Thermogenic drugs for the treatment of obesity: sympathetic stimulants in animal models

BY A. G. DULLOO AND D. S. MILLER*

Department of Nutrition, Queen Elizabeth College, University of London, Campden Hill Road, London W8 7AH

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1. Thirty-three drugs known to stimulate the sympathetic nervous system have been screened for thermogenic properties. The results presented are for seven of them.

2. The drugs were tested in five animal models of obesity (genetic (mice and rats), hypothalamic (mice) and dietary (mice and rats)) as well as in lean mice. Energy-balance studies were undertaken using the comparative-carcass technique as well as by measurement of daily oxygen consumption.

3. All seven drugs in obese animals tended to reduce body-weight and fat without loss of body protein: they acted by increasing metabolic rate without increasing food intake. They were much less effective in lean animals. These findings lend support to the concept that obesity is due to a diminished activity of the sympathetic nervous system.

4. Differences in the effectiveness of the drugs are discussed in relation to differences between the animal models of obesity. Ephedrine and tranylcypromine were found to be the most effective drugs in this series of experiments and a *prima facie* case is made for human clinical trials.

The methodology for screening thermogenic drugs for the treatment of obesity has been outlined by Massoudi *et al.* (1983) who defined an ideal drug as being one that not only increases metabolic rate and causes loss of body fat but should achieve this without a reduction in food intake or a loss of body protein. They also emphasize the need to test such drugs using obese rather than lean animals, since obesity should be regarded as a faulty homeostatic system involving a metabolic defect. At the present time, the most promising drug is ephedrine (Massoudi & Miller, 1977; Rothwell & Stock, 1979; Arch *et al.* 1982; Morgan *et al.* 1982; Massoudi *et al.* 1983). Since ephedrine may be considered to act as though it were a long-acting noradrenaline, the results of experiments with a further six sympathomimetic drugs are presented here in comparison with ephedrine as a positive control. The six new drugs were selected from preliminary screening of the thirty-three drugs shown in Table 1, which act at various sites along the line of sympathetic control. Those selected are all described in the pharmacopoeias but with applications in many fields other than obesity.

The use of thermogenic drugs in the treatment of obesity has enormous potential therapeutically but also could be of value in understanding the metabolic basis of obesity and leanness. There are three main types of animal model used in the study of the aetiology of obesity (hypothalamic, genetic and dietary) all of which have been shown to have a high efficiency of energy utilization (Miller, 1979). It is not known which is appropriate to human obesities, and it is wise therefore to use as many animal models as possible.

METHODS

Six energy-balance experiments, based on the comparative-carcass technique, were carried out to study the potential thermogenic effects of seven sympathomimetic drugs in five different obese models, and also in lean mice.

* For reprints.

Table 1. *Sympathomimetic agents screened for thermogenic properties*

Site and mode of action	Type of drug	Drug name	Main pharmacological use
Stimulation of postsynaptic adrenergic receptors	Non-selective β-agonists	Orciprenaline Methoxyphenamine Isoprenaline Isoxsuprine	Vasodilators used in the treatment of bronchial asthma and bronchitis
	Selective β_2-agonists	Salbutamol Terbutaline	
	α-agonists	Phenylephrine Naphazoline Xylometazoline	Vasoconstrictor used in rhinitis and sinusitis
Stimulation of NA synthesis	NA-precursors	Tyrosine Dopa Dopamine	Parkinsonism. Treatment of hypotension and shock
Enhancement of NA release from storage sites	NA vesicular-release promoters	Ephedrine Phenylpropanolamine Tyramine	Bronchospasm; as a nasal decongestant
Blockade of negative feed-back inhibition of NA release	Presynaptic α_2-antagonist	Yohimbine Tolazoline Phenoxybenzamine	As an antidiuretic vasodilator used in peripheral vascular disease
Prevention of enzymatic inactivation of NA	Monoamine oxidase (*EC* 1.4.3.4) inhibitors	Tranylcypromine Iproniazid Pargyline Phenelzine	Antidepressants
	COMT-inhibitor	Pyrogallol Tropolone	
Prevention of uptake of NA from synaptic junction	Neuronal NA-reuptake inhibitors	Imipramine Trimipramine Amitriptyline Iprindole	Antidepressants
	Extraneuronal uptake inhibitor	Normetanephrine	
Prolongation of cAMP action	Phosphodiesterase (*EC* 3.1.4.1) inhibitor	Caffeine Theophylline Theobromine Papaverine	In treatment of peripheral vascular disease, chronic bronchitis, bronchial asthma and coronary spasm

NA, noradrenaline; COMT, catechol-*O*-methyltransferase (*EC* 2.1.1.6).

Animals

Mice

These were conducted on 3–4-month-old males and lasted for 7 weeks. Three obese models and one lean strain were studied in the following experiments:

Expt 1 (*MSG*). Mice of the CFLP strain were made obese by chemical lesioning in the hypothalamus following injections of monosodium glutamate during the first week of life (Miller, 1979).

Expt 2 (*HPHF*). Mice of the CFLP strain were made obese by feeding them a high-protein, high-fat diet (described by Miller, 1979) from weaning onwards.

Expt 3 (ob/ob). Genetically-obese mice of the *ob/ob* strain were used.

Expt 4 (*lean*). Lean mice of the CFLP strain were used.

Rats

These experiments were carried out on 5–7-month-old female rats and lasted for 9 weeks. Two types of obese rats were studied in the following experiments:

Expt 5 (fa/fa). Obese rats of the Zucker strain were used.

Expt 6 (*HPHF*). Rats were of the Hooded strain, made obese by feeding them the same energy-dense diet as in Expt 2.

