The Effects of Cortisol, Corticotropin and Thyroxine on the Synthesis of Glycerolipids and on the Phosphatidate Phosphohydrolase Activity in Rat Liver

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1. Male rats were injected daily for 5 days with 0.15M-NaCl, corticotropin, cortisol or L-thyroxine and the rates of glycerolipid synthesis were measured in the livers after intraportal injection of [14C] palmitate and [3H]glycerol. 2. Injection of all three hormones decreased the rates of body-weight gain. 3. Cortisol treatment increased the weight of the liver relative to body weight. 4. Thyroxine treatment increased the relative rate of triacylglycerol synthesis from [3H]glycerol and decreased the relative accumulation of 3H and 14C in diacylglycerol. It did not significantly alter the accumulation of these isotopes in phosphatidate nor the activity of the soluble phosphatidate phosphohydrolase in the total liver. However, this activity increased by 1.5-fold when expressed relative to the soluble protein of the liver. The increased triacylglycerol synthesis appears to be related to a general increase in the turnover of fatty acids in the liver. 5. Treatment with cortisol and corticotropin increased the relative rate of triacylglycerol synthesis from [3H]glycerol, decreased the accumulation of 3H in phosphatidate and increased the flux of both isotopes from phosphatidate to diacylglycerol. This appeared to be caused by the increased activity of the soluble phosphatidate phosphohydrolase that was observed in the livers of the cortisol-treated rats. 6. It is proposed that cortisol could be directly or indirectly involved in increasing the activity of hepatic phosphatidate phosphohydrolase in starvation, diabetes, laparotomy, subtotal heptatectomy, liver damage, ethanol feeding and in obesity. This enzyme adaptation could contribute to the potential of the liver to increase its synthesis and accumulation of triacylglycerols or to secrete very-low-density lipoproteins.

Recent experimental evidence indicates that phosphatidate phosphohydrolase is an important regulatory enzyme in the synthesis of triacylglycerols in the liver (Fallon et al., 1977; Brindley, 1978a,b). Although the responses of this enzyme to a number of physiological and pharmacological changes are documented, there is little information about the alterations of phosphatidate phosphohydrolase activity during hormonal modification. It appears that this activity in the liver is not maintained by insulin, since it is increased in starvation and diabetes and in the stress caused by laparotomy and subtotal heptatectomy (Brindley, 1978a,b).

In the present experiments rats were injected with thyroxine, corticotropin (ACTH) and cortisol, since these hormones are thought to modify glycerolipid metabolism in the liver. This was tested by studying the fate of intraportally injected [3H]glycerol and [14C]palmitate and by measuring the activity of the soluble phosphatidate phosphohydrolase in the liver.

Materials and Methods

Materials

The source of most of these has been described (Brindley et al., 1976; Sturton & Brindley, 1977). Cortisol (as the 21-acetate), corticotropin and L-thyroxine (sodium salt) were purchased from Sigma (London) Chemical Co., Kingston upon Thames, Surrey, U.K.

Treatment of rats

Male Wistar rats [176% (s.D. ± 16), n = 68] were allowed free access to a 41B diet and water. They were divided into four groups and were given daily intramuscular injections into the thigh for 5 days. The injection consisted of (1) 1 ml of 0.15M-NaCl/kg body wt. (control rats), or the equivalent volume of 0.15M-NaCl containing a dose of (2) 100mg of cortisol as a suspension/kg body wt., (3) 580μg...
(50 i.u.) of corticotropin/kg body wt. or (4) 500 μg of L-thyroxine/kg body wt.

**Measurement of the rate of hepatic glycerolipid synthesis in vivo**

At 3 h after the injection with 0.15 M NaCl or hormones on day 5, the rate of glycerolipid synthesis in the liver was measured 1 min after the intraportal injection (0.25 ml) of 212 μM-[1-14C]palmitate (sp. radioactivity 58 μCi/μmol) and 188 μM-[1,3-3H]-glycerol (sp. radioactivity 1638 μCi/μmol) (Brindley et al., 1976; Glenny et al., 1978).

