Topiramate Reduces Energy and Fat Gains in Lean (*Fa/?*) and Obese (*fa/fa*) Zucker Rats

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Abstract

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Objective: This study examined the effects of topiramate (TPM), a novel neurotherapeutic agent reported to reduce body weight in humans, on the components of energy balance in female Zucker rats.

Research Methods and Procedures: A 2 × 3 factorial experiment was performed in which two cohorts of Zucker rats differing in their phenotype (phenotype: lean, *Fa/?*; obese, *fa/fa*) were each divided into three groups defined by the dose of TPM administered (dose: TPM 0, vehicle; TPM 15, 15 mg/kg; TPM 60, 60 mg/kg).

Results: The reduction in body weight gain induced by TPM in both lean and obese rats reflected a decrease in total body energy gain, which was more evident in obese than in lean rats. Whereas TPM administration did not influence the intake of digestible energy in lean rats, it induced a reduction in food intake in obese animals. In lean, but not in obese rats, apparent energy expenditure (as calculated by the difference between energy intake and energy gain) was higher in rats treated with TPM than in animals administered the vehicle. The low dose of TPM decreased fat gain (with emphasis on subcutaneous fat) without affecting protein gain, whereas the high dose of the drug induced a reduction in both fat and protein gains. The effects of TPM on muscle and fat depot weights were representative of the global effects of TPM on whole body fat and protein gains. The calculated energetic efficiency (energy gain/energy intake) was decreased in both lean and obese rats after TPM treatment. TPM dose independently reduced hyperinsulinemia of obese rats, but it did not alter insulinemia of lean animals.

Discussion: The present results provide sound evidence for the ability of TPM to reduce fat and energy gains through reducing energetic efficiency in both lean and obese Zucker rats.

Key words: anticonvulsant drug, food intake, energy expenditure, adipose tissue, body composition

Introduction

The effects of antiepileptic drugs (AEDs) on energy balance have not been thoroughly investigated. Nonetheless, increases in body weight gain have been reported, in particular after administration of anticonvulsant drugs that predominantly potentiate γ-aminobutyric acid (GABA) inhibitory neurotransmission. Indeed, drugs such as valproate and benzodiazepine, which enhance the activity of the $GABA_A$ receptor, and vigabatrin, which inhibits the breakdown of GABA, have been reported to promote weight gain in clinical trials (1–3).

Topiramate (TPM) is a structurally novel neurotherapeutic agent synthesized from D-fructose and it contains a sulfamate moiety that is essential for pharmacological activity (4). TPM currently is indicated for the treatment of epilepsy, and is undergoing development for a wide variety of other indications including neuropathic pain, bipolar disorder, and migraine. TPM has been reported to exert multiple biochemical/pharmacological effects that may determine its broad range of activities including anticonvulsant, analgesic, and mood-stabilizing properties. In contrast to most AEDs, TPM seems to promote body weight loss in humans (1,5). Mechanistically, the basis for this effect is not known. Five biochemical pharmacological properties of TPM have been identified including the following: a positive modulatory effect on the activity of GABA at $GABA_A$ receptors (6,7), a negative modulatory effect on the activity of glutamate at kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (8,9), a negative modulatory effect on voltage-dependent sodium channels (10–14), and some negative effect on high voltage-activated calcium

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channels (15). The fifth known property is an inhibitory effect on carbonic anhydrase (CA), particularly CA-II and CA-IV (16). Although the modulatory effect of TPM on $GABA_A$ receptors differs from that of other AEDs (4), this property would be expected to promote weight gain rather than weight loss. Recently, evidence has been reported suggesting that AEDs, which inhibit the activity of some glutamatergic receptors, could promote weight loss (2). A possible role for the glutamate *N*-methyl-D-aspartate receptor in body weight control was suggested by a study in which the *N*-methyl-D-aspartate receptor coagonist glycine stimulated feeding behavior when administered into the lateral hypothalamus of rats (17).