Experimental procedures

Before the start of each experiment, the animals were given a powdered form of the stock diet (CRM, Christopher Hill Group, London) for an adaptation period of at least 2 weeks. The composition of the diet (g/kg) was: 180 protein, 24 fat, 570 carbohydrate, 36 crude fibre, 14200 kJ metabolizable energy (ME)/kg. At the beginning of each experiment, the animals were divided into nine groups of four animals such that each group within an experiment had the same mean body-weight. One group (the initial control group) was killed and retained for estimation of initial carcass energy. Another group was given the stock diet only and served as the no-drug control group, while the remaining groups were given the stock diet to which was added one of the seven sympathomimetic drugs under investigation. For each drug, the same dose (found to be most effective during the preliminary screening experiments) was administered throughout the whole experimental period. The dose (mg/kg diet) for each drug is as follows: ephedrine hydrochloride (Thornton & Ross (Linthwaite Laboratories); Huddersfield) 1000, methoxyphenamine hydrochloride (Upjohn; Crawley, Sussex) 1000, yohimbine hydrochloride (Sigma; Poole, Dorset) 500, tranylcypromine sulphate (Smith, Kline and French; Welwyn, Herts) 500, amitriptyline hydrochloride (William Warner (Parke Davis); Eastleigh, Hants) 500, iprindole hydrochloride (Wyeth; Maidenhead, Berks) 1000, theophylline (Riker; Loughborough, Leics) 1000.

The authors are aware that this method of dosing is unusual for pharmacological studies but consider it to have many advantages for this type of long-term nutritional investigation. Firstly, it avoids frequent daily handling of animals for injection or oral gavage and this reduces stress. Secondly, it ensures a continuous administration of the drug in association with the diet and increases the likelihood of drug-potentiation of thermogenesis associated with food. Thirdly, it overcomes the problem of deciding whether to dose the animals per kg body-weight, per kg to the power of 0·75 or per kg lean body mass: such considerations are clearly important when dealing with animals of different body size and different degrees of obesity. Finally, pharmacologists might consider this method of stating dose rates when transferring the results of animal metabolic experiments to man, since metabolic rate is more closely related to food intake than to body-weight (Kleiber, 1961; Harwood, 1963;

Schmidt-Nielson, 1972). It is possible to calculate the doses given in this paper in terms of mg/kg body-weight from the data given in the tables but it is our experience that animals given drugs in their food can tolerate higher doses than when the drug is administered acutely by injection or oral gavage and hence comparison with other work may be misleading.

In the mice experiments, the animals in each group were housed together in a cage, while in the rat experiments, the animals were paired per cage. All animals were kept at $25 \pm 1°$ during the experiments. Food and water were given *ad lib.*; food intake was measured weekly and for all experimental weeks. The energy digestibility, determined over at least 1 week, was used to calculate the ME intake using the formula of Miller & Payne (1959). The 24 h oxygen consumption (V_{O_2}) was measured twice for each group during the second half of each experimental period; the calorimeter apparatus has been described by Boroumand & Miller (1976).

At the end of each experiment, the animals were killed and all carcasses (including those of the initial controls) were analysed for energy content using the ballistic bomb calorimeter (Miller & Payne, 1959); total carcass fat was determined by the Soxhlet fat-extraction method (Colowick & Kaplan, 1957). Carcass protein was calculated using a general formula relating the energy derived from fat with the total energetic value of the carcass and the energy derived from protein (Djazayery *et al.* 1979). The energy values (kJ/g) for fat and protein used in the equation were 38·6 and 22·7 respectively (Boroumand, 1977). Thus,

$$\text{protein (g)} = 0{\cdot}044 \text{ energy content (kJ)} - 1{\cdot}7 \text{ fat (g)}.$$

From the values of total ME intake and carcass energy contents, the total heat production was calculated using the following formula:

$$\text{total heat production} = I - (B - B_0),$$

where I is the ME intake, B is the final carcass energy, B_0 is the initial carcass energy.

Statistical analysis

Values for body composition are presented as means with their standard errors and statistical analysis of results was performed using the Student's t test for unpaired values.

RESULTS

Expt 1. MSG mice

The body-weights and carcass compositions are shown in Table 2. At the end of the 7-week experiment, the no-drug control group had gained 9·0 g in body-weight, this being mostly due to a 35% increase in body fat.

In contrast, methoxyphenamine, yohimbine, tranylcypromine and amitriptyline all caused great reduction in body-weight and in body fat compared with either the no-drug control group or the initial control group. For example, relative to the no-drug control group, methoxyphenamine and tranylcypromine caused losses of 76 and 64% in body fat respectively, while body fat was reduced by 68 and 52% respectively when compared with the initial control group. On the other hand, ephedrine, iprindole and theophylline treatments did not cause significant weight reduction, but they prevented the 20% weight gain that occurred in the no-drug control. Moreover, ephedrine and iprindole caused much loss of total body fat and percentage body fat even when compared with the initial controls. The loss in body fat without a concomitant reduction in body-weight was due to the fact that there was a corresponding gain in body water and body protein in the ephedrine- and iprindole-treated groups. Theophylline treatment, however, had no influence on the carcass

Table 2. *Final body-weight, carcass composition and energy balance of MSG-obese mice treated with seven sympathomimetic drugs for 7 weeks*

(Mean values with their standard errors for four animals per group)

Treatment group	Body-wt (g)		Body fat				Body protein				Carcass energy gain† (kJ)	Metabolizable energy intake† (kJ/d)		Heat production† (kJ/d)		24 h oxygen consumption† (l/d)	
			g		% body-wt		g		% body-wt			/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE							
No-drug control	48·9	1·5	20·7	0·9	42·3	2·4	6·39	0·34	13·0	0·4	+232	53·6	549	48·8	496	2·1	22·3
Ephedrine (1000 mg)‡	39·0**	2·0	12·1*	2·3	30·4*	4·4	5·79	0·19	15·0	0·9	−112	45·6	527	47·9	555	2·3	26·7
Methoxyphenamine (1000 mg)	31·3***	2·2	4·9***	0·9	15·5***	2·0	5·33	0·32	17·0***	0·3	−399	44·0	581	52·1	684	2·2	28·8
Yohimbine (500 mg)	32·4***	1·1	6·7***	1·5	20·8**	4·8	5·14*	0·32	15·9*	0·8	−338	39·2	492	46·1	580	2·2	27·1
Tranylcypromine (500 mg)	32·4***	1·9	7·4***	2·1	22·2**	5·0	5·06*	0·23	15·7*	0·7	−316	43·2	576	49·7	659	2·3	30·7
Amitriptyline (500 mg)	34·9***	1·8	9·5***	1·3	26·8**	2·4	5·17*	0·14	14·9*	0·4	−230	38·4	490	43·1	553	2·2	29·1
Iprindole (1000 mg)	38·8**	1·6	12·1**	1·4	31·0*	2·8	5·95	0·32	15·3*	0·5	−111	43·0	505	45·3	531	2·1	23·8
Theophylline (1000 mg)	39·8**	1·3	15·1**	1·2	37·8	1·7	5·38*	0·06	13·6	0·3	−4	41·6	480	41·7	482	1·9	21·6
Initial control	39·9	1·2	15·4	1·2	38·6	1·5	5·10	0·10	12·7	0·3	—	—	—	—	—	—	—

$W^{0.75}$, body-weight$^{0.75}$.

