Topiramate (TPM) is a novel neurotherapeutic agent currently indicated for the treatment of epilepsy and undergoing development for other central nervous system indications including neuropathic pain, bipolar disorder, and migraine prophylaxis. TPM is synthesized from D-fructose and contains a sulfamate moiety that is essential for its pharmacologic activity. TPM has been observed to significantly reduce body weight in patients treated for seizure, which has prompted the realization of preclinical studies to characterize the effects of TPM in the regulation of energy balance. Studies carried out in various strains of rats have provided good evidence for the ability of TPM to blunt energy deposition. Body composition analyses from rat trials have demonstrated that TPM inhibits fat deposition while reducing the activity of lipoprotein lipase (LPL) in various white adipose tissue depots. High doses of TPM (likely above the therapeutic dose range) have also been observed to reduce protein gain without catabolic effects. Although TPM cannot be described as a potent anorectic agent, it seems to have the ability to reduce food intake; significant reductions in food intake have been observed in female obese (fa/fa) Zucker rats and in female Wistar rats. TPM can also reduce energy deposition in the absence of alterations in food intake. This effect has been clearly emphasized in female lean (Fa/-) Zucker rats. In female Sprague–Dawley rats, TPM also increased energy expenditure and it has been observed to increase LPL activity in brown adipose tissue, which could indicate that TPM has the ability to enhance regulatory thermogenesis. In addition, TPM stimulates LPL activity in skeletal muscles, further emphasizing its potential to promote substrate oxidation. The mechanisms whereby TPM affects the regulation of energy balance have yet to be understood. TPM represents an antiepileptic drug (AED) with complex biochemical/pharmacologic actions. Its negative effects on energy deposition cannot be readily predicted from these actions, as AEDs generally expected to stimulate body weight gain. Recent data, obtained from investigations aimed at assessing the effects of TPM on neuropeptidergic systems involved in the regulation of energy balance, have failed to demonstrate any significant effects of TPM on the neuropeptide Y and proopiomelanocortin systems. In conclusion, it is clear that TPM can reduce fat deposition by either reducing food intake or stimulating energy expenditure. The mechanisms whereby an AED such as TPM controls food intake and energy expenditure remains to be delineated. Nutrition 2000;16:961–966. ©Elsevier Science Inc. 2000

Key words: topiramate, anticonvulsant drug, food intake, energy expenditure, obesity, insulin, leptin, glucose, corticosterone
Female Sprague–Dawley rats were treated with TPM for 5 weeks. TPM was administered by gavage at a daily dose of 30 mg of TPM per kg of body weight. Rats were fed either a standard stock diet or a purified high-sucrose/high-fat diet (in grams per 100 g: sucrose, 45; maize oil, 10; lard, 10; casein, 22.5; dl-methionine, 0.3; vitamin mix, 1.2; mineral mix, 5.5; fiber, 5.5). Food intake was measured daily and digestible energy intake estimated at 95% of the gross energy ingested, which was calculated by multiplying total food intake by the energy density of diets. Energy (bomb calorimetry) and fat gains were determined from carcass analyses done at the beginning and at the end of the study.\(^{42}\) Apparent energy expenditure was calculated as the difference between energy intake and energy gain, and energetic efficiency as the ratio energy gain to digestible energy intake. Multivariate analysis of variance (MANOVA) was used to determine the main and interaction effects of food and drug on energy balance.

TPM, topiramate.

The observation that TPM may significantly reduce body weight in humans and laboratory rodents prompted the realization of preclinical investigations in laboratory rodents to describe in detail the components of energy balance that are affected by TPM and to delineate the potential mechanisms of action of this drug in the regulation of energy balance. This short review summarizes the effects of TPM on the regulation of energy balance.

**TPM AND ENERGY BALANCE**

Preclinical studies conducted in the rat have provided strong evidence that TPM can reduce energy deposition. A study carried out in female lean and obese Zucker rats\(^{17}\) demonstrated the ability of TPM to significantly reduce energy gain over a period of 28 d of treatment. The effect was particularly evident in obese mutants, in which TPM doses of 15 and 60 mg/kg per day were about equally effective at reducing energy gain by as much as 25%. Another investigation performed in Sprague–Dawley rats subjected to an obesity-promoting diet also demonstrated the potential of TPM to reduce energy gain. Some of the main results of this study are presented in this review (Table I and Fig. 1). To assess possible gender differences in the chronic effects of TPM on energy balance, this study was performed in lean male and female rats. The obesity-promoting diet that was used consisted of a diet high in sucrose and fat, which is known to create metabolic syndrome X in animals, TPM had an effect on energy balance that was consistent with that observed in female animals (reduction in energy and fat deposition, and in energetic efficiency), whereas it had no effect on energy balance in rats provided with the obesity-promoting diet.