The observation that TPM may exert reducing effects on body weight in humans prompted us to undertake a series of experiments in the rat, with the objective of describing in detail the components of energy balance that are affected by the drug. To this end, a 2 × 3 factorial experiment was performed in which two cohorts of Zucker rats differing in their phenotype (phenotype: lean, *Fa/?*; obese, *fa/fa*) were each divided into three groups defined by the dose of TPM administered (dose: TPM 0, vehicle; TPM 15, 15 mg/kg; TPM 60, 60 mg/kg).

Research Methods and Procedures

Animals and Treatments

Lean (*Fa/?*) and obese (*fa/fa*) female Zucker rats, aged 4 to 5 weeks, were purchased from the Canadian Breeding Laboratories (St-Constant, Canada). Females were used instead of males because the latter were not available at the time this study was realized. Gender-dependent effects of TPM were not expected *a priori*, as TPM had not been systematically tested for its effects on body weight. All rats were cared for and handled in accordance with the Canadian Guide for the Care and Use of Laboratory Animals. Obese and lean rats were age-matched at the beginning of the study. Rats were individually housed in stainless cages under controlled temperature (23 ± 1 °C) and lighting (light, 6:00 AM until 4:00 PM; dark, 4:00 PM until 6:00 AM). The animals were allowed unrestricted access to food and water. Throughout the study, rats were given a purified, high-carbohydrate diet, which was composed of the following (in g/100 g): 31.2 cornstarch, 31.2 DL -dextrose, 6.4 corn oil, 20.0 casein, 0.3 DL -methionine, 1.0 vitamin mix (Teklad no. 40060; Teklad, Madison, WI), 4.9 AIN-76 mineral mix (ICN Biochemicals, Montréal, Canada), and 5.0 fiber (Alphacel; ICN Biochemicals). The energy content of the diet consisted of 64.9% carbohydrate, 14.5% fat, and 20.6% protein, and its density was 4.01 kcal/g. A week after their arrival, both lean and obese rats were chronically treated either with vehicle (dose 0) or TPM at two doses (15 and 60 mg/kg) given by gavage. TPM (RWJ-17021–000-DO) was provided by the R.W. Johnson Pharmaceutical Research Institute (Raritan, NJ). The doses were selected based on previous pharmacokinetic trials (4). One-third of the dose was given in the morning, and the remaining two-thirds were administered 2 hours before dark to obtain maximal effects of TPM during the period of peak activity of the animals. The doses of TPM were adjusted every other day after the recording of body weight. Rats were treated for 4 weeks.

Body Weight, Food Intake, and Body Gains in Energy, Fat, and Protein

Throughout the study, body weight and the amount of food ingested were monitored every other day. Food spilled on the absorbent paper was carefully collected, allowed to dry, and accounted for in the food-intake calculations. Energy intake was calculated by multiplying cumulated intakes of food by the digestible energy (DE) content of the diet. The DE was determined as being 95% of the gross energy density of the diet. This determination was based on previous studies (18,19), in which the energy content of the feces was analyzed.

At the end of the experimental treatment, overnight-fasted rats (from 7:00 AM to the time of killing [1:00 PM]) were anesthetized with an intraperitoneal injection of 0.4 mL/kg of a ketamine (20 mg/mL) and xylazine (2.5 mg/mL) solution. The rats were killed between 1:00 PM and 3:00 PM. The time of killing alternated among rats to balance the effect of fasting duration among groups. Blood was harvested immediately thereafter by cardiac puncture and centrifuged (1500 × *g*, 15 minutes at 4 °C); the separated plasma was stored at −70 °C until later biochemical measurements. Carcasses were autoclaved at 125 kPa for 15 minutes. This procedure, which had been reported not to affect energy yield (20), was used to soften hard tissues. Once autoclaved, carcasses were homogenized in a volume of water corresponding to two times their weight. The homogenized carcasses were then freeze-dried pending the determination of their energy and nitrogen contents. Carcass energy content was determined by adiabatic bomb calorimetry, whereas carcass nitrogen was determined in 250- to 300-mg samples of dehydrated carcasses using the Kjeldahl procedure. Carcass protein content was computed by multiplying the nitrogen content of the carcass by 6.25. The energy as protein was subtracted from total carcass energy to determine energy as nonprotein matter. Because carbohydrate represents a negligible part of carcass total energy (21), energy from nonprotein matter was assumed to be essentially that of fat. Such an assumption tends to be confirmed by studies in which energy, fat, and protein were directly determined (22). Values of 5.62 and 9.39 kcal/g were used for the calculation of the energy content of protein and fat, respectively (21). Initial energy, fat, and protein contents of the carcasses were estimated from the live body weight of lean and obese rats with reference to a