**Measurement of the soluble phosphatidate phosphohydrolase activity**

Rats were killed by cervical dislocation 3 h after the fifth injection with hormones. The particle-free supernatant was prepared, dialysed and the activity of the enzyme was determined by measuring the release of Pi from phosphatidate (Whiting et al., 1977). This assay gives results that are equivalent to those obtained when the formation of diacylglycerol is measured (Sturton & Brindley, 1978).

**Experimental and Results**

Injection of cortisol, corticotropin or thyroxine significantly decreased the weight gain of the rats over the 5-day period by 14, 3 and 5% respectively (Table 1). With the exception of the cortisol treatment, in which a weight loss was recorded, the changes are relatively small. The same dose of thyroxine was used by Roncari & Murthy (1975) and they did not obtain a significant effect on body weight. However, Coates et al. (1978) did report a small decrease in weight gain with a larger dose (about 2 mg/kg body wt.) of thyroxine. The injection of 225 mg of cortisol daily for 5 days to rats has been reported to produce a 9% decrease in body weight (Weber & Singhal, 1964). Walker (1975) attributed the decreased body-weight gain in rats receiving dexamethasone, a synthetic glucocorticoid, in conjunction with a 20% (by weight) rapeseed-oil diet to an increased mobilization of fat-depots.

The liver weights of the rats treated with hormones were not significantly different from those of the controls, although the livers of the cortisol-treated rats were heavier than those of the thyroxine-treated rats (Table 1). The livers of the rats given cortisol were heavier than those of the other groups if the results are expressed relative to the body weight. Other authors have reported that injecting cortisol increases this ratio (Weber & Singhal, 1964; Bates & Garrison, 1974), which is probably partly caused by an increase in the content of liver glycogen (Weber & Singhal, 1964) and triacylglycerol (Ožegović et al., 1975). The liver/body weight ratio was also increased by 20–30% after daily treatment for 5 days with corticotropin (80 i.u./160–200 g rat), but this dose is 8–10-fold greater than was used in the present work.

**Effect of injecting cortisol, corticotropin and thyroxine on the hepatic synthesis of glycerolipids in vivo**

The experiments were carried out to provide evidence that injecting the hormones caused changes in the hepatic glycerolipid metabolism of the rats described in Table 1. This approach has already been used to study the effects of dietary modification and the effects of drugs (Brindley et al., 1976; Savolainen, 1977; Pritchard & Brindley, 1977; Glenny et al., 1978).

(a) Comparison of the control rats with those injected with cortisol or corticotropin. The injection of cortisol decreased the concentration of total 14C-labelled lipid from [14C]palmitate that was isolated in the liver. Despite this, increased proportions of [14C]palmitate and [3H]glycerol were isolated in triacylglycerols (Tables 2 and 3). Klausner & Heimberg (1967) found that cortisol did not alter the uptake of fatty acids in a perfused-liver system.

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**Table 1. Effects of injecting cortisol, corticotropin and L-thyroxine on the liver and body weights of rats**

<table>
<thead>
<tr>
<th></th>
<th>(I) Saline-treated control</th>
<th>(II) Cortisol-treated</th>
<th>(III) Corticotropin-treated</th>
<th>(IV) Thyroxine-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body wt. change (g/100 g)</strong></td>
<td>6 ± 3 (22)</td>
<td>−8 ± 4 (17)</td>
<td>3 ± 4 (12)</td>
<td>1 ± 4 (17)</td>
</tr>
<tr>
<td><strong>Liver wt. (g)</strong></td>
<td>7.4 ± 1.2 (12)</td>
<td>8.1 ± 1.0 (12)</td>
<td>7.3 ± 1.1 (10)</td>
<td>6.8 ± 0.8 (11)</td>
</tr>
<tr>
<td><strong>Liver wt./body wt. × 100</strong></td>
<td>4.1 ± 0.3 (12)</td>
<td>5.1 ± 0.5 (12)</td>
<td>4.1 ± 0.2 (11)</td>
<td>3.9 ± 0.3 (10)</td>
</tr>
<tr>
<td><strong>Soluble protein (mg/liver)</strong></td>
<td>440 ± 90 (10)</td>
<td>421 ± 62 (5)</td>
<td>Not measured</td>
<td>398 ± 60 (5)</td>
</tr>
</tbody>
</table>