Mean values for the various drug-treated groups were significantly different from that for the no-drug control: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

† Values represent grouped values.

‡ Values in parentheses represent dose (mg/kg diet) administered.

composition which remained similar to that of the initial controls. In all drug-treated groups, the total carcass protein was lower than that of the no-drug control group. However, if a comparison was made with the initial controls, there was no reduction in total body protein. In fact, the proportion of carcass protein in the drug-treated groups was in each case higher than that of the no-drug control group. Thus, with the exception of theophylline, all the other six drugs caused great reduction in body fat without causing loss of body protein.

The values for energy intake show that treatment with the drugs reduced food intake by 20–30% compared with that of control values. However, when expressed on a per kg metabolic body size ($W^{0.75}$) basis, the food intakes were similar to that of the controls. Nevertheless, both food intake and energy expenditure values remained lower than those of controls in the theophylline-treated group whichever way the results were expressed. Clearly, theophylline prevented the positive energy balance that occurred in the controls mainly by an anorectic effect. The values for total heat production (estimated by comparative-carcass technique) and 24 h V_{O_2} (estimated by calorimetric technique) showed that the other six drugs markedly elevated metabolic rate when allowance was made for the smaller body size of these treated groups. For example, the metabolic rate was increased by 29–38% with methoxyphenamine and tranylcypromine, by 12–30% with ephedrine, yohimbine and amitriptyline, and by 7% with iprindole. Moreover, even when expressed per animal, the metabolic rates of most treated groups were higher than that of the much heavier control group: methoxyphenamine and tranylcypromine increased V_{O_2} by 5 and 10% respectively in animals which weighed about 35% less than the controls at the time of V_{O_2} measurements.

The thermogenic activities of these six drugs were further illustrated by comparing values with those of the theophylline-treated group. It was found that despite the fact that absolute food intakes (expressed per animal) were similar or higher than those of the theophylline-treated group, they had higher metabolic rates (per animal) and much lower body fat and body energy contents. For instance, both tranylcypromine- and methoxyphenamine-treated groups consumed 6% more food per animal than the theophylline-treated group, and yet their V_{O_2} values were about 20% higher and they lost 400 and 316 kJ respectively, while the theophylline-treated group lost only 4 kJ.

Thus, with the exception of theophylline, the other six drugs brought about a state of negative energy balance in MSG-obese mice mainly by a thermogenic effect.

Expt 2. HPHF mice

At the end of this experiment, the no-drug control group weighed 5% more than at the start; this weight gain was due to increases in both body fat and protein with no change in body water (Table 3). Compared with the no-drug controls, all seven sympathomimetic drugs caused very marked reductions in body-weight and body fat but had little or no effect on total body protein and water content. Yohimbine caused the most profound reduction in body fat (75% loss), while the other drugs produced between 40 and 60% reduction in both total fat and percentage body fat. The fact that decreases in body-weight were unaccompanied by reductions in total body protein and water resulted in significantly higher values for percentage body protein and percentage water in all drug-treated groups. When compared with the initial control group, the drug-treated groups also had much lower body fat, whereas body protein was actually higher than in the initial control group.

Energy intakes, if expressed per animal, were similar in all groups, except for a 10% reduction in the yohimbine-treated group. However, this latter difference was abolished when the smaller body-weight of the yohimbine group was taken into consideration. Thus, food intakes, expressed as a function of body-weight, were either the same or higher than

Table 3. *Final body-weight, carcass composition and energy balance of HPHF-mice treated with seven sympathomimetic drugs for 7 weeks*

(Mean values with their standard errors for four animals per group)

Treatment group	Body-wt (g)		Body fat				Body protein				Carcass energy gain† (kJ)	Metabolizable energy intake† (kJ/d)		Heat production† (kJ/d)		24 h oxygen consumption† (l/d)	
			g		% body-wt		g		% body-wt			/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE							
No-drug control	45·7	0·2	5·98	0·21	13·10	0·50	8·43	0·10	18·5	0·1	+72	62·6	645	61·1	618	2·9	29·7
Ephedrine (1000 mg)‡	42·8**	0·6	2·63***	0·22	6·12***	0·43	8·70*	0·10	20·3**	0·5	−51	62·5	662	63·5	667	3·1	32·9
Methoxyphenamine (1000 mg)	42·9**	0·5	3·36***	0·06	7·83***	0·08	8·44	0·12	19·7***	0·1	−29	60·3	639	60·9	641	3·0	31·4
Yohimbine (500 mg)	39·7***	0·1	1·47***	0·17	3·69***	0·44	7·95*	0·16	20·0*	0·5	−113	56·9	618	59·2	659	2·8	32·1
Tranylcypromine (500 mg)	41·0***	0·2	2·84***	0·12	6·94***	0·25	8·33	0·13	20·3***	0·2	−52	66·8	720	67·9	722	3·4	36·7
Amitriptyline (500 mg)	40·5**	1·4	2·77***	0·41	6·73***	0·80	7·72*	0·26	19·0**	0·1	−68	61·0	657	62·4	673	3·0	32·3
Iprindole (1000 mg)	42·1***	0·4	2·63***	0·11	6·24***	0·26	8·03**	0·10	19·1**	0·1	−67	61·8	660	63·1	677	3·2	35·1
Theophylline (1000 mg)	42·2**	0·9	2·46***	0·28	5·81***	0·63	8·59	0·18	20·4***	0·2	−61	60·3	639	61·6	665	2·9	31·4
Initial control	43·2	0·2	5·00	0·20	11·60	0·40	6·90	0·10	16·1	0·1	—	—	—	—	—	—	—

$W^{0.75}$, body-weight$^{0.75}$.

Mean values for the various drug-treated groups were significantly different from that for the no-drug control: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

† Values represent grouped values.

‡ Values in parentheses represent dose (mg/kg diet) administered.