baseline group of rats killed at the beginning of the experimental period. Such estimates allow gains in energy, fat, and protein to be determined for the treatment period. The rats (eight per phenotype) in the baseline groups were killed at the beginning of the energy balance trial, and the carcass of each animal was analyzed for energy (mean initial values: lean, 234 ± 11 [from 205 to 259 kcal]; obese, 958 ± 74 [from 741 to 1186 kcal]), protein (mean initial values: lean, 141 ± 6 [from 124 to 154 kcal]; obese, 156 ± 11 [from 109 to 185 kcal]), and fat (mean initial values: lean, 93 ± 6 [from 80 to 109 kcal]; obese, 802 ± 64 [from 598 to 1001 kcal]). The densities in energy (kilocalories of energy per gram of body weight), protein (grams of protein per gram of body weight), and fat (grams of fat per gram of body weight) were then computed and averaged. The average densities were multiplied by the initial body weight of each rat ascribed to experimental groups. Rats in the initial group were identical in every respect (e.g., age and gender) to those of the experimental groups. Apparent energy expenditure was calculated by subtracting the energy gain from DE intake. Gross energetic efficiency was expressed as the ratio of energy gain to DE intake multiplied by 100.

Plasma Determinations

Plasma glucose concentrations were measured with a glucose analyzer (Beckman Instruments, Carlsbad, CA). Insulin was determined by radioimmunoassay using a reagent kit from Linco Research (St. Charles, MO) with rat insulin as standard. Plasma corticosterone was determined by a competitive protein-binding assay (sensitivity, 0.047 nmol/L; interassay coefficient of variation, 8.6%) using plasma from a dexamethasone-treated female Rhesus monkey as the source of transcortin (23).

Statistical Analysis

A 2 × 3 factorial analysis of variance was used to determine the main and interactive effects of "phenotype" (lean, *Fa/?*; obese, *fa/fa*) and "TPM dose" (TPM 0, vehicle; TPM 15, 15 mg/kg; and TPM 60, 60 mg/kg). When appropriate, *a posteriori* comparisons were performed using Fisher's protected least squares difference test. Differences were considered statistically significant at $p < 0.05$. A total of 10 rats were assigned to each condition.

Results

TPM attenuated body weight gain, as depicted in Figure 1. Expressed as a percentage of total body weight ([{TPM 0 − TPM 15 or TPM 60}/TPM 0] × 100), the effect of TPM was 4.6% in lean and 7.4% in obese rats treated with the low dose of the drug and 8.9% in lean and 11.2% in obese animals treated with the high dose of TPM. The effect of TPM was manifest throughout the study as shown by the rate of weight gain, which tended to be more attenuated by the drug in lean than in obese animals. Final body weight (Figure 1A) and total weight gain (Figure 1B) were significantly reduced in both lean and obese TPM-treated animals. In obese rats, TPM induced a marked reduction in food intake (Figure 2). This effect of the drug had vanished by the end of the treatment period. In lean rats, TPM had no effect on food intake, regardless of the dose or the period of the study over which the intake measurement was made.

