Pharmacology of thermogenic drugs[1-3]

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ABSTRACT Thermogenic combinations of ephedrine with caffeine and newer selective β_3-agonists are being assessed for the treatment of obesity. The actions of β-agonists may be multifaceted, with acute stimulation of thermogenic mechanisms in various tissues. During chronic treatment recruitment of brown fat may occur and hypertrophy of skeletal muscle may occur and simultaneously increase lean body tissue and reduce fat mass by stimulation of lipolysis and energy expenditure. The weight-reducing effect of an ephedrine-caffeine combination was superior to placebo treatment during 24 wk of energy restriction in obese women, whereas caffeine and ephedrine separately had no effect. In a second study it was found that ephedrine-caffeine compared with placebo preserved fat-free mass and enhanced fat loss, which could be accounted for both by anorexia (75%) and by increased thermogenesis (25%). The ephedrine-caffeine compound seems useful for the treatment of obesity and may serve as reference in the clinical assessment of new β-agonists. *Am J Clin Nutr* 1992;55:246S–8S.

KEY WORDS Anorectics, β-agonist, body composition, energy expenditure, ephedrine, obesity, sympathomimetics, thermogenesis, caffeine

Introduction

A wide variety of naturally occurring agents have been reported to possess thermogenic properties in animals and in humans, including hormones such as insulin, growth hormone, thyroid hormones, androgens, serotonin, and catecholamines. Potassium, magnesium, phosphate, and even zinc have also been suggested as thermogenic agents. In addition, synthetic and semisynthetic congeners to the naturally occurring hormones and neurotransmitters seem to be the most promising tool for pharmacologic reversal of obesity.

Currently a number of sympathomimetic compounds with either anorectic or thermogenic effects, or with both effects, are either in use or are presently being introduced as adjuvants to dietary treatment of obesity. Although the impact of some of the older compounds on energy balance is regarded to consist of a central anorectic effect and a peripheral thermogenic effect, the thermogenic effect is conceivably mediated through a central activation of the sympathetic nervous system (SNS). By contrast, the promising newer group of thermogenic compounds, the β_3-agonists, acts entirely peripherally with no, or insignificant, anorectic properties (1). Agents such as β_2-adrenergic agonists (clenbuterol, cimaterol) are also thermogenic and have been used in a variety of species to manipulate growth and body composition, enhancing the deposition of body protein and reducing fat stores, thereby being termed repartitioning compounds (**Table 1**). In this context, the anabolic effect in animals, which takes place mainly in muscle without decreasing deposition of proteins in the internal organs and skin but at the expense of fat (2–5), may be of relevance for the treatment of obesity. The most favorable antiobesity action may be obtained by a central anorectic effect combined with a peripheral β_2 and β_3 action.

Use of β-agonists in humans

In the assessment of the pharmacologic effects, the single-dosing and chronic-treatment effects should be distinguished, ie, β-agonists increase plasma glucose after the first dose, whereas some decrease plasma glucose during chronic treatment. In addition, that an agent possesses thermogenic effects in an single dosing does not necessarily imply that this effect is maintained or that it may result in fat loss during chronic treatment.

A number of compounds with β_3-agonistic properties have been shown to possess thermogenic activity in humans and also to result in weight loss when given with an energy-restricted diet. Ro 16-8714 was found to be thermogenic and lipolytic in lean (6) and obese (7) subjects, whereas the effect on weight loss has not been reported. Two clinical trials with BRL26830A reported improved weight loss over placebo when given with energy restriction (8, 9) whereas another trial failed to detect any difference (10). As tachycardia and slight tremor, respectively, were reported with these two compounds, they may also possess some β_2-agonistic properties. At present more selective β_3-agonists are undergoing clinical evaluation and our group is at the moment testing the effect of 2 wk treatment with a highly selective β_3-agonist, D7114, on 24-h energy expenditure in obese subjects. However, as only a few of the newer agents are available for studies, we have concentrated on old compounds such as ephedrine and caffeine, which seem promising in combination.

