \) values are given in picomoles per min per mg of protein ± S.E. \( K_m \) values are also given ± S.E. |

<table>
<thead>
<tr>
<th>Cell Fraction</th>
<th>( V_{\text{max}} ) ( K_m ) A</th>
<th>( V_{\text{max}} ) B</th>
<th>( V_{\text{max}} ) C</th>
<th>( V_{\text{max}} ) D</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Control&quot;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( V_{\text{max}} ) A</td>
<td>1460 ± 318 (5)</td>
<td>2275 ± 443 (5)</td>
<td>2208 ± 403 (5)</td>
<td>1314 ± 283 (4)</td>
</tr>
<tr>
<td>( K_m ) A</td>
<td>49 ± 4 ( \mu )M</td>
<td>49 ± 4 ( \mu )M</td>
<td>49 ± 6 ( \mu )M</td>
<td>37 ± 1 ( \mu )M</td>
</tr>
<tr>
<td>( V_{\text{max}} ) B</td>
<td>300 ± 78 (5)</td>
<td>465 ± 100 (5)</td>
<td>322 ± 99 (4)</td>
<td>289 ± 67 (3)</td>
</tr>
<tr>
<td>( K_m ) B</td>
<td>2.2 ± 0.7 ( \mu )M</td>
<td>2.2 ± 0.7 ( \mu )M</td>
<td>2.4 ± 0.8 ( \mu )M</td>
<td>2.9 ± 0.9 ( \mu )M</td>
</tr>
<tr>
<td>( V_{\text{max}} ) C</td>
<td>723 ± 165 (4)</td>
<td>1051 ± 122 (4)</td>
<td>665 ± 63 (4)</td>
<td>613 ± 74 (4)</td>
</tr>
<tr>
<td>( K_m ) C</td>
<td>19 ± 6 ( \mu )M</td>
<td>20 ± 5 ( \mu )M</td>
<td>21 ± 6 ( \mu )M</td>
<td>25 ± 4 ( \mu )M</td>
</tr>
<tr>
<td>( V_{\text{max}} ) D</td>
<td>604 ± 60 (4)</td>
<td>1046 ± 110 (4)</td>
<td>556 ± 278 (3)</td>
<td>499 ± 2 (2)</td>
</tr>
</tbody>
</table>

\( V_{\text{max}} \) A = Maximum velocity of cyclic AMP PDE extrapolated from the linear portion of the Lineweaver-Burk plots at high substrate concentrations.

\( K_m \) A = Michaelis-Menten constant \( (K_m) \) derived from the extrapolated lines deriving \( V_{\text{max}} \) A.

\( V_{\text{max}} \) B = \( V_{\text{max}} \) of cyclic AMP PDE determined as above except with low substrate concentrations.

\( K_m \) B = \( K_m \) derived from extrapolated lines determining \( V_{\text{max}} \) B.

\( V_{\text{max}} \) C = \( V_{\text{max}} \) of cyclic GMP PDE.

\( K_m \) C = \( K_m \) for cyclic GMP PDE.

\( N \) = No. of separate cell preparations.
The particulate fraction iodothyronine (7'3) on low K_cyclic AMP phosphodiesterase of xanthine normal cells (4). However, epinephrine in the presence of theophylline is as responsive to isoproterenol and glucagon as those from rats is consistent with previously discussed data that indicate that elevation of the lipolytically significant levels of cyclic AMP with epinephrine in the presence of phosphodiesterase inhibitors or with dibutyl cyclic AMP results in enhanced lipolysis in the fat cells from hypothyroid rats. The observation that dibutyl cyclic AMP stimulates lipolysis in fat cells from hypothyroid rats less effectively than in fat cells from control rats might also be explained by enhanced low K_cyclic AMP phosphodiesterase. The observed shift in the equilibrium of cyclic AMP-independent to cyclic AMP-dependent protein kinase could not explain the thyroid dependency of catecholamine-stimulated lipolysis but does suggest that the basal cyclic AMP levels which affect protein kinase activity are lower in fat cells of propylthiouracil-treated rats.

Besides the observed correlation between the low K_c cyclic AMP phosphodiesterase and thyroid hormone, data presented in this report also indicate a correlation between thyroid status and activity of soluble cyclic GMP phosphodiesterase. However, this enzyme would appear to be less involved than the low K_c cyclic AMP phosphodiesterase.