The reduction in body weight gain induced by TPM reflected a decrease in total body energy gain, which tended to be more marked in obese than in lean rats (Table 1). Although TPM administration did not influence the intake of DE in lean rats, the drug reduced this intake by either 239 (lower dose) or 382 (higher dose) kcal in obese animals. In lean rats, apparent energy expenditure (as calculated by the difference between energy intake and energy gain) was higher in rats treated with TPM than in animals administered with the vehicle. This variable was not affected by TPM in obese animals. The calculated energetic efficiency (energy gain/energy intake), which represents an estimate of the amount of energy in food that is stored in tissues, was decreased in both lean and obese rats after TPM treatment. The effects of TPM on energetic efficiency tended to be stronger in lean rats than in obese mutants; in lean rats, the high dose of TPM reduced efficiency by >50%.

The effects of TPM on fat and protein gains are summarized in Table 2. TPM reduced fat gain in both lean and obese rats. The high dose of TPM led to reductions of 11.4 and 30.4 g in the fat gains of lean and obese rats, respectively. However, it is noteworthy that the high dose of TPM was associated with a significant reduction in protein gain in both strains. This reduction in lean body mass accretion was not induced by the low dose of TPM, which suggests a specific action of TPM on fat.

The effects of TPM on muscle and fat depot weights (Table 3) were representative of the global effect of TPM on whole body fat and protein gain. The two doses of TPM led to a reduction in the sum of harvested white adipose tissues in both lean and obese rats, in agreement with their effect on fat gain, whereas the high dose of TPM led to a reduction in the weights of the soleus and tibialis muscles, in congruence with its effect on protein gain. The effect of TPM on white adipose tissue was more striking in the subcutaneous (inguinal) depot than in the deep (retroperitoneal and parametrial) depots. Control obese rats exhibited heavier interscapular brown adipose tissue than their lean counterparts (9- to 10-fold), and TPM reduced the weight of brown adipose tissue in lean animals only.

Plasma concentrations of glucose were lower in control obese rats than in control lean rats (Table 4). TPM had no effect on glycemia in either phenotype. On the other hand, TPM dose independently reduced the hyperinsulinemia of obese rats, whereas it did not alter insulinemia in lean animals.

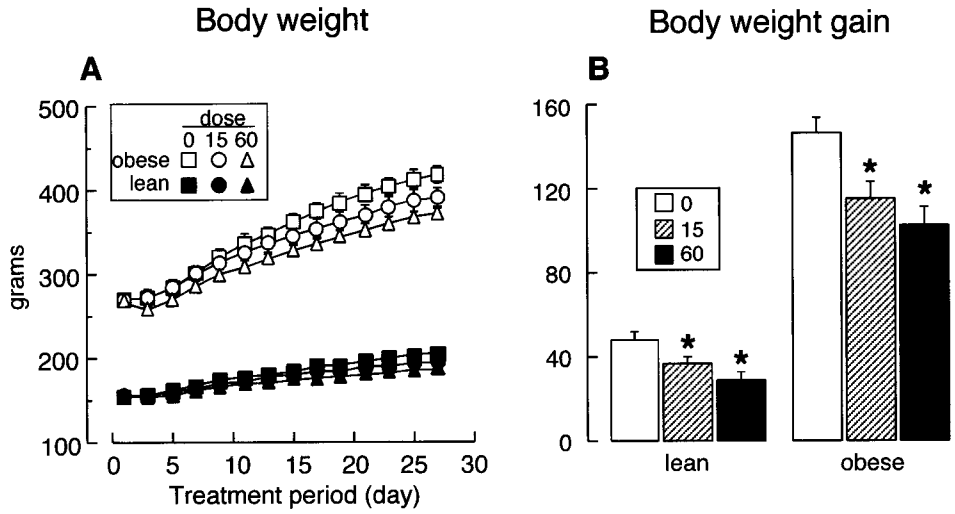

Figure 1. Body weight of lean and obese Zucker rats treated for 4 weeks with two doses of the anticonvulsant drug TPM. Growth curves are illustrated in A, whereas final body weight gains are depicted in B. Symbols represent means ± SEM of 9 or 10 animals. Statistical analyses were applied to weekly gains. An asterisk indicates a difference from rats treated with vehicle ($p < 0.05$).