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TABLE 1
Pharmacologic effects of β-receptor agonists

Effects	Side effects
Acute	
Increased energy expenditure	Tremor
Increased lipolysis	Tachycardia
Hyperglycemia and hyperinsulinemia	Increased systolic blood pressure
Chronic	
Weight loss	Muscle fatigue
Body fat loss	Stress
Muscle hypertrophia	
Improved insulin sensitivity	

Acute and chronic effects of ephedrine and caffeine

Chronic administration of various agents stimulating the SNS is effective in increasing energy expenditure and in reducing body fat content in genetically obese rodents (11). In particular, the sympathomimetic agent ephedrine has been shown to exhibit potent thermogenic and antiobesity properties (12, 13). However, in combination with methylxanthines such as caffeine and theophylline, the thermogenic effect can be markedly enhanced and body composition can be restored to normal (12, 13). Interestingly, the administration of methylxanthines alone seems to have little or no effect on body weight (14).

In humans, a double-blind, placebo-controlled study has shown that caffeine stimulates thermogenesis and lipolysis dose-dependently (15). There are indications that the mechanism of the thermogenic effect is composed of a skeletal muscle component (16), the extracellular fatty acid/triglyceride cycle (15), and perhaps increased vasoconstriction (hot pipes) (17). Ephedrine also suppresses appetite and stimulates thermogenesis in humans (18) and the effect is maintained during long-term administration (19, 20). Ephedrine lacks the classical dose-dependent increase in thermogenic response, which may be explained by its dual sympathomimetic action with both direct β-adrenergic properties and indirect activation of SNS with the release of noradrenaline (21). Ephedrine also increases plasma glucose, insulin, and C peptide dose-dependently, while having no significant effect on glycerol and nonesterified fatty acids (21). We have previously found that ephedrine in vivo stimulates skeletal muscle thermogenesis in humans (22), but it was not known if this effect was exerted directly or indirectly.

A number of studies by Dulloo and Miller (18) have shown that the effect of ephedrine is potentiated by methylxanthines such as caffeine and theophylline, and they have suggested that the addition of methylxanthines was necessary to obtain a sufficient antiobesity effect of ephedrine. Dulloo and Miller (18) reported that a preparation containing 22 mg ephedrine, 30 mg caffeine, and 50 mg theophylline was twice as effective as ephedrine alone in increasing energy expenditure, both in normal subjects and in formerly obese subjects. On a daily basis they found, in formerly obese subjects, that the energy intake decreased by 16% and energy expenditure increased by 8%, which points to a dual action on energy balance (18).

We have recently found a supraadditive thermogenic synergism between ephedrine and caffeine in a certain dose ratio (20 mg:200 mg) (23), whereas the interaction in the two other tested combinations was only additive (**Fig 1**). There was also a supraadditive interaction on systolic blood pressure.

Clinical trials on ephedrine-caffeine

To establish whether the benefits from the acute studies also may accrue from chronic treatment, a randomized, placebo-controlled, double-blind trial was carried out to test whether the combination (ephedrine 20 mg, caffeine 200 mg) given tid was more effective than placebo, caffeine, or ephedrine given separately as adjuvants to a 4.2 MJ/d diet in 180 obese patients treated for 24 wk (24). The ephedrine-caffeine combination resulted in weight losses superior to those seen with placebo, caffeine, and ephedrine; the additional weight loss compared with the placebo group was 3.6 kg after 24 wk. Caffeine and ephedrine given separately did not improve weight loss compared with placebo. Side effects were transient (tremor, insomnia, and dizziness) and comparable to placebo after 8 wk of treatment. Systolic and diastolic blood pressure fell similarly in all four groups, while heart rate decreased less in the ephedrine-caffeine–treated patients than in the placebo group (24).