Table 4. *Final body weight, carcass composition and energy balance of obese* ob/ob *mice treated with seven sympathomimetic drugs for 7 weeks*

(Mean values with their standard errors for four animals per group)

Treatment group	Body-wt (g)		Body fat				Body protein				Carcass energy gain† (kJ)	Metabolizable energy intake† (kJ/d)		Heat production† (kJ/d)		24 h oxygen consumption† (l/d)	
			g		% body-wt		g		% body-wt			/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE							
No-drug control	68·3	0·9	29·4	0·4	43·0	0·3	8·00	0·34	11·7	0·5	+37	72·0	555	71·2	547	3·2	24·4
Ephedrine (1000 mg)‡	60·9	3·5	24·2*	1·8	39·5**	0·7	7·07*	0·17	11·7	0·7	−188	66·4	548	70·2	584	3·3	26·6
Methoxyphenamine (1000 mg)	62·4*	1·8	30·5	0·6	48·9**	1·3	6·10	1·12	9·7	1·7	+34	61·5	506	60·8	502	3·0	24·2
Yohimbine (500 mg)	62·9	5·0	27·9	2·5	44·4	0·5	7·30	0·70	11·6	0·2	−37	62·0	506	62·8	514	3·0	24·0
Tranylcypromine (500 mg)	56·7**	2·5	21·3**	2·1	37·1*	2·1	6·84	0·62	12·1	0·5	−305	63·1	546	69·3	600	3·4	29·0
Amitriptyline (1000 mg)	63·4	4·8	27·7	2·3	43·7	0·6	8·23	0·70	13·0	0·1	−25	62·5	512	63·0	516	3·1	24·6
Iprindole (1000 mg)	60·6	3·3	26·5	2·3	43·5	1·8	6·41*	0·37	10·6	0·4	−113	59·1	494	61·4	514	3·0	24·4
Theophylline (1000 mg)	67·9	4·2	32·8	2·7	48·1**	1·1	9·95	0·82	14·6**	0·3	+210	71·7	572	67·4	539	3·0	24·0
Intial control	61·7	2·6	28·5	0·8	46·2	1·2	7·90	1·30	12·8	1·5	—	—	—	—	—	—	—

$W^{0·75}$, body-weight$^{0·75}$.

Mean values for the various drug-treated groups were significantly different from that for the no-drug control: * $P < 0·05$, ** $P < 0·01$.

† Values represent grouped values.

‡ Values in parentheses represent dose (mg/kg diet) administered.

controls. The tranylcypromine-treated group consumed between 7 and 13% more food, depending on the way in which the results were expressed, and yet this group lost about 50% body fat when compared with the no-drug control group. In fact, even when expressed in absolute terms, the metabolic rates of some drug-treated groups were found to be higher than those of controls despite their lower body-weight. For example, tranylcypromine, ephedrine and iprindole raised the 24 h V_{O_2} per animal by 15, 7, and 11% respectively, while the total heat production was higher by 11, 4, and 3% respectively than the control values. When total heat production was expressed per metabolic body size, all drugs showed substantial thermogenic effects. These were confirmed by values for 24 h V_{O_2} which showed that metabolic rates were increased by about 24% with tranylcypromine, 18% with iprindole, and between 6 and 9% with the other drugs.

Thus, in this dietary obese model, all seven sympathomimetic drugs caused negative energy balance by virtue of their thermogenic effects.

Expt 3. (ob/ob) *mice*

The body-weights and carcass compositions are shown in Table 4. At the end of the experiment, the no-drug control group had gained 6·6 g in body-weight, but this was mostly due to an increase in body water, with only a slight increase of 1·0 g in body fat content and no change in body protein. Consequently, when expressed as a percentage of body-weight, both the body fat and protein values were lower than those of the initial controls.

Only tranylcypromine caused substantial reduction in body-weight with respect to the initial control value. However, when comparisons were made with the no-drug control, all drug treatments (except theophylline) did reduce body-weight, although significant differences were obtained only for tranylcypromine ($P < 0{\cdot}01$) and methoxyphenamine ($P < 0{\cdot}05$). Total body fat was reduced by 18 and 28% in the ephedrine- and tranylcypromine-treated groups respectively, and this was associated with about 13% less body protein than in the no-drug controls. However, it should be noted that these losses of total body protein were not reflected in changes in the percentage of protein in the carcass. For example, tranylcypromine- and ephedrine-treated groups had similar values for percentage body protein as the no-drug controls. The other drugs had little effect on body fat but, in methoxyphenamine- and theophylline-treated groups, the percentage body fat was elevated, and was significantly higher: about 12% above control values. The theophylline-treated group also had increased percentage body protein ($P < 0{\cdot}01$).

Table 4 shows that, with the exception of theophylline, the other drugs caused 10–20% reduction in absolute food intake. However, such differences were abolished when food intakes were expressed as kJ/kg $W^{0{\cdot}75}$. The results for total heat production and 24 h V_{O_2} revealed that only ephedrine and tranylcypromine elevated metabolic rate substantially by 8 and 10–19% respectively.

Thus, in the genetic *ob/ob* obese model, only ephedrine and tranylcypromine were found to have thermogenic activities and to cause substantial loss of body fat.

Expt 4. Lean mice

Table 5 shows that only the tranylcypromine-treated group showed a significant weight loss compared with the no-drug controls. Surprisingly, the ephedrine-treated animals had an elevated body-weight, although not significantly; this was due to a greater body water retention. Both ephedrine and tranylcypromine treatments reduced body fat content by 14 and 17% respectively when compared with the no-drug controls. However, comparison of carcass composition with that of initial controls revealed that both these latter drugs reduced fat deposition rather than caused fat losses. Similarly, tranylcypromine treatment caused

Table 5. *Final body-weight, carcass composition and energy balance in lean mice treated with seven sympathomimetic drugs for 7 weeks*

(Mean values with their standard errors for four animals per group)