Plasma corticosterone, which was higher in obese than in lean animals, was not significantly affected by TPM treatment.

Discussion

The present results provide clear evidence for the ability of TPM to reduce energy gain in lean and obese rats. The effects of the drug were gradual and persistent throughout the treatment period. The effect of TPM on energy gain compares quantitatively with those of estrogen (24) and serotoninergic agonists such as dexfenfluramine (19), although the action of TPM on energy balance did not invariably involve an anorectic component. In lean rats, TPM did not alter food intake but yet produced a marked reduction in energy gain. This decreased energetic efficiency strongly suggests that TPM can stimulate energy expenditure, especially since we recently observed that TPM does not alter the digestibility of food (D. R. and P. S., unpublished data). The mechanisms underlying this increase in energy expenditure remain to be elucidated. The reduction in brown adipose tissue weight after administration of TPM in lean

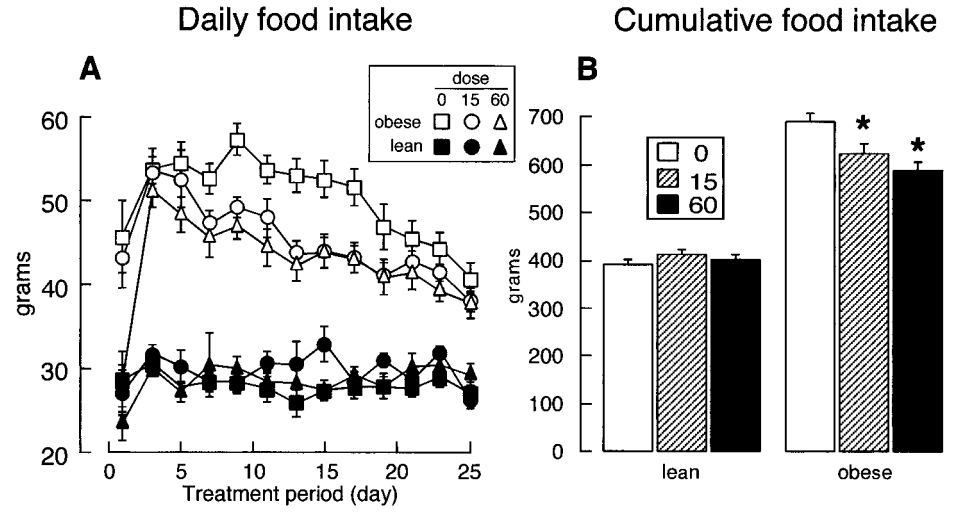

Figure 2. Food intake in lean and obese Zucker rats treated for 4 weeks with two doses of the anticonvulsant drug TPM. Daily food intakes are illustrated in A, whereas cumulative food intakes are depicted in B. Symbols represent means ± SEM of 9 or 10 animals. Statistical analyses were applied to weekly intakes. An asterisk indicates a difference from rats treated with vehicle ($p < 0.05$).

Table 1. Effects of topiramate on energy balance of lean and obese Zucker rats

	Phenotype								
Dose	**Lean (*Fa/?*)**			**Obese (*fa/fa*)**			**ANOVA (*p*)**		
Dose	0	15	60	0	15	60	Phenotype (P)	Dose (D)	Interaction (P × D)
Initial body energy (kcal)	267 ± 5	270 ± 6	268 ± 4	1035 ± 28	1036 ± 28	1022 ± 21	<0.0001	0.91	0.92
Final body energy (kcal)	506 ± 25	446 ± 27	385* ± 29	2222 ± 78	1957* ± 94	1899* ± 56	<0.0001	0.001	0.14
Energy gain (kcal)	238 ± 22	175 ± 23	116*† ± 27	1187 ± 61	921* ± 71	877* ± 56	<0.0001	0.0001	0.07
Digestible energy intake (kcal)	1479 ± 49	1565 ± 35	1517 ± 46	2620 ± 68	2376* ± 71	2233* ± 68	<0.0001	0.01	0.001
Apparent energy expenditure (kcal)	1240 ± 33	1390* ± 30	1401* ± 51	1433 ± 37	1455 ± 29	1357 ± 31	0.02	0.08	0.007
Energetic efficiency (%)	15.9 ± 1.0	11.1* ± 1.4	7.7*† ± 1.7	45.1 ± 1.6	38.4* ± 2.0	39.0* ± 1.6	<0.0001	<0.0001	0.45

* Different from dose 0 within same phenotype ($p < 0.05$).
† Different from dose 15 within same phenotype ($p < 0.05$).