The effects of TPM on energy balance reported here and observed earlier\(^{17}\) are consistent with data of others (R. Shank, personal communication; D. York, personal communication). Shank et al. (personal communication) demonstrated in long-term preclinical studies that the effect of TPM on body weight is sometimes more readily seen in female than in male rats. It is also worthy of mention that the effects of TPM on energy balance are mild, though constant and gradual over long periods of time.

**TABLE I.**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TPM</th>
<th>Placebo</th>
<th>TPM</th>
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<tbody>
<tr>
<td>Stock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive energy intake (kJ)</td>
<td>7251 ± 208</td>
<td>7221 ± 165</td>
<td>8693 ± 394</td>
<td>8731 ± 402</td>
</tr>
<tr>
<td>Energy gain (kJ)</td>
<td>701 ± 82</td>
<td>524 ± 106</td>
<td>1845 ± 256</td>
<td>1592 ± 220</td>
</tr>
<tr>
<td>Apparent energy expenditure (kJ)</td>
<td>6550 ± 154</td>
<td>6697 ± 139</td>
<td>6848 ± 165</td>
<td>7139 ± 215</td>
</tr>
<tr>
<td>Energetic efficiency (%)</td>
<td>9.54 ± 0.99</td>
<td>7.16 ± 1.36</td>
<td>20.6 ± 2.16</td>
<td>17.8 ± 1.84</td>
</tr>
<tr>
<td>Final body energy (kJ)</td>
<td>1755 ± 91</td>
<td>1571 ± 112</td>
<td>2936 ± 268</td>
<td>2694 ± 231</td>
</tr>
<tr>
<td>Fat gain (g)</td>
<td>10.1 ± 2.03</td>
<td>5.4 ± 2.21</td>
<td>38.2 ± 6.10</td>
<td>33.4 ± 5.39</td>
</tr>
<tr>
<td>MANOVA</td>
<td>Food (F)</td>
<td>Drug (D)</td>
<td>F × D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0001</td>
<td></td>
<td>0.005</td>
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**TPM AND BODY COMPOSITION**

**Fat Mass and Storage**

The effect of TPM on energy balance seems in large part accounted for by a reduction in fat gain\(^{17}\) (Table I). The effects of diet and TPM on fat gain in female Sprague–Dawley rats were reflected in the weights of both the inguinal (subcutaneous) and retroperitoneal (visceral) adipose depots (Fig. 1). Subcutaneous and visceral adipose depots share many common metabolic characteristics. However, unlike subcutaneous fat, visceral fat drains into the portal vein and is an important source of lipid substrates (non-esterified fatty acids) for the liver.\(^{21}\) In addition, the activity of some of the metabolic processes typical of adipose tissue (lipolysis, etc.) may in some conditions differ between visceral and subcutaneous fat.

The TPM-induced reduction in the adipose fat mass of female rats was accompanied by a large reduction in lipoprotein lipase (LPL) activity in both the inguinal and retroperitoneal depots (Fig. 1). The reduction was observed regardless of the type of diet provided. LPL is synthesized by various tissues, mainly adipose tissue and muscle. The enzyme is secreted by parenchymal cells of these tissues and migrates to the vascular surface of endothelial cells, where it binds to heparan sulfate proteoglycans.\(^{22}\) The interaction of bloodborne triacylglycerol-rich lipoproteins (chylomicrons and very low-density lipoprotein) with LPL results in the gradual hydrolysis of their triacylglycerol moiety. Fatty acids thus released are taken up by the underlying tissues or spill over into the circulation. Therefore, LPL is a limiting factor in the intravascular
hydrolysis of triacylglycerols. In addition, because it is modulated in a tissue-specific fashion, LPL influences the distribution of triacylglycerol-derived fatty acids among storage (adipose) and oxidizing (muscle) tissues. Adipose tissue LPL is closely associated with fat mass. For instance, high adipose LPL activity is observed frequently in obesity, whereas weight loss is normally accompanied by a reduction in enzyme activity. LPL is therefore a valuable long-term marker of adipose tissue lipid metabolism.