Treatment group	Body-wt (g)		Body fat				Body protein				Carcass energy gain† (kJ)	Metabolizable energy intake† (kJ/d)		Heat production† (kJ/d)		24 h oxygen consumption† (l/d)	
			g		% body-wt		g		% body-wt			/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$	/mouse	/kg $W^{0.75}$
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE							
No-drug control	31·7	0·4	2·19	0·02	6·91	0·03	6·35	0·16	20·0	0·4	+22	55·1	738	54·7	733	2·5	32·9
Ephedrine (1000 mg)‡	32·5	0·3	1·89***	0·03	5·81***	0·04	6·63	0·11	20·5	0·2	+16	58·3	762	58·0	773	2·8	36·1
Methoxyphenamine (1000 mg)	32·1	0·1	2·25	0·06	7·01	0·19	6·29	0·05	19·6	0·1	+23	50·8	683	50·4	677	2·4	31·6
Yohimbine (500 mg)	31·6	0·3	2·64	0·40	8·36	1·10	5·73	0·16	18·8	0·4	+29	51·3	691	50·7	683	2·3	31·1
Tranylcypromine (500 mg)	29·6***	0·2	1·82**	0·09	6·17*	0·27	5·71**	0·03	19·2	0·1	−7	54·7	753	54·8	761	2·7	37·2
Amitriptyline (500 mg)	31·7	0·2	2·38	0·10	7·51	0·34	6·20	0·16	19·6	0·5	+25	54·3	726	53·8	718	2·5	33·4
Iprindole (1000 mg)	31·2	0·8	2·42	0·17	7·72	0·70	6·43	0·16	20·6	0·9	+29	56·0	760	55·4	751	2·4	33·3
Theophylline (1000 mg)	33·8	1·0	2·42	0·22	7·15	0·50	6·36	0·09	18·9	0·3	+31	57·2	753	56·5	743	2·6	32·8
Initial control	30·5	0·3	1·95	0·09	6·41	1·00	5·78	0·02	19·0	0·3	—	—	—	—	—	—	—

$W^{0.75}$, body-weight$^{0.75}$.

Mean values for the various drug-treated groups were significantly different from that for the no-drug control: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

† Values represent grouped values.

‡ Values in parentheses represent dose (mg/kg diet) administered.

reduction in protein deposition, but the final percentage body protein content was not lower than that of controls. Ephedrine had no effect on either total or percentage body protein. The other drugs did not alter the carcass composition of these lean animals compared with the no-drug controls.

The values for food intake, total heat production and 24 h V_{O_2} are also shown in Table 5. It is noticed that the ephedrine-treated animals consumed about 3% more food than the controls but this increase in intake was over-compensated by a 6% increase in total heat production, such that this group gained less body energy than the controls. Tranylcypromine-treated animals, on the other hand, had similar absolute energy intake and total heat production; however, if the results were expressed as a function of metabolic body size ($W^{0.75}$) it was found that the food intake and heat production were increased by about 2 and 4% respectively. Measurements of 24 h V_{O_2}, however, showed more marked increases in metabolic rate in both tranylcypromine- and ephedrine-treated groups: absolute V_{O_2} was higher by 9 and 13% respectively while $V_{O_2}/W^{0.75}$ was elevated by 13 and 10% respectively.

In the cases of theophylline- and iprindole-treated animals, both the absolute food intake and heat production were slightly elevated (by 3–4%), while in the methoxyphenamine- and yohimbine-treated groups they were reduced (by 6–8%). However, the body composition and body energy content of these treated groups remained similar to those of the no-drug control group, and therefore suggest that these four drugs had little influence on the net energy balance of these lean mice.

Thus, with the lean mice, only tranylcypromine and ephedrine caused substantial thermogenic effects that led to reduced body fat deposition.

Expt 5. Zucker fa/fa *rats*

The no-drug control group gained 8% more weight during the course of the 9-week experiment. However, like the *ob/ob* mice (Expt 3), this increase in body-weight was largely due to an increase in body water; body fat was only slightly increased while body protein remained unaltered (Table 6). All seven sympathomimetic drugs caused much loss in both total and percentage body fat. These effects were more marked with ephedrine, tranylcypromine and iprindole: these drugs caused total body fat to be reduced to about one-half and percentage body fat to two-thirds that of control values. The remaining drugs also reduced body fat by 25–35% of control values. Total body protein of the animals treated with ephedrine, tranylcypromine and iprindole was similar to that of the no-drug control group.

The food intake per animal was reduced in all groups when compared with controls. This effect was most pronounced with groups treated with tranylcypromine and iprindole; the food consumption (per animal) was only two-thirds that of the controls. When food intake was expressed per kg $W^{0.75}$, the difference in food intake was abolished in most drug-treated groups; but food intakes per kg $W^{0.75}$ of the tranylcypromine- and iprindole-treated animals were still 25% less than that of the controls.

On the other hand, values for metabolic rate showed that all these seven drugs possess thermogenic activities. In fact, the 24 h V_{O_2} results indicate that if the smaller metabolic body size of the treated animals compared with the no-drug controls is taken into account, then the metabolic rate was increased by 18–26% with ephedrine, tranylcypromine and methoxyphenamine, and by 6–14% with the remaining drugs. Similarly, total heat production (per kg $W^{0.75}$) was higher in all drug-treated groups: ephedrine and tranylcypromine caused a 30% increase in heat production, while the other drugs elevated the metabolic rate by 15–20% above that of the control group. Furthermore, despite the smaller body-weights compared with the control group during much of the experimental period, the total heat production expressed in abolute terms was higher by 5–13% in those groups treated with ephedrine, methoxyphenamine, yohimbine, amitriptyline and theophylline.

Table 6. *Final body-weight, carcass composition and energy balance of obese* fa/fa *rats treated with seven sympathomimetic drugs for 9 weeks*

(Mean values with their standard errors for four animals per group)