Table 2. Effects of topiramate on protein and fat gains of lean and obese Zucker rats

	Phenotype								
	Lean (*Fa/?*)			**Obese (*fa/fa*)**			**ANOVA (*p*)**		
Dose	0	15	60	0	15	60	Phenotype (P)	Dose (D)	Interaction (P × D)
Protein gain (g)	7.2 ± 0.7	6.8 ± 0.7	4.5*† ± 0.6	12.8 ± 0.9	11.2 ± 0.9	8.3*† ± 0.6	<0.0001	<0.0001	0.47
Fat gain (g)	21.1 ± 2.1	14.6 ± 2.3	9.7* ± 2.8	119.0 ± 6.4	91.7* ± 7.6	88.6* ± 5.8	<0.0001	0.0002	0.08

* Different from dose 0 within same phenotype ($p < 0.05$).
† Different from dose 15 within same phenotype ($p < 0.05$).

Table 3. Effects of topiramate on adipose tissue and skeletal muscle weights of lean and obese Zucker rats

	Phenotype						ANOVA (*p*)		
	Lean (*Fa/?*)			Obese (*fa/fa*)					
Dose	0	15	60	0	15	60	Phenotype (P)	Dose (D)	Interaction (P × D)
Parametrial WAT	1.35 ± 0.16	0.99 ± 0.10	1.02 ± 0.10	5.61 ± 0.46	4.84 ± 0.21	4.85 ± 0.48	<0.0001	0.13	0.74
Retroperitoneal WAT	1.17 ± 0.10	0.95 ± 0.10	0.82* ± 0.09	4.65 ± 0.35	3.94 ± 0.28	4.05 ± 0.33	<0.0001	0.09	0.61
Inguinal WAT	1.23 ± 0.13	0.81* ± 0.09	0.79* ± 0.10	8.91 ± 0.50	7.46* ± 0.27	6.40* ± 0.39	<0.0001	<0.0001	0.004
Sum of harvested WAT	3.76 ± 0.34	2.75* ± 0.24	2.63* ± 0.26	19.17 ± 1.10	16.23* ± 0.53	15.30* ± 0.78	<0.0001	0.0007	0.10
Interscapular BAT	0.53 ± 0.05	0.41* ± 0.02	0.41* ± 0.03	3.91 ± 0.26	4.29 ± 0.29	3.63 ± 0.22	<0.0001	0.21	0.19
Soleus (mg)	88 ± 2	87 ± 3	80 ± 2	86 ± 5	82 ± 4	75 ± 1	0.15	0.03	0.92
Vastus lateralis	0.67 ± 0.02	0.66 ± 0.04	0.59 ± 0.03	0.58 ± 0.02	0.56 ± 0.02	0.51 ± 0.02	<0.0001	0.009	0.97

WAT, white adipose tissue; BAT, brown adipose tissue.
* Different from dose 0 within same phenotype ($p < 0.05$).

