Introduction

Recent developments in the field of obesity management have demonstrated the efficacy of using pharmacological agents both instead of and in addition to diet and exercise. Specifically, many studies have focused on the effects of increasing sympathetic nervous system stimulation in order to increase basal metabolic rates, thereby providing a long-term therapeutic option for obese patients. The sympathetic branch of the autonomic nervous system is a potent regulator of thermogenesis in mammals. Because low metabolic rate is characteristic of obesity and sympathetic activity has been shown to increase this metabolic rate (1-2), a role for sympathetic stimulation in the treatment for obesity has a well-established physiological rationale. Unfortunately, however, the economic advantages of synthesizing and marketing these treatments have rapidly overshadowed the need for adequate research to assess their efficacy and safety.

One of these sympathetic stimulants is a combination drug consisting of the stimulants ephedrine, caffeine, and aspirin (ECA), and is sold in commercial forms as HydroxyCut and Xenadrine. Highly visible full-page advertisements market these products as thermogenic and anti-catabolic, suggesting that they increase fat catabolism while sparing proteins, leading to lower body weight but a retained lean muscle mass (3). However, our current knowledge of the mechanisms of this catabolism, as well as an appreciation of the safety and efficacy of long-term use, is lacking. Here, we will coordinate what is known and what is not known about the ECA combination in obesity management, and suggest what future steps should be taken in order to ensure appropriate use of this therapy.

Mechanism of Action

Most of the early investigations on the use of ECA combinations concentrated on the effects of ephedrine and caffeine combinations (E + C) on the sympathetic nervous system. Both ephedrine and caffeine stimulate weight loss by increasing the sympathetic tone of various resting tissue beds, notably fat. It has been shown that both ephedrine and (to a lesser degree) caffeine are capable of mimicking a sympathetic response when given alone. However, when given in combination, there is a synergistic increase in the levels of thermogenesis, such that the stimulated levels are greater than the added sum of the separate effects of caffeine and ephedrine given alone (2, 4-5). The exact mechanisms of this enhanced action are still being clarified.

Several studies on rats have demonstrated that the predominant effect of E + C when given in low doses is on the stimulation of sympathetic post-synaptic nerves to release greater amounts of norepinepherine (NE) onto the richly innervated adipose tissue. This central effect stimulates thermogenesis indirectly by increasing sympathetic stimulation throughout the body. The thermogenic response is blunted in the presence of a chemical sympathetic denervating agent, suggesting that intact sympathetic nerve endings releasing NE are necessary for the effects (4). However, Dulloo et al. demonstrated that there is also a direct effect on peripheral tissues (4). By using rat brown adipose tissue as a peripheral tissue target, and using tissue respiration (production of O2) as a marker of thermogenesis, the direct effects of ephedrine and caffeine were measured. Ephedrine, as a sympathomimetic, is a beta-adrenergic receptor agonist like NE. This binding induces the classical beta-adrenergic-dependent synthesis of cyclic adenosine monophosphate (cAMP). Elevation of cytoplasmic cAMP is responsible for the increased thermogenesis. Caffeine, while not a sympathomimetic, is known to increase cAMP levels by inhibiting the enzyme responsible for destruction of cAMP, phosphodiesterase (PDE). Also, caffeine is an adenosine receptor antagonist, preventing the inhibition of NE release by extracellular adenosine, thereby increasing cAMP levels in the adipose cell. It is believed that the multiple mechanisms utilized by ephedrine and caffeine for increasing intracellular cAMP are responsible for the synergistic interaction that increases thermogenesis. Follow-up studies (5). on rat adipose tissue were conducted in the presence of either PDE inhibitors or adenosine antagonists and showed that the PDE inhibition, and not adenosine antagonism, has a more substantial role in facilitating E + C interactions. It was also shown that caffeine metabolites, specifically theobromine, theophylline, and paraxanthine can mimic caffeine's interaction with sympathetic stimulation to increase thermogenesis (5-6).