Lean Mass

In addition to reducing fat gain, TPM also seems to blunt protein gain. In female Sprague–Dawley rats (data not shown), TPM reduced carcass protein gain regardless of dietary conditions (−19% in both dietary cohorts). TPM was also observed to reduce protein gain in lean and obese Zucker rats. Whether this effect applies only to young growing rats such as those used in most of our studies has yet to be ascertained. It is noteworthy that in lean and obese Zucker rats, the blunting effect of TPM on protein gain was not observed at a dose of 15 mg/kg per day. Yet, at this dose TPM significantly decreased fat gain, which suggests some specific action of the drug on fat mass. In addition, it is important to note that TPM-treated animals, in which the gain in lean mass is reduced, do not lose but gain less protein mass compared with untreated rats, and therefore are generally not in a catabolic state.

Further studies are required to understand this effect of TPM on lean mass with higher doses (likely above the therapeutic dose range), which can occur even in absence of a reduction in food intake.

TPM, FOOD INTAKE, THERMOGENESIS, AND FOOD DIGESTIBILITY

TPM cannot be regarded as exhibiting potent anorectic and thermogenic actions. Yet, TPM reduces energetic efficiency and can significantly affect energy balance over weeks. Also, the effects of TPM cannot be described as being either predominantly anorectic or thermogenic, these being determined by numerous factors. The results expressed in Figure 2 illustrate how TPM could create an energy deficit by modulating food intake and energy expenditure. In that study, we examined, over a period of 5 d, food intake and energy expenditure (indirect calorimetry) of female Wistar rats already under treatment with TPM. We observed that TPM exerted its effect on energy balance by slightly reducing food intake while preventing energy expenditure from significantly falling.

Food Intake

The results expressed in Figure 2 demonstrate the ability of TPM to reduce food intake. The anorectic potential of the drug has also been clearly exemplified in the obese Zucker rat, in which TPM reduces food intake well below that of obese untreated animals. TPM has also been observed to decrease food intake in acute conditions, for instance at the very beginning of a treatment in the rat (data not shown). However, despite the reported effects of TPM...
stimulated thermogenesis even when it reduced food intake. A decrease in energy expenditure, indicating that TPM probably did not accompany a concomitant significant change in food intake (Table I). In Wistar rats (Fig. 2), the decrease in food intake contributed to either a balanced laboratory diet or a high-sucrose/high-fat diet without quantitatively affecting food ingestion.

**Energy Expenditure**

Although the thermogenic action of TPM cannot be readily demonstrated (at least from indirect calorimetry trials, Fig. 2), it is clear that TPM has the ability to stimulate thermogenesis. In fact, TPM has confirmed its capacity to reduce energy gain, even in the absence of a reduction in food intake. The effect of TPM on energy expenditure was particularly well illustrated in lean Zucker rats, in which TPM increased this variable by more than 10%. An increase in energy expenditure accompanied by a decrease in energetic efficiency was also seen in female Sprague–Dawley rats subjected to either a balanced laboratory diet or a high-sucrose/high-fat diet (Table I). In Wistar rats (Fig. 2), the decrease in food intake following TPM was not accompanied by a concomitant significant decrease in energy expenditure, indicating that TPM probably stimulated thermogenesis even when it reduced food intake.

The mechanisms whereby TPM stimulates energy expenditure are not fully understood. However, the increase in BAT LPL activity (Fig. 3) seen in female Sprague–Dawley rats treated with TPM suggests that TPM could activate BAT thermogenesis, a sympathetically mediated process capable of dissipating large amounts of energy in small mammals. TPM also activates LPL in skeletal and cardiac muscles (Fig. 3), suggesting that these tissues could also participate in the effects of TPM on energy expenditure. In oxidative (red) muscle tissue, LPL activity has been associated with the efficiency of insulin action on glucose metabolism. Hence, low muscle LPL is observed in insulin resistance (e.g., type II diabetes). High muscle LPL is found in physically active individuals who are highly sensitive to insulin. There is evidence that LPL activity is positively associated with the efficiency of fatty acid oxidation in muscle tissue. LPL is therefore a valuable long-term marker of muscle glucose and lipid metabolism. The increased LPL activity in oxidative tissues such as BAT and muscles and the decreased activity of this enzyme in white adipose tissue seen in TPM-treated rats has been observed to be associated with a reduction in the levels of circulating triacylglycerols (Fig. 3). This observation could suggest that lipid substrates are efficiently channeled toward BAT and muscles in TPM-treated rats. This putative action of TPM is not overwhelmed by the high-sucrose/high-fat diet and can be seen as a beneficial effect of TPM on lipid metabolism.