The results are expressed as means ± S.D. and the number of rats is shown in parentheses. The significance of the difference between groups is indicated by: *P < 0.05; †P < 0.005; ‡P < 0.001.
Table 2. Effect of injecting cortisol, corticotropin and L-thyroxine on the synthesis of hepatic glycerolipids from [¹⁴C]palmitate in vivo
Rat were injected daily for 5 days with hormones (see the Materials and Methods section) and 3h after the fifth injection the rates of glycerolipid synthesis were measured in the liver (Brindley et al., 1976). Results are expressed as means ± s.d. There were nine control rats, 12 cortisol-treated rats, 10 corticotropin-treated rats and eight thyroxine-treated rats. The flux from phosphatidate to diacylglycerol was calculated by summing the incorporations into glycerolipids other than phosphatidate for each rat. The significance of the difference between groups is indicated by: *P < 0.05; **P < 0.02; ***P < 0.01; †P < 0.005; ††P < 0.001.

<table>
<thead>
<tr>
<th>Incorporation of [¹⁴C]palmitate</th>
<th>(10⁻³ × d.p.m./liver)</th>
<th>Percentage composition in terms of radioactive lipid (d.p.m./100 d.p.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) Saline control</td>
<td>(II) Cortisol-treated</td>
<td>(III) Corticotropin-treated</td>
</tr>
<tr>
<td>Phosphatidylinositol + phosphatidylserine</td>
<td>26 ± 17</td>
<td>31 ± 20</td>
</tr>
<tr>
<td>Phosphatidylcholine</td>
<td>277 ± 166</td>
<td>200 ± 88</td>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
<td>101 ± 60</td>
<td>62 ± 27</td>
</tr>
<tr>
<td>Phosphatidate</td>
<td>330 ± 174</td>
<td>163 ± 83</td>
</tr>
<tr>
<td>Diacylglycerol</td>
<td>577 ± 369</td>
<td>538 ± 246</td>
</tr>
<tr>
<td>Triacylglycerol</td>
<td>351 ± 279</td>
<td>478 ± 220</td>
</tr>
<tr>
<td>Flux from phosphatidate to diacylglycerol</td>
<td>1306 ± 854</td>
<td>1277 ± 501</td>
</tr>
<tr>
<td>¹⁴C in whole liver lipid</td>
<td>2909 ± 1123</td>
<td>1975 ± 445</td>
</tr>
<tr>
<td>Glycerolipid ¹⁴C in liver</td>
<td>2354 ± 852</td>
<td>1557 ± 496</td>
</tr>
<tr>
<td>Non-lipid ¹⁴C in liver</td>
<td>86 ± 43</td>
<td>107 ± 54</td>
</tr>
</tbody>
</table>
Table 3. Effect of injecting cortisol, corticotropin and \(\text{L-thyroxine}\) on the synthesis of hepatic glycerolipid from \(\text{[H]}\)glycerol in vivo

The conditions of the experiment and the presentation of the results is as described in Table 2 except that the incorporation of \(\text{[H]}\)glycerol is depicted.

### Incorporation of \(\text{[H]}\)glycerol

<table>
<thead>
<tr>
<th>Compound</th>
<th>(10(^{-3}) × d.p.m./liver)</th>
<th>Percentage composition in terms of radioactive lipid (d.p.m./100 d.p.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(I) Saline control</td>
<td>(II) Cortisol-treated</td>
</tr>
<tr>
<td>Phosphatidylinositol +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>phosphatidylserine</td>
<td>60 ± 42</td>
<td>92 ± 88</td>
</tr>
<tr>
<td>Phosphatidylcholine</td>
<td>300 ± 188</td>
<td>379 ± 194</td>
</tr>
<tr>
<td>Phosphatidylethanolamine</td>
<td>216 ± 121</td>
<td>173 ± 93</td>
</tr>
<tr>
<td>Phosphatidate</td>
<td>714 ± 493</td>
<td>453 ± 328</td>
</tr>
<tr>
<td>Diacylglycerol</td>
<td>1557 ± 1018</td>
<td>1826 ± 1304</td>
</tr>
<tr>
<td>Triacylglycerol</td>
<td>902 ± 507</td>
<td>1533 ± 591</td>
</tr>
<tr>
<td>Flux from phosphatidate to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diacylglycerol</td>
<td>2975 ± 1814</td>
<td>3090 ± 1938</td>
</tr>
<tr>
<td>Total lipid</td>
<td>5227 ± 2369</td>
<td>3969 ± 2574</td>
</tr>
<tr>
<td>Non-lipid (\text{[H]})</td>
<td>21 076 ± 5867</td>
<td>20 673 ± 12 717</td>
</tr>
</tbody>
</table>
but they did conclude that cortisol treatment promotes the esterification of fatty acid to triacylglycerol. The increased esterification measured in Tables 2 and 3 is accompanied by a decrease in the proportion of radioactive phosphatidate that was isolated, and by an increase in the flux of phosphatidate to diacylglycerol (Tables 2 and 3). Cortisol injection also decreased the proportion of \[^{14}C\] palmitate in phosphatidylcholine and phosphatidylethanolamine (Table 2), but only significantly decreased the relative incorporation of \[^{3}H\]glycerol into phosphatidylethanolamine (Table 3).