In preliminary experiments, cyclic GMP phosphodiesterase in fat cells of propylthiouracil-treated rats was restored to normal values by treatment of these rats with dexamethasone. However, in these fat cell preparations, lipolysis was still unresponsive to epinephrine and the particulate low K_c cyclic AMP phosphodiesterase activity was still higher than normal.

We postulate that the low K_c cyclic AMP phosphodiesterase is in close proximity to adenyl cyclase, so that an increase in the maximum velocity of this membrane phosphodiesterase as seen in thyroid-deficient animals prevents accumulation of the cyclic AMP needed to stimulate lipolysis. A close proximity of these two enzymes in relation to hormone action has been previously hypothesized (4), and some histochemical support for this hypothesis has been suggested recently (16). The membrane-bound, low K_c cyclic AMP phosphodiesterase is perhaps an integral part of a hormone-adenyl cyclase receptor mechanism or part of a separate hormone receptor mechanism related to growth and development. Some support for this model is provided by observations that insulin and growth hormone also affect the activity of the low K_c cyclic AMP phosphodiesterase (17-21).

The observed thyroid-dependent changes in the maximum velocity of a low K_c membrane cyclic AMP phosphodiesterase could result from (a) increased specific protein synthesis, (b) effects of activating or inhibiting factors, (c) conformational changes in the enzyme, or (d) changes in equilibrium between soluble and particulate enzymes. It is interesting to speculate as to which mechanism may be involved but the exact mechanism is presently unknown.

Direct or indirect effects of thyroid hormones on fat cell membranes could involve conformational changes of enzyme which result in alteration of the kinetic parameters of the enzyme.

![Graph](image-url)

**Table III**

**Protein kinase in fat cells of normal and hypothyroid rats**

Values are from three separate pooled cell preparations.

<table>
<thead>
<tr>
<th></th>
<th>- Cyclic AMP</th>
<th>+ Cyclic AMP</th>
<th>+ Cyclic AMP/ - cyclic AMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µmol/min·mg protein ± S.E.</td>
<td>µmol/min·mg protein ± S.E.</td>
<td>µmol/min·mg protein ± S.E.</td>
</tr>
<tr>
<td>Control</td>
<td>29 ± 1</td>
<td>128 ± 16</td>
<td>4.4 ± 0.5</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>13 ± 3</td>
<td>134 ± 32</td>
<td>10.3 ± 0.3</td>
</tr>
</tbody>
</table>

**DISCUSSION**

These studies indicate that a particulate low K_c cyclic AMP phosphodiesterase activity in fat cells is modulated by the action of thyroid hormones. This hypothesis is primarily based on the correlation of thyroid hormone status with alterations of the responses of fat cells to lipolytic agents and concomitant changes in the maximum velocity of this cyclic nucleotide phosphodiesterase.

Many previous studies have indicated that modulation of cellular cyclic AMP is an important mechanism in the regulation of lipolysis (14, 15). Our results support this hypothesis and suggest that regulation of the hydrolysis of cyclic AMP is an important determinant of cellular cyclic AMP concentrations. In fat cells of propylthiouracil-treated rats, epinephrine does not stimulate lipolysis or enhance accumulation of cyclic AMP, even though adenyl cyclase of adipocyte "ghosts" from hypothyroid rats is as responsive to isoproterenol and glucagon as those from normal cells (4). However, epinephrine in the presence of theophylline (0.5 mM) causes both cyclic AMP accumulation and stimulation of lipolysis in these cells. (This concentration of theophylline in vitro inhibits particulate low K_c cyclic AMP phosphodiesterase 100%, but only inhibits soluble cyclic GMP phosphodiesterase 40%) Furthermore, exogenous dibutyl cyclic AMP will stimulate lipolysis in fat cells of propylthiouracil-treated rats.

The above evidence indicates that hormone binding, cAMP synthesis, and triglyceride lipase activation of fat cells from hypothyroid rats can function normally. Furthermore, protein kinase, when assayed in the presence of cyclic AMP, was the same in fat cells from hypothyroid and normal rats. This is consistent with previously discussed data that indicate that elevation of the lipolytically significant levels of cyclic AMP with epinephrine in the presence of phosphodiesterase inhibitors or with dibutyl cyclic AMP results in enhanced lipolysis in the fat cells from hypothyroid rats. The observation that dibutyl cyclic AMP stimulates lipolysis in fat cells from hypothyroid rats less effectively than in fat cells from control rats might also be explained by enhanced low K_c cyclic AMP phosphodiesterase.