An additional claim made by proponents of ECA-induced weight loss is that the thermogenic effects are limited to fat catabolism, and that there is no protein catabolism, increased heart rate, or tremors which are associated with other sympathetic stimulation. One hypothesis is that the main stimulation by ephedrine is through beta2- and beta3-adrenergic receptor subtypes (2, 7), both of which are predominantly responsible for lipolysis and protein synthesis, but are not associated with cardiovascular and central nervous system effects mediated by beta1-receptor (2). Tolerance rapidly develops to the effects of ephedrine on heart rate, but does not develop to the thermogenic effects (2, 8-12), suggesting that different mechanisms are responsible for these different effects, and that ephedrine has longer-acting effects on thermogenesis.

The third component of the ECA combination, aspirin, enhances the peripheral actions of ephedrine and caffeine by inhibiting prostaglandin (PG) synthesis. PGs, like adenosine, have been implicated in inhibiting NE release from the post-synaptic nerve terminal, and in inhibiting the lipolytic actions of sympathetic stimulants (2). However, these effects have been limited to only one study, and more experiments must be performed before this effect can be conclusively linked to aspirin.

In summary, the effects of ephedrine, caffeine, and aspirin in rat brown adipose tissue involve a significant central component of increased NE release, and a contributing peripheral part that has direct action on the target tissue. These peripheral actions act to directly increase stimulation of beta-adrenergic receptors (especially the beta2- and beta3-subtypes), to inhibit the regulatory mechanisms of negative feedback by adenosine and PGs extracellularly, and to inhibit the destruction of cAMP by PDE intracellularly. This overall scheme is depicted in Figure 1.

Figure 1

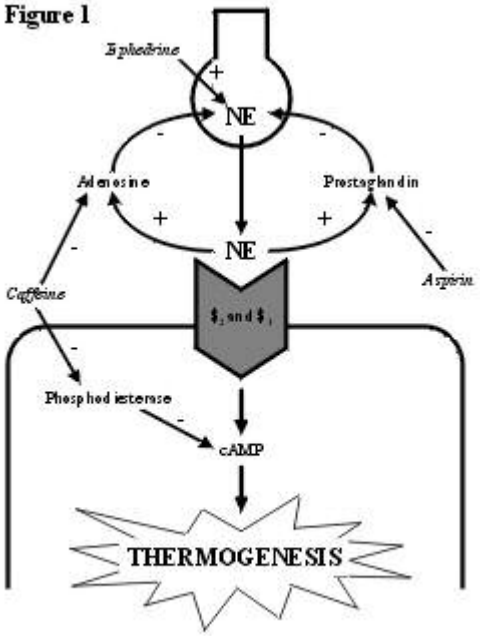

Figure adapted from Dulloo, 1993.

Efficacy

While studies with rats generally agree on the efficacy of the ECA combination in producing weight loss, studies using human tissue or subjects have resulted in widely disparate results. Shannon et al. demonstrated that there is no significant peripheral action of ephedrine on adipose tissue (13). and that all thermogenic effects are mediated by the increase in NE release. Also, while Liu et al. suggested that human beta3-adrenergic receptor may be responsible for protein-sparing, lipolytic thermogenesis in humans as it does in rats (14). his experiments were unable to adequately discriminate between different types of human receptors, and studies performed under more stringent conditions show that human beta3-receptors actually

have very poor specific activation by ephedrine (13, 15-17). Vansal et al. further showed that ephedrine has very low affinity for the beta3-receptors as compared with beta1- and beta2-subtypes (15). and suggested that the positive effect seen by Liu is actually the thermogenic effect of the beta2- and a putative novel beta4-subtype (15, 18).