**Food Digestibility**

There is a priori no indication that TPM affects energy balance by altering the digestibility of food. We nonetheless tested the effects of the drug on food digestibility in Wistar rats. Food intake was measured and feces collected over a period of 2 wk in groups of female rats treated with TPM (drug mixed in a purified diet, 60 mg/kg per day) or given a placebo. The results demonstrated the digestibility of the diet to be identical in placebo- and TPM-treated rats (placebo, 92.04 ± 0.21%; TPM, 92.26 ± 0.20% of gross energy that is not eliminated in the feces).

**TPM AND REGULATION OF ENERGY BALANCE**

The mechanisms whereby TPM modulates energy balance have yet to be delineated. The description of these mechanisms remains a very complex and challenging task, given the intricate biochemical/pharmacologic actions of TPM. The drug exerts (i) a positive modulatory effect on the activity of GABA_A receptors; (ii) a negative modulatory effect on the activity of glutamate at kainate/AMP receptors; (iii) a negative modulatory effect on voltage-dependent sodium channels; (iv) an inhibitory action on high-voltage-activated calcium channels, and (v) an inhibitory action on CA isoforms, particularly CA-II and CA-IV.

**Endocrine and Neuroendocrine Mechanisms**

The regulation of energy balance is strongly influenced by leptin, insulin, and corticosteroids, three circulating hormones capable of signaling the brain about variations in energy stores. Leptin, which is secreted by the adipocyte in function of its size, induces strong anorectic and thermogenic effects capable of markedly impairing fat deposition. Insulin has also been reported to reduce energy intake and to enhance thermogenesis provided its hypoglycemic effect is prevented. Finally, corticosteroids, in contrast to leptin and insulin, promote fat storage by increasing energy intake and down-regulating thermogenesis.

The influence of TPM on leptin, insulin, and glucocorticoids has not been thoroughly investigated. Nonetheless, recent observations from our laboratory provided clear evidence that TPM reduces circulating levels of leptin (Fig. 4). The decrease in plasma levels of leptin seems to merely parallel the reduction in the growth of white adipose depots led by TPM and probably does not contribute much to the effect of TPM in the regulation of energy balance. TPM has also been reported to reduce circulating levels of leptin, insulin, and glucocorticoids in animal models.
either insulin\(^{17}\) or glucose (Fig. 4), suggesting that TPM can increase the sensitivity of glucose metabolism to insulin. An increased sensitivity to insulin could facilitate the anorectic and thermogenic action of the hormone. However, further studies need to be carried out to ascertain this possibility. Finally, TPM, when provided in the diet, has also been reported to reduce corticosterone levels (D. York, personal communication) and to down-regulate the expression of hypophyiotropic corticotropin-releasing hormone (CRH) in the hypothalamic paraventricular nucleus (data not shown). A decrease in the hypothalamic–pituitary–adrenal axis activity would represent an adaptation congruent with the effects of TPM on energy balance, given that corticosterone stimulates food intake and down-regulates thermogenesis.

**Brain Neuropeptidergic Systems**

The literature of the past 10 y in the field of obesity and energy metabolism has emphasized the importance of the neuropeptide Y (NPY), CRH, and proopiomelanocortin (POMC) systems in the regulation of energy balance.\(^{37–39}\) Activation of the NPY system has been reported to be anabolic by increasing food intake and reducing thermogenesis, whereas activation of the CRH (excluding those that inhibit breakdown of GABA such as vigabatrin have been reported to promote weight gain in clinical trials.\(^{14–16}\)

Interestingly, however, it appears that not all anticonvulsant drugs promote energy gain. In this respect, the observation has been made that anticonvulsant drugs that predominantly inhibit the activity of the glutamatergic system could promote weight loss,\(^{16}\) in contrast with those that induce GABA neurotransmission. Whether such a balance of action on GABAergic and glutamatergic systems applies to TPM remains to be determined. A possible role for the glutamate N-methyl-D-aspartate (NMDA) receptor in body weight control was suggested by a study in which the NMDA receptor co-agonist glycine stimulated feeding behavior when administered into the lateral hypothalamus of rats.\(^{40}\) Finally, the extent to which other properties of TPM such as its inhibitory effect on CA isoforms may contribute to the loss of body weight has yet to be determined. It is also not clear as to whether the negative modulatory effect of TPM on both voltage-dependent sodium channels and high-voltage-activated calcium channels may also influence the regulation of energy balance. Calcium channel blockers have been reported to stimulate metabolic rate in the rat.\(^{41}\)

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