The observed shift in the equilibrium of cyclic AMP-independent to cyclic AMP-dependent protein kinase could not explain the thyroid dependency of catecholamine-stimulated lipolysis but does suggest that the basal cyclic AMP levels which affect protein kinase activity are lower in fat cells of propylthiouracil-treated rats.

Besides the observed correlation between the low K_c cyclic AMP phosphodiesterase and thyroid hormone, data presented in this report also indicate a correlation between thyroid status and activity of soluble cyclic GMP phosphodiesterase. However, this enzyme would appear to be less involved than the low K_c cyclic AMP phosphodiesterase.

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We postulate that the low K_c cyclic AMP phosphodiesterase is in close proximity to adenyl cyclase, so that an increase in the maximum velocity of this membrane phosphodiesterase as seen in thyroid-deficient animals prevents accumulation of the cyclic AMP needed to stimulate lipolysis. A close proximity of these two enzymes in relation to hormone action has been previously hypothesized (4), and some histochemical support for this hypothesis has been suggested recently (16). The membrane-bound, low K_c cyclic AMP phosphodiesterase is perhaps an integral part of a hormone-adenyl cyclase receptor mechanism or part of a separate hormone receptor mechanism related to growth and development. Some support for this model is provided by observations that insulin and growth hormone also affect the activity of the low K_c cyclic AMP phosphodiesterase (17-21).

The observed thyroid-dependent changes in the maximum velocity of a low K_c membrane cyclic AMP phosphodiesterase could result from (a) increased specific protein synthesis, (b) effects of activating or inhibiting factors, (c) conformational changes in the enzyme, or (d) changes in equilibrium between soluble and particulate enzymes. It is interesting to speculate as to which mechanism may be involved but the exact mechanism is presently unknown.

Direct or indirect effects of thyroid hormones on fat cell membranes could involve conformational changes of enzyme which result in alteration of the kinetic parameters of the enzyme.
These shifts in kinetics are apparently independent of protein synthesis and are affected by insulin and reduced glutathione. From such cells have failed to show differences between the fat lum (34-36). Low K, cyclic AMP phosphodiesterase has been shown to be bound to plasma membrane and endoplasmic reticulum (17-21, 37). Altered membrane phospholipid composition (18, 20, 22) showed changes in the kinetic parameters of phosphodiesterase in response to varying growth conditions of cells in culture. These shifts in kinetics are apparently independent of protein synthesis and are affected by insulin and reduced glutathione.

The primary mode of action of thyroid hormones has been postulated by many investigators to involve protein synthesis (23-26), a hypothesis enhanced by the discovery of high affinity binding sites to triiodothyronine in nuclei (27). Several rapidly occurring effects of thyroid hormone such as those on heart rate and respiration (1, 28-32) and on cyclic AMP levels and motility of spermatozoa (33), are difficult to explain on the basis of protein synthesis. However, it seems possible that the interaction between triiodothyronine and thyroid hormone "receptors" could lead to effects other than those involving synthesis of new proteins.

Thyroid hormones also affect some membrane systems, e.g. (sodium- and potassium ion-activated-ATPase, membrane depolarization, and calcium translocation in sarcoplasmic reticulum (34-36). Low K, cyclic AMP phosphodiesterase has been shown to be bound to plasma membrane and endoplasmic reticulum (17-21, 37). Altered membrane phospholipid composition has been suggested as a basis for an altered epinephrine sensitivity in fat cells (38), but detailed analysis of "ghosts" from such cells have failed to show differences between the fat cell membranes from normal and hypothyroid rats (39).

In summation, modulation of membrane-bound low K, cyclic AMP phosphodiesterase activity appears to be a mechanism by which thyroid hormones affect triglyceride metabolism in rat epididymal fat cells. In this way, thyroid hormones seem to regulate the ability of lipolytic agents to stimulate the accumulation of cyclic AMP. Altered cyclic nucleotide hydrolysis can result in impaired cyclic AMP accumulation even if occurring in conjunction with increased synthesis caused by hormone stimulation. These results are consistent with the hypothesis that regulation of cyclic nucleotide hydrolysis is an important parameter in hormone action.

REFERENCES


These results are consistent with the hypothesis that regulation of cyclic nucleotide hydrolysis is an important parameter in hormone action.

Cyclic nucleotide phosphodiesterases and thyroid hormones.
R G Van Inwegen, G A Robison and W J Thompson


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