Injection of corticotropin also decreased the relative proportion of \[^{3}H\]glycerol that accumulated in phosphatidate and increased the relative flux of phosphatidate to diacylglycerol (Tables 2 and 3). A decrease in the relative accumulation of diacylglycerol and an increase in the relative rate of triacylglycerol synthesis were observed with \[^{3}H\]glycerol as a precursor (Table 3), but these values were not significantly different from the control for \[^{14}C\] palmitate incorporations (Table 2). The changes produced by corticotropin in the incorporation of \[^{14}C\] palmitate into glycerolipids were not identical to those produced by cortisol (Table 2), although the patterns of \[^{3}H\]glycerol incorporation were similar (Table 3). It is likely that corticotropin exerted part of its effects by stimulating corticosterone release.

(b) Comparison of the control rats and those injected with thyroxine. The rats injected with thyroxine had a smaller accumulation of both precursors into diacylglycerol and a greater proportion of \[^{3}H\]glycerol in triacylglycerol. The relative flux of \(^3H\) from phosphatidate to diacylglycerol was increased (Table 3) and the recovery of the total \(^{14}C\) labelled glycerolipids from the livers of the thyroxine-treated rats was significantly lower than that in the controls (Table 2).

Effect of injecting rats with cortisol and l-thyroxine on the soluble activity of phosphatidate phosphohydrolase

The results in Tables 2 and 3 show that injections of cortisol and thyroxine alter the rates of hepatic triacylglycerol synthesis in vivo. These changes may be partly caused by alterations in the activities of the enzymes responsible for this synthesis. The activity of phosphatidate phosphohydrolase was investigated, since it is this activity that normally changes the most rapidly and dramatically when the synthesis of triacylglycerols in the liver is altered (Brindley, 1978a,b).

The specific activity of phosphatidate phosphohydrolase was increased by 2.4-fold (relative to protein) and by 2.8-fold based on the activity per liver in the cortisol-treated rats (Table 4). Thyroxine treatment produced a 1.5-fold increase in specific activity of the phosphohydrolase (relative to protein), but it did not significantly alter the activity expressed per liver. The latter way of expressing the results is more meaningful, since thyroxine treatment may alter the concentration of soluble protein in the liver, although this change did not reach the level of significance (Table 1). In addition, the soluble-protein concentration is affected by the extent to which the livers were perfused, and this adds a further variable.

Discussion

The doses of hormones used in the present experiments are within the ranges employed by other authors who have studied the metabolic effects of cortisol (Weber & Singhal, 1964; Litwack & Singer, 1972; Walter & Anabitarte, 1973; Bates & Garrison, 1974), corticotropin (Szabo et al., 1973) and thyroxine (Tepperman & Tepperman, 1964; Gibson

Table 4. Effect of injecting rats with cortisol and l-thyroxine on the soluble activity of phosphatidate phosphohydrolase in the liver

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Experiment A</th>
<th>Experiment B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(I) Saline control</td>
<td>(II) Cortisol-treated</td>
</tr>
<tr>
<td>Phosphatidate hydrolysed (nmol/min per mg of soluble protein)</td>
<td>1.5 ± 0.18</td>
<td>3.6 ± 0.49</td>
</tr>
<tr>
<td>Phosphatidate hydrolysed (nmol/min per liver)</td>
<td>548 ± 88</td>
<td>1540 ± 405</td>
</tr>
</tbody>
</table>

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et al., 1972; Roncari & Murthy, 1975). However, these treatments produce far higher initial concentrations of hormones in the blood than are found physiologically and the results may be related to the pharmacological as well as the physiological effects of these hormones.