Treatment group	Body-wt (g)		Body fat				Body protein				Carcass energy gain† (kJ)	Metabolizable energy intake† (kJ/d)		Heat production† (kJ/d)		24 h oxygen consumption† (l/d)	
			g		% body-wt		g		% body-wt			/rat	/kg $W^{0.75}$	/rat	/kg $W^{0.75}$	/rat	/kg $W^{0.75}$
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE							
No-drug control	671	16	390	19	58·1	1·5	59·8	3·2	8·88	0·25	+343	346	481	340	471	15·7	21·0
Ephedrine (1000 mg)‡	490***	18	194***	17	39·3***	2·0	45·2*	3·8	9·16	0·45	−7522	267	447	386	644	15·3	25·9
Methoxyphenamine (1000 mg)	548***	9	251***	4	45·9***	1·5	31·9***	0·4	5·82***	0·16	−5636	269	412	358	549	16·0	24·9
Yohimbine (500 mg)	569**	17	283***	7	49·9**	0·8	33·8***	0·8	5·95***	0·11	−4335	296	450	365	554	15·6	24·0
Tranylcypromine (500 mg)	427***	14	164***	7	38·4***	0·4	40·7**	1·9	9·53	0·15	−8800	193	382	333	637	13·2	26·4
Amitriptyline (500 mg)	580*	25	286**	8	49·8*	2·7	35·3***	0·7	6·13***	0·30	−4213	305	460	372	560	15·2	23·0
Iprindole (1000 mg)	462***	17	203***	4	43·9***	0·8	39·8***	0·8	8·62	0·17	−7342	210	352	326	549	12·6	22·2
Theophylline (1000 mg)	568**	22	252***	8	44·4***	0·5	35·1***	1·4	6·20***	0·11	−5548	295	438	383	568	16·4	23·4
Initial control	621	14	381	4	61·3	0·8	60·4	2·9	9·75	0·70	—	—	—	—	—	—	—

$W^{0.75}$, body-weight$^{0.75}$.

Mean values for the various drug-treated groups were significantly different from that for the no-drug control: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

† Values represent grouped values.

‡ Values in parentheses represent dose (mg/kg diet) administered.

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Table 7. *Final body-weight, carcass composition and energy balance of HPHF-rats treated with seven sympathomimetic drugs for 9 weeks*

(Mean values with their standard errors for four animals per group)

Treatment group	Body-wt (g)		Body fat				Body protein				Carcass energy gain† (kJ)	Metabolizable energy intake† (kJ/d)		Heat production† (kJ/d)		24 h oxygen consumption† (l/d)	
			g		% body-wt		g		% body-wt								
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE		/rat	/kg $W^{0.75}$	/rat	/kg $W^{0.75}$	/rat	/kg $W^{0.75}$
No-drug control	285	2	58·2	3·0	20·3	0·9	48·5	1·8	17·2	0·9	+177	177	460	174	457	8·2	21·0
Ephedrine (1000 mg)‡	251**	6	18·4***	2·1	7·2***	0·7	50·1	1·2	20·0*	0·2	−1326	151	428	172	492	8·9	25·2
Methoxyphenamine (1000 mg)	208***	2	19·9***	0·3	9·5***	0·2	41·7*	1·2	20·1*	0·8	−1460	130	403	153	476	6·9	22·0
Yohimbine (500 mg)	243***	2	28·3***	3·4	11·6***	1·3	42·0*	1·4	17·2	0·6	−1125	148	421	166	475	8·5	24·6
Tranylcypromine (500 mg)	226***	4	13·0***	1·7	5·8***	0·8	44·2	1·2	19·5*	0·4	−1665	151	469	177	554	9·1	27·2
Amitriptyline (500 mg)	244***	5	35·5***	1·9	14·5***	0·3	43·0*	0·5	17·6	0·2	−827	156	451	169	484	8·9	25·7
Iprindole (1000 mg)	220***	3	20·2***	1·5	9·2***	0·9	43·2*	0·6	19·8*	0·1	−1413	135	408	157	478	7·7	23·4
Theophylline (1000 mg)	263*	8	29·0***	0·9	11·1***	0·5	44·9	1·7	17·1	0·3	−1040	176	476	193	522	9·3	25·1
Initial control	266	2	56·6	2·8	20·6	1·0	43·7	1·5	16·6	1·0	—	—	—	—	—	—	—

$W^{0.75}$, body-weight$^{0.75}$.

Mean values for the various drug-treated groups were significantly different from that for the no-drug control: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

† Values represent grouped values.

‡ Values in parentheses represent dose (mg/kg diet) administered.

Thus, all seven sympathomimetic drugs showed thermogenic effects in this genetically-obese model although, in the case of treatment with iprindole and tranylcypromine, anorectic effects were observed, particularly during the first 2–3 weeks of the experiment. Nevertheless, over several weeks the thermogenic effects of these drugs played a more important role in causing fat losses than any initial anorectic effects.

Expt 6. HPHF rats

The body-weights and carcass compositions are shown in Table 7. The 7% increase in body-weight of the no-drug control group relative to the initial controls resulted from increases in body fat, protein and water, such that the percentages of the latter body components were similar in both the final and initial control groups. All drug-treated groups lost body-weight compared with the no-drug controls. With the exception of theophylline, all drug-treated groups had significantly lower body-weights at the end of the experiment than at the start of the experiment. Both the total body fat and the percentage body fat were markedly reduced in all drug-treated groups compared with the no-drug controls; this effect was most pronounced with tranylcypromine (78% loss), followed by ephedrine, methoxyphenamine and iprindole (65% loss), while the yohimbine and theophylline treatments caused 50% loss of body fat. Ephedrine treatment had no effect on total body protein. The other drugs, on the other hand, prevented deposition of protein although they did not cause loss of protein compared with the initial controls. Thus all seven drugs caused marked reductions in body fat without causing loss of body protein.

The values for food intake indicate that, with the exception of the theophylline-treated animals, all the other drug-treated groups consumed between 12 and 27% less food (per animal) than the controls. However, when due allowances were made for their smaller body-weights, many of the differences in food intake were abolished. The values for 24 h V_{O_2} (per rat) indicate that metabolic rates were elevated by about 4–13% in the drug-treated groups, except those given methoxyphenamine and iprindole. However, when expressed as a function of body size, both the 24 h V_{O_2} and the total heat production were elevated with all drugs. For example, V_{O_2}, expressed per metabolic body size, was increased by 5% with methoxyphenamine, by about 30% with tranylcypromine and by 10–20% with the remaining drugs.

Thus, in this dietary model too, the seven sympathomimetic drugs showed thermogenic activities.

DISCUSSION

It is well known that there are marked differences between the various models of animal obesity (Miller, 1979). Since it is difficult in the present state of knowledge to say which is the most relevant model of obesity and since human obesity most probably does not have a single aetiology, it seemed better to work with a broad selection of obese models in the search for insight into the involvement of a possible reduced sympathetic nervous system activity underlying obesity.