Despite these apparent dissimilarities in mechanism between humans and rats, there are several clinical studies suggesting that E + C combinations are effective means for weight loss in humans. Astrup et al., in a study with a total of six patients, showed that 20 mg ephedrine plus 200 mg caffeine (E + C 20 mg/200 mg) three times per day increases total energy expenditure more than ephedrine or caffeine given alone (8-9). Astrup also later conducted the first long-term (24 weeks), high sample (180 participants) study on the efficacy of E + C on obese patients on a 1000 kcal/day diet (10-12), and found that E + C 20 mg/200 mg three times per day for 24 weeks resulted in weight loss modestly but significantly greater than placebo (16.6 kg vs. 13.2 kg). Interestingly, this study also demonstrated that E + C dramatically spared muscle catabolism, and that approximately 85% of the weight loss was due to loss in fat mass, compared with 50% of weight loss in placebo (10). Studies whose end-point was too early or those that looked only at total weight loss often came up with negative results (19-21). Other groups have reported similar protein-sparing fat loss results as Astrup, using E + C 20 mg/200 mg (22). or using ECA in doses of 75-150 mg/150 mg/330 mg (23). More recent studies by Bell et al. examined the effects of E + C on endurance in healthy people, and found that E + C 75 mg/375 mg ingested 1.5 hours before a treadmill or cycle test to exhaustion significantly increased the time to exhaustion versus placebo (24-25). Due to a high incidence of nausea (25%), Bell conducted a follow-up study that showed that E + C at the reduced dose of 60 mg/320 mg resulted in the same increased endurance, and no incidences of nausea (26).

Safety

While the efficacy of the ECA combination appears to be well established, its safety has yet to be adequately addressed. Especially lacking is information on the effects of long-term use of these products for weight loss. However, several groups have reported side effects in the short-term use of ECA combinations. The majority of the side effects are, unsurprisingly, the result of over-stimulation of the sympathetic nervous system. They include headache, tremor, insomnia, tachycardia, and palpitations (8-12, 22-24). Side effects occurred transiently in about 60% of E + C treated groups, and were vastly diminished after 4 to 8 weeks of treatment, such that the incidence of side effects was identical between E + C and placebo (8-12, 22-23). Upon ending E + C treatment after 24 weeks, withdrawal symptoms developed, notably headaches and fatigue, but were resolved within two weeks (12). Daly et al., using a study with 24 obese participants, mention that side effects were generally mild, transient, present indistinguishably in both ECA and placebo groups, and quickly resolved (23).

However, long-term use and the potential dangers of ECA abuse have not been sufficiently addressed. The side effects of using caffeine and aspirin have been examined in the past, and are generally found to be of mild and acceptable nature (27). with only somewhat greater incidence of side effects noted with caffeine withdrawal. Of greater concern is the effect of long-term ephedrine use. An amphetamine-like substance, ephedrine has been shown to be addictive in rats (27). It also attenuates the development of opiate tolerance (27). However, in the two studies that have addressed the effects of long-term (15 weeks and 24 weeks) E + C use, side effects and withdrawal symptoms were found to be mild and transient (12, 22).

Conclusions

The biochemical mechanism of action of ECA is well established in rats, but is still controversial in humans. While there appears to be some homology between the species, specific enzymes and novel pathways have yet to be clarified. While outside of the scope of this paper, it is important to note that many molecular biologists are attempting to isolate the change in gene expression resulting from activation by the ECA combination. Another significant result is the blunted response seen in humans: while ECA does appear to increase thermogenesis and promote fat loss, it does not result in the dramatic differences apparent in the rat studies. The complications of doing in vivo experiments in humans are undeniably clouding this area with conflicting results, and several more large-scale long-term studies must be

performed. These studies should also address the possible interactions between diet and exercise in addition to the use of ECA.

Also, there have been no studies that have examined the maintenance of ECA-induced fat loss over time, or the cellular and physiological changes accompanying long-term use. Dieting alone is considered an ineffective means of fat loss, mainly because of the decreased sympathetic tone and decreased metabolism accompanying reduced caloric intake predispose the body to fat storage (2). Similarly, long-term use of ECA may alter sympathetic tone for the whole body, thereby "resetting" its normal levels of sympathetic stimulation. Removal of the ECA stimulus (e.g., when a person reaches their desired physique) may result in reflexively low levels of endogenous sympathetic stimulation, leading to an accumulation of fat. Therefore, future studies of long-term ECA use must evaluate not only withdrawal symptoms upon removal of the stimulus, but also the maintenance of the lost weight.

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