Table 4. Effects of topiramate on plasma levels of glucose, insulin, and corticosterone in lean and obese Zucker rats

	Phenotype						ANOVA (*p*)		
	Lean (*Fa/?*)			Obese (*fa/fa*)					
Dose	**0**	**15**	**60**	**0**	**15**	**60**	**Phenotype (P)**	**Dose (D)**	**Interaction (P × D)**
Glucose (mmol/L)	9.0 ± 0.3	8.3 ± 0.4	8.3 ± 0.4	7.8 ± 0.4	7.7 ± 0.4	8.1 ± 0.3	0.03	0.65	0.41
Insulin (nmol/L)	0.09 ± 0.03	0.04 ± 0.00	0.03 ± 0.00	0.95 ± 0.17	0.74* ± 0.08	0.65* ± 0.10	<0.0001	0.13	0.39
Corticosterone (μmol/L)	0.42 ± 0.16	0.77 ± 0.23	0.68 ± 0.18	0.74 ± 0.17	1.22 ± 0.15	1.13 ± 0.20	0.008	0.06	0.92

* Different from dose 0 within same phenotype ($p < 0.05$).

rats does not support a role for this tissue in the potential increase in energy expenditure induced by TPM. It is noteworthy that brown adipose tissue weight is largely determined by its fat content and that TPM could have reduced this component.

TPM can also act on energy balance by reducing food intake. Such an effect was clearly evident in obese Zucker rats, particularly in the initial period of the study. This phenotype-related difference in the mode of action of TPM in affecting energy balance possibly relates to the fact that the drug acts centrally on the regulation of energy balance, leading to responses to effectors of food intake and energy expenditure that could differ according to phenotype. In concomitance with a reduction in food intake, TPM also reduced energetic efficiency in obese rats. This suggests a stimulating effect of TPM on thermogenic processes, given that a decrease in food intake generally predicts a decrease in energy expenditure (25), which was not the case in TPM-treated *fa/fa* rats in the present study.

The reducing effects of TPM on energy gain translated into a reduction in fat gain and adipose tissue weights. This effect was seen in both lean and obese rats. In addition to reducing fat mass, high doses of TPM also attenuated protein gain. Whether this effect applies only to young, growing rats such as those used in this study has yet to be investigated. However, this effect was observable only with the high dose of TPM. In addition, it is important to note that TPM-treated animals did not lose, but merely gained less, protein mass compared with untreated rats. At the low dose, TPM did not blunt the gain in protein mass while it significantly decreased fat gain, which points to some specific action of the drug on fat mass.

Another germane finding of this study is that TPM reduced fasting plasma insulin in obese rats. This could be an indication that the sensitivity of glucose metabolism to insulin is improved after TPM. Insulin sensitivity is grossly deteriorated in obese Zucker rats (26). Not surprisingly, TPM did not affect the already low fasting plasma insulin of lean animals. The lowering action of TPM on insulinemia in obese animals may have been caused by the concomitant reduction in food intake elicited by the drug. Interestingly, glucose levels were significantly lower in obese rats compared with lean animals. The reason for this is unknown, although the possibility exists that this diminution could be associated with the length of the period of fasting preceding the killing of the rats. Given that young obese Zucker rats are in a dynamic phase of developing obesity, it can be argued that fasting has a stronger effect than in lean rats. An 8-hour period of fasting represents a stress that is much more challenging to obese than lean adult Zucker rats (27), suggesting that obese and lean rats do not respond similarly to fasting.

The potentiation of central GABAergic transmission and the inhibition of the excitatory actions mediated through the kainate/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamatergic receptor (28–30), which are two mechanisms of action of TPM, are not predictive *a priori* of an increase in energy expenditure. Indeed, one would predict an increase in energy gain after treatment with drugs that stimulate GABAergic pathways and antagonize glutamatergic transmission, which are characteristic actions of anticonvulsants. However, it seems that not all anticonvulsant drugs promote energy gain. In this respect, the observation has been made that, in contrast to anticonvulsant drugs that predominantly potentiate GABA neurotransmission, those that mainly inhibit the activity of the glutamatergic system could promote weight loss (2). Whether such a balance of action on GABAergic and glutamatergic systems applies to TPM remains to be determined.

In conclusion, this study provides clear evidence for the ability of TPM to reduce the gains in body weight, body energy, and body fat in lean as well as in obese Zucker rats. In lean animals, TPM increased energy expenditure without altering food intake, whereas in obese mutants, TPM reduced food intake without altering energy expenditure.

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