Mechanisms of action of ephedrine-caffeine

The mechanisms behind the weight reducing effect of ephedrine-caffeine are not well understood. Because of its close similarity to noradrenaline, ephedrine is considered to suppress food intake via adrenergic pathways in the hypothalamus and related structures, and this effect may be potentiated by caffeine. Actually, the present ephedrine-caffeine combination was chosen by its superior ability, compared with its components given in other proportions, to stimulate energy expenditure as measured

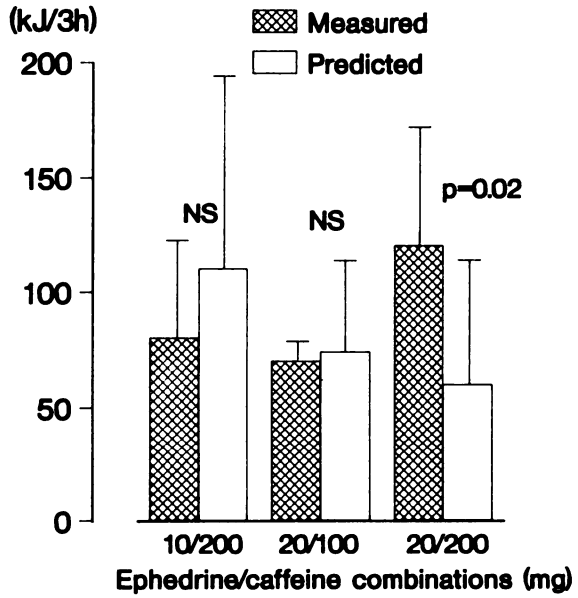

FIG 1. Predicted and measured integrated thermogenic responses above baseline to different combinations of ephedrine and caffeine (23). Only in the ephedrine-caffeine ratio 20 mg:200 mg did the components show a supraadditive synergism. The predicted figures are calculated as the sum of the responses to ephedrine and caffeine measured separately. The responses to placebo were subtracted from each measured response.

by indirect calorimetry in humans. To study the effect on 24-h energy expenditure measured in respiration chambers, and on body composition as estimated by bioimpedance, 14 obese women were prescribed a 4.2 MJ/d diet and treated with either ephedrine-caffeine (E + C) or placebo (PB) three times a day for 8 wk in a double-blind design. After 8 wk of treatment, weight losses were similar in the two groups (E + C: 10.1 vs PB: 8.4 kg, $P = 0.22$), but more fat was lost (E + C: 9.0 kg vs PB: 4.5 kg, $P = 0.02$), and fat-free mass was better preserved (E + C: 1.1 kg vs PB 3.9 kg, $P = 0.02$) in the ephedrine-caffeine–treated patients as compared with placebo (A Astrup, B Buemann, N Christensen, S Toubro, G Thorbek, O Victor, and F Quaade unpublished observations, 1991). The 24-h energy expenditure decreased in both groups when their diet was changed from weight maintenance to 4.2 MJ/d, but the fall was less in the ephedrine-caffeine–treated group. The stimulation of energy expenditure was entirely based on increased lipid oxidation, and the effect was maintained during the 8 wk of treatment. From the present study it was possible to calculate that 75% of the weight loss caused by ephedrine-caffeine was due to an anorectic effect and 25% was due to a thermogenic effect. The results also underline that changes in body weight during treatment with compounds with β-adrenergic properties do not necessarily reflect fat loss, which may be underestimated.

Recent data provided by studies on growing pigs found that with ephedrine-caffeine in the diet the same growth was obtained but on 20% lower energy intake, that the proportion of muscle was increased by 10%, and that intermuscular and subcutaneous fat were reduced by 30% as compared with control animals (N Oksbjerg and M Sørensen, unpublished observations, 1991).

Conclusion

The ephedrine-caffeine compound seems useful for the treatment of obesity as it possesses both anorectic and thermogenic properties with only mild, transient side effects. The introduction of the newer selective β-agonists with thermogenic, repartitioning, and antidiabetic effects is a promising field for further research.

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