Roncari & Murthy (1975) reported that treating rats with thyroxine increased the rate of triacylglycerol synthesis from glycerol phosphate in cell-free preparations of the livers. Our results from experiments in vivo with $[^3H]$glycerol (Table 3) agree with this conclusion. There appeared to be relatively less $[^{14}C]$palmitate and $[^3H]$glycerol accumulating in phosphatidate, but the changes were not significant (Tables 2 and 3). Although the specific activity of phosphatidate phosphohydrolase did increase when expressed relative to protein, the activity of this enzyme in the liver was not significantly increased (Table 4). The major change in product composition that accompanied the thyroxine-induced increase in triacylglycerol synthesis was a decreased accumulation of $[^{14}C]$palmitate and $[^3H]$glycerol in diacylglycerol (Tables 2 and 3). It is likely that this is mediated through an increased activity of diacylglycerol acyltransferase (EC 2.3.1.20) (Young & Lynen, 1969).

The increased synthesis of triacylglycerols may be partly responsible for the hypertriglyceridaemia that has been reported to occur in hyperthyroid states (Nikkilä & Kekki, 1972). However, there is evidence that the hepatic triacylglycerol is preferentially oxidized within the liver, and that the secretion of very-low-density lipoproteins is decreased (Diamant et al., 1972; Keyes & Heimberg, 1978). This agrees with the hypotriglyceridaemia that has been observed in thyrotoxic patients (Tulloch et al., 1973). The degradation of hepatic triacylglycerol is probably catalysed by an acid lipase that is increased in activity after thyroxine treatment (Coates et al., 1978). This increased turnover of triacylglycerols is a further example of the thermogenic effect of thyroxine, which is mediated through substrate cycling. It is already known that thyroxine stimulates the synthesis and $\beta$-oxidation of fatty acids in the liver (Diamant et al., 1972).

Thyroxyne treatment also increases the synthesis of triacylglycerol (Roncari & Murthy, 1975), the accumulation of triacylglycerol and the rate of $\beta$-oxidation (Bressler & Wittels, 1966) in the myocardium. The hearts of hyperthyroid animals showed an increased synthesis of phosphatidate and an increased activity of the Mg$^{2+}$-stimulated release of P$_i$ from phosphatidate in the microsomal and lysosomal fractions. However, the activity of the Mg$^{2+}$-stimulated phosphatidate phosphohydrolase in the soluble fraction was not increased (Kako & Patterson, 1975).

The administration of corticotropin and cortisol significantly increased the relative proportion of glycerol incorporated into triacylglycerol (Table 3). This was accompanied by (a) an increase in the relative flux of phosphatidate to diacylglycerol (Tables 2 and 3), (b) a decrease in the accumulation of $[^{14}C]$palmitate and $[^3H]$glycerol in phosphatidate for the cortisol-treated rats and (c) an increased specific activity of the soluble phosphatidate phosphohydrolase in the cortisol-treated rats (Table 4). It is therefore likely that the increased phosphohydrolase activity is one of the adaptive changes that predisposes the livers of these rats to synthesize more triacylglycerol. Corticotropin is likely to have produced part of its effect by stimulating the release of cortisol. This release appears to be necessary for producing the fatty liver that is seen after injection of corticotropin (Ožegović et al., 1975). Cortisol and other corticosteroids can also produce a fatty liver (Hill & Droke, 1963; Ožegović et al., 1975) and increase the secretion of very-low-density lipoproteins (Klausner & Heimberg, 1967; Reaven et al., 1974).