The present studies indicate that elevation of thermogenesis and fat losses can be induced in different models of animal obesity and to a lesser extent in lean mice by drugs known to act at various points along the line of the sympathetic control of noradrenaline action. Moreover, in support of previous investigations by Massoudi *et al.* (1983), the present work also shows that important differences are revealed when the animal models are given drugs. Some of the major differences are discussed later (p. 193). However, in order to simplify the understanding of the whole study, the effects of each of the seven drugs used on each of the models have been expressed relative to the appropriate no-drug control animals. Such values are presented in Table 8 and include values for the effects of each drug on final body-weight (g), carcass fat (g), and protein (g), total ME intake (kJ/kg $W^{0.75}$), total heat

production (MJ/kg $W^{0.75}$) and 24 h V_{O_2} (litres O_2/kg $W^{0.75}$). Thus, the values given for the treated MSG mice are relative to the untreated (no-drug control) animals for each of these factors.

Hypothalamic obesity

Table 8 indicates that, with the exception of theophylline, all the other six sympathomimetic drugs caused marked elevation in metabolic rate and were effective in causing a great reduction in body fat. Such effects were accompanied by little reduction in body protein and the food intake was only minimally affected. The values for both the total heat production and 24 h V_{O_2} indicate that methoxyphenamine and tranylcypromine were most potent in increasing thermogenesis in this model without reducing food intake: both drugs elevated metabolic rate by 30% or more. Although yohimbine and amitriptyline caused approximately 10% reduction in food intake, they also showed similar potent thermogenic activities to ephedrine and increased total heat production by 12–17%.

This experiment therefore confirms the results of the screening procedure adopted in the preliminary experiments for the detection of drugs (Table 1) with potential thermogenic properties (Dulloo, 1982). It is therefore quite likely that some other drugs which were not chosen for the main experiment, but which showed some thermogenic potential, may also prove to be capable of increasing metabolic rate if fully investigated. In the case of theophylline, the preliminary results suggested that it has potential thermogenic effects but the complete energy-balance study reported here failed to show any thermogenic activity. This discrepancy could be due to the fact that much of the weight loss that occurred in the preliminary screening experiment was due to loss of body water. Such findings therefore lend support to the view that changes in body-weight may not necessarily be due to changes in body energy stores and that long-term energy-balance studies are necessary to support any claim of thermogenic potential.

Genetic obesity

Table 8 shows that all seven drugs produced marked reductions in body-weight and fat in the Zucker *fa/fa* rats, but only those animals on ephedrine and tranylcypromine were thermogenically active in the *ob/ob* animals. Moreover, although tranylcypromine was more potent than ephedrine in raising metabolic rate and causing fat losses in the *ob/ob* mice, these two drugs were of equal potency for such effects in the Zucker *fa/fa* rats.

Thus, although there are similarities between these two genetic autosomal recessive models of obesity, there are also marked differences in their responses to these drugs.

Dietary-induced obesity

Since the same technique to produce obesity was used in both the CFLP mice and the Hooded rats, it may be expected that these two dietary models of obesity would respond in a similar way to these drugs. Certainly, a number of similarities are apparent; for example, in each of these models, all seven drugs caused elevation in metabolic rate and brought about much reduction in body-weight and body fat, with little change in body protein. Furthermore, in both these models, tranylcypromine was found to be the most potent drug in raising heat production, whereas methoxyphenamine was least thermogenically effective.

However, Table 8 also shows that there are several differences in the response of these two models to the drugs. For instance, tranylcypromine treatment caused an 11% increase in food intake of the dietary obese mice, but not in the rat model. On the other hand, methoxyphenamine and iprindole caused a 10% reduction in food intake of the treated rats, but not of the treated mice. Differences in thermogenic potency of some drugs were also apparent: iprindole had greater thermogenic effects in the mice than in the rats; conversely, theophylline produced a more marked elevation of metabolic rate in the rat model than in the mouse model.

Table 8. *Ratio of drug-treated group: no-drug control group for body-weight, carcass fat and protein, food intake, total heat production and 24 h oxygen consumption of groups of animals given seven sympathomimetic drugs*

Aetiology of obesity...		Hypothalamic obesity	Dietary obesity		Genetic obesity		
Animal model... Drug treatment		Mice	Mice	Rats	*ob/ob* mice	*fa/fa* rats	Lean mice
Ephedrine	Body-wt	0·80	0·94	0·88	0·89	0·73	1·02
	Fat	0·58	0·44	0·32	0·82	0·50	0·86
	Protein	0·91	1·03	1·03	0·88	0·76	1·04
	ME intake	0·96	1·03	0·93	0·99	0·93	1·03
	Heat production	1·12	1·08	1·08	1·07	1·36	1·06
	24 h V_{O_2}	1·20	1·11	1·20	1·09	1·23	1·10
Methoxyphenamine	Body-wt	0·64	0·94	0·73	0·91	0·82	1·01
	Fat	0·24	0·56	0·34	1·04	0·64	1·03
	Protein	0·83	1·00	0·86	0·76	0·53	0·99
	ME intake	1·06	0·99	0·88	0·91	0·86	0·93
	Heat production	1·38	1·04	1·04	0·92	1·16	0·92
	24 h V_{O_2}	1·29	1·06	1·05	0·99	1·18	0·96
Yohimbine	Body-wt	0·66	0·87	0·85	0·92	0·85	1·00
	Fat	0·33	0·24	0·49	0·95	0·73	1·20
	Protein	0·80	0·94	0·87	0·91	0·57	0·90
	ME intake	0·90	0·96	0·92	0·91	0·94	0·94
	Heat production	1·17	1·07	1·04	0·94	1·18	0·93
	24 h V_{O_2}	1·22	1·08	1·17	0·98	1·14	0·95
Tranylcypromine	Body-wt	0·66	0·90	0·79	0·83	0·64	0·94
	Fat	0·36	0·47	0·22	0·72	0·42	0·83
	Protein	0·79	0·99	0·91	0·86	0·68	0·90
	ME intake	1·05	1·11	1·02	0·98	0·79	1·02
	Heat production	1·33	1·17	1·21	1·10	1·35	1·04
	24 h V_{O_2}	1·38	1·24	1·30	1·19	1·26	1·13
Amitriptyline	Body-wt	0·71	0·89	0·86	0·93	0·86	1·00
	Fat	0·46	0·46	0·61	0·94	0·73	1·08
	Protein	0·81	0·92	0·89	1·03	0·59	0·98
	ME intake	0·89	1·02	0·98	0·92	0·96	0·98
	Heat production	1·12	1·09	1·07	0·94	1·18	0·98
	24 h V_{O_2}	1·30	1·09	1·22	1·01	1·10	1·01
Iprindole	Body-wt	0·79	0·92	0·77	0·89	0·69	0·98
	Fat	0·58	0·44	0·35	0·90	0·52	1·10
	Protein	0·93	0·95	0·89	0·80	0·67	1·01
	ME intake	0·92	1·02	0·89	0·89	0·73	1·03
	Heat production	1·07	1·10	1·05	0·94	1·16	1·03
	24 h V_{O_2}	1·07	1·18	1·11	1·00	1·06	1·01
Theophylline	Body-wt	0·81	0·92	0·92	0·99	0·85	1·07
	Fat	0·73	0·41	0·50	1·11	0·65	1·10
	Protein	0·84	1·02	0·93	1·24	0·59	1·00
	ME intake	0·87	0·99	1·03	1·03	0·91	1·02
	Heat production	0·97	1·08	1·14	0·99	1·21	1·01
	24 h V_{O_2}	0·97	1·06	1·20	0·98	1·11	1·00

ME, metabolizable energy; V_{O_2}, oxygen consumption.

Thermogenic effectiveness of the drugs

These complete energy balance experiments confirmed the thermogenic effects of the drugs in several different models of animal obesity. However, the thermogenic effectiveness of these seven drugs varied considerably among the different types of obesity (Table 8).

The indirectly-acting sympathomimetic amine ephedrine, and the monoamine oxidase

(*EC* 1.4.3.4) inhibitor tranylcypromine, were found to be most potent in elevating thermogenesis in all five obese models. The β-agonist methoxyphenamine and the presynaptic α_2-antagonist yohimbine, although ineffective in the *ob/ob* mice, showed substantial thermogenic activities in the hypothalamic MSG and genetic *fa/fa* models, and also to a lesser extent in the two dietary-obese models. The noradrenaline-uptake blockers, amitriptyline and iprindole, were also without effect in the *ob/ob* model but showed substantial thermogenic properties in the hypothalamic and dietary and genetic *fa/fa* models. Finally, the phosphodiesterase (*EC* 3.1.4.1) inhibitor, theophylline, was ineffective in the hypothalamic and *ob/ob* animals, but it produced marked elevation of metabolic rate in the two dietary-obese models and also in the genetically-obese *fa/fa* rats.

In general, the drugs were found to be more effective in the obese than in the lean animals. This is to be expected if obesity is due to a metabolic defect. Thus drugs that would correct the defect in the obese would effectively increase thermogenesis in these animals, whereas they would be of relatively little value in normal lean animals that have no such defective mechanisms. In fact, the existence of a better regulation of body energy stores in the lean animals is supported by the fact that some of the drugs caused alterations in energy expenditure that tended to be opposed by similar alterations in energy intake. Nonetheless, although ephedrine and tranylcypromine caused both the metabolic rate and food intake to increase, the extra food consumed was not enough to compensate for the elevated heat production and the animals lost some fat.

Metabolic basis of obesity

Human obesity probably does not have a single aetiology, inasmuch that possible disorders of the sympathetic nervous system are many: in addition, there could be peripheral resistance to noradrenaline. Since the thermogenic drugs described here have different modes of action in stimulating the sympathetic nervous system, such drugs could be useful diagnostic tools in establishing the various types.

The results presented here indicate that these sympathomimetic drugs were more effective in raising metabolic rate in obese than in lean animals, and therefore suggest that the metabolic defect in the obese may be attributed to a reduced sympathetic neural activity. Thus the drugs were less capable of further increasing a normal sympathetic tone in the lean but were more effective in increasing a low sympathetic tone in the obese. This point is well illustrated in the case of the MSG-model: drugs that are capable of increasing noradrenaline levels at the sympathetic neuro-effector junctions or of simulating noradrenaline action on cell membrane β-adrenoreceptors, were effective in causing marked increases in thermogenesis. On the other hand, the inhibition of phosphodiesterase by theophylline did not have much effect because, in the absence of sufficient noradrenaline, such inhibition is unlikely to cause drastic changes in cAMP levels. These results are therefore compatible with a diminished sympathetic tone as being causative of the reduced thermogenesis that occurs in MSG-obesity following hypothalamic lesions.

However, the results with the other models are more complicated. The genetic *fa/fa* model responded to all drugs, including theophylline. In contrast, phosphodiesterase inhibition was ineffective in the *ob/ob* model. The latter model also failed to respond to the β-agonist and α_2-antagonist, although they responded to ephedrine and the monoamine oxidase inhibitor, tranylcypromine. The seven drugs therefore fail to point out a definite site of defect such as that found in the MSG-obesity model. Nonetheless, the different responses of the genetic models to these drugs lend support to the idea that these two genetic obesities have different aetiologies.

In the case of the dietary-obese models, it is obvious that there are no clear-cut hypothalamic or genetic disorders underlying their reduced thermogenesis. However, it is possible that in animals given such a high-fat diet, the biochemical pathways involved in fat

metabolism are less energy-wasteful. In fact, it is known that the energy cost of depositing dietary lipid is about half as much as the net energy cost of depositing triglyceride synthesized from carbohydrate (Rothwell & Stock, 1982). The drugs described here, however, do not specifically demonstrate that a reduced neural release of noradrenaline is causative for the elevated energetic efficiency in these dietary models, since the latter were responsive to all seven drugs.

The original concept of using drugs as tools to establish the site of the metabolic defect in the various models of obesity has not been fully realized. In the MSG-obese model, however, the results are compatible with an insufficiency of sympathetically-released noradrenaline as being causative for the reduced heat production that occurs following hypothalamic lesioning. However, the defective sympathetic nervous system activity in the genetic and dietary models of obesity is more complicated. Nevertheless, the experiments described here show that by interfering at different steps in noradrenaline transmission, it is possible to stimulate sympathetic nervous system activity and to potentiate thermogenesis and body fat losses in different animal models of obesity. There is thus a *prima facie* case for human clinical trials especially with those drugs which are already in current use (Table 1) and comparatively safe. No pathological changes were observed in the drug-treated animals.

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