This increased synthesis and secretion of triacylglycerols by the liver may partly result from the increased lipolysis and decreased fatty acid esterification in adipose tissue that can be produced by corticotropin and cortisol (Lebovitz et al., 1965; Scow et al., 1965; Chernick et al., 1972; Litwack & Singer, 1972; Bizzi et al., 1972). The mobilization of fatty acids together with protein loss from muscle could be responsible for the decreased weight gain observed in the rats treated with corticotropin and cortisol (Table 1).

High serum concentrations of cortisol are also associated with conditions of excessive fat accumulation such as in Cushing's syndrome and obesity (Rudman & Di Girolamo, 1971; Herber & Coleman, 1977). These conditions involve an increased synthesis of fatty acids, which are then incorporated into triacylglycerols. Cortisol appears to be involved in this phenomenon, although its effect may be mediated through insulin (Salmon & Hems, 1973; Diamant & Shafrir, 1975; Kirk et al., 1976). The increased synthesis of triacylglycerols in the livers and adipose tissue of obese (ob/ob) mice is probably facilitated by the increased activity of phosphatidate phosphohydrolase in these organs (Jamdar et al., 1976; Fallon et al., 1977).

Glucocorticoids appear to play a permissive role in stimulating hepatic triacylglycerol synthesis, and cortisol is known to play an important part in regulating intermediary metabolism in starvation, diabetes and stress conditions. The liver is also responsible for degrading a large portion of the circulatory cortisol, and thus removal is impaired by liver damage (Peterson, 1971). Adrenalectomized

1978
animals fail to develop fatty livers in response to the hepatotoxic effects of phosphorus, ethionine and colchicine, or in starvation, diabetes, partial hepatectomy and in other forms of metabolic stress. There is evidence that adrenalectomy has some direct effects on the liver that are not entirely caused by a defect in fat mobilization (Ramey & Goldstein, 1957; Rudman & Di Girolamo, 1971). The activity of phosphatidate phosphohydrolase in the liver is increased in starvation (Vavřečka et al., 1969; Mangiapane et al., 1973), diabetes (Whiting et al., 1977), subtotal hepatectomy (Mangiapane et al., 1973), after the stress of surgery (Mangiapane et al., 1973) and as a result of the toxic effects of hydrazine administration (Lamb & Blank, 1977). There are also marked increases in this activity after ethanol ingestion (Lamb & Fallon, 1977; Savolainen, 1977; Pritchard et al., 1977; Sturton et al., 1978). This condition is also accompanied by increased concentrations of circulating glucocorticoids, which may be mediated through an enhanced corticotropin release or by liver damage (Mendelson, 1971). The results from the present work establish that cortisol could be directly or indirectly involved in producing these increases in phosphatidate phosphohydrolase activity.

An increased specific activity of phosphatidate phosphohydrolase is also seen in foetal lung during the development of its capacity to synthesize surfactant, but parallel increases in the foetal liver were reported not to have occurred (Johnston et al., 1975). Glucocorticoids are known to promote the maturation of the lung. Treatment of pregnant rabbits with cortisol increased the activity of the membrane-associated phosphatidate phosphohydrolase in the lungs of the foetuses, but this increase did not reach the level of significance (Possmayer et al., 1977). Injection of pregnant rabbits with betamethasone does increase the specific activity of the phosphatidate phosphohydrolase in the foetal lungs, but a decreased activity was reported for the foetal livers (Brehier et al., 1977). The activity of phosphatidate phosphohydrolase in the latter three series of experiments appears to have been measured by the release of Pi. This method of assay can overestimate phosphatidate phosphohydrolase activity in particulate fractions of liver. This may have obscured changes in activity that may have been detected had the formation of diacylglycerol been determined (Sturton & Brindley, 1978; Sturton et al., 1978).

The present paper demonstrates that injecting rats with corticotropin, cortisol and thyroxine increases the relative rate of hepatic triacylglycerol synthesis. Thyroxine is known to produce a generalized increase in metabolism and it stimulates the synthesis and degradation of fatty acids and triacylglycerols in the liver. Thyroxine did not produce a marked increase in the hepatic activity of phosphatidate phosphohydrolase, but there was evidence that the flux of diacylglycerol to triacylglycerol was increased. Cortisol treatment increased phosphatidate phosphohydrolase activity in the liver by about 2.8-fold, and this increase appears to be associated with a net stimulation of triacylglycerol production.

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