THE EFFECTS OF AN EPHEDRINE/CAFFEINE MIXTURE ON OBESE HUMANS

by

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ABSTRACT

Several studies have shown that a mixture consisting of ephedrine, a β-agonist, and caffeine, an adenosine antagonist, has the ability to stimulate thermogenesis in humans, and thus offer a treatment for obesity. However, most studies have also included a very low calorie diet and sometimes exercise in addition to the ephedrine/caffeine combination. The purpose of this study was to determine the amount of weight loss achievable using the ephedrine/caffeine mixture without controlling for diet and exercise.

In a double-blind, placebo controlled, cross-over, repeated measures design, 20 obese subjects were administered a mixture containing ephedrine (20 mg), and caffeine (200 mg) or placebo, t.i.d. for 8 weeks. Body weight, resting metabolic rate (RMR), waist to hip ratio (WHR), body mass index (BMI), and sum of girths were measured. Fourteen subjects completed the study: 1 withdrew because of lack of interest; 1 encountered food poisoning; and 4 were dropped because of missed follow-up appointments. The treatment was well tolerated and side effects were transient. The most common side effects were insomnia and tremor. Withdrawal symptoms included headaches and tiredness. Change in body weight was -2.8 ± 2.4 kg (mean ± SD) after ephedrine/caffeine treatment and 0.5 ± 1.1 kg after placebo treatment ($p<0.001$). Body Mass Index (BMI) was 33.0 ± 5.4 kg/m^2 after treatment and 33.8 ± 5.9 kg/m^2 after placebo ($p<0.001$). There were no significant differences in RMR, WHR, and sum of girths.

The results of this study show that an ephedrine/caffeine combination is able to promote weight loss without diet restriction and exercise.

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I. INTRODUCTION

Several barriers exist in the treatment of obesity. Obese people expect treatment, mainly with drugs to cure their condition. When clinical treatment fails people look elsewhere. Bray (1991) indicated that only 35 million dollars per year is spent on obesity research, yet 35 billion is spent by the general public in their quest for leanness. Because of the lack of funding few clinical trials exist. Nevertheless, obesity is a very common disease which when left untreated can lead to several other associated conditions such as hypertension, coronary heart disease, congestive heart failure, and diabetes mellitus just to name a few. It is estimated that about 33% of the North American population are overweight, and about half eventually become obese (Atkinson and Hubbard, 1994). The recent international symposium on obesity (Colorado, USA, Oct. 1996) concluded that obesity is a chronic disease, and thus is never cured; it can only be treated. The cause of obesity is not known, however it seems to be an interaction between genetic, social, psychological, environmental, and hormonal factors. However, some believe obesity is due to a defective thermogenic response as a result of decreased sympathetic nervous system (SNS) activity (Dulloo and Miller, 1986; Pasquali et al., 1987; Astrup et al., 1992; Astrup, 1995; Astrup et al., 1995) Thus, stimulating the SNS will increase the rate of norepinephrine (NE) release and increase metabolic activity (Dulloo and Miller, 1989; Dulloo, 1993; Astrup and Toubro, 1993). In addition, the SNS is involved in the control of diet-induced thermogenesis (DIT) which is the rapid increase in energy expenditure in response to ingestion of a meal. Diet-induced thermogenesis is thought to be defective in obese people (Dulloo Miller, 1986; Pasquali et al., 1987; Astrup et al., 1992). This leads

to an increased ability to store energy as fat (Pasquali et al., 1987). Therefore, compounds like ephedrine and caffeine (Appendix 1) that mimic activity of the SNS by increasing NE release should increase the metabolic rate and offer a therapeutic potential to treat obesity (Astrup, 1989). Though obesity is associated with greater health risk in men than women, more studies exist on women. Since traditional approaches in treating obesity such as restricted diet and increased activity, have for the most part failed, so there is a need for newer approaches, especially in men (Guy-Grand, 1997).

In this study twenty obese subjects were administered a combination of ephedrine and caffeine to stimulate weight loss without controlling for diet intake and exercise. No single study has documented the effects of this combination on obese subjects without controlling for diet intake or exercise (Pasquali and Casimirri, 1993). An additional objective of this research project was to document the safety of the treatment by assessing the side effects.

The study was proposed in order to determine the extent to which an ephedrine/caffeine mixture potentiates the body's metabolic rate and thermogenic response after food intake. It was hypothesized that treatment with an ephedrine (20 mg) and caffeine (200 mg) mixture three times a day for 8 weeks before a meal would result in a significant decrease in body weight (fat loss) when compared to the placebo treatment. Thus, the purpose of this study was to find out the total amount of weight loss that can be obtained with this mixture as well as determine the composition of that loss. Was it due to an increased metabolic rate, a decreased appetite, or both?

Mimicking the SNS with ephedrine and caffeine should potentiate the thermogenic response and thus increase energy expenditure. The results of this study should prove

beneficial for obese subjects who would like to reduce their weights to a reasonable level so that they can avoid obesity related complications. In addition, significant weight loss will allow obese individuals to become more upwardly mobile and thus be able to exercise.

II. REVIEW OF THE LITERATURE

The preliminary study to determine if ephedrine promotes weight loss in low-energy-adapted obese women was conducted by Pasquali et al. (1987). In this study a double blind, cross-over design was used in 10 selected adults who had shown difficulty losing weight with low calorie diets. Thus, using a low calorie diet (1000-1400 kcal/day) plus 50 mg of ephedrine three times a day before each meal or a placebo for 2 months in each treatment, weight loss was significantly ($p<0.05$) greater during ephedrine treatment (2.41 kg) than during placebo treatment (0.64 kg) with caloric restriction. Therefore, this initial study provided positive results in terms of promoting weight loss using a sympathomimetic. There were no serious side-effects found.

Dulloo and Miller (1986) were the first to look at the effects of an ephedrine/caffeine mixture on both men and women. The purpose of their study was to determine the thermogenic properties of this particular mixture. This was done by measuring the 24-h energy expenditure in a respirometer as well as measuring resting metabolic rate using the Douglas bag technique. The subjects used in this study were lean or predisposed to obesity. The authors indicated that those predisposed to obesity are subjects who are unable to maintain normal weight or having a weight problem. Subjects predisposed to obesity are those who only maintain normal body weight when dieting, and gain weight back within a few months after dieting. There were 8 subjects in the lean group and 8 in the predisposed to obesity group. Each of the groups contained equal numbers of men and women.

Measurements of metabolic rate on both groups involved five different treatments on each subject on five different days. The treatments were as follows: a) 22 mg of ephedrine + 200 ml of water, b) 22 mg of ephedrine, 30 mg of caffeine and 50 mg of theophylline + 200 ml of water, c) 1.25-MJ liquid meal, d) 1.25-MJ liquid meal, 22 mg of ephedrine, 30 mg of caffeine and 50 mg of theophylline, and e) 200 ml of water. All subjects presented themselves in the morning after an overnight fast and without breakfast. The subjects were seated in a chair and allowed to relax for a half hour prior to measuring metabolic rate. Treatment was given once the fasting metabolic rate was steady. Measurements were conducted for 5 min periods with 10 min intervals for a total of 150 min.

Twenty-four hour energy expenditure was measured using a closed room respirometer. The room contained all the necessary elements (bed, food, toilet, television, phone, etc.). The food intake was recorded as well as air flow. Each subject was required to spend the entire 24 hours in the respirometer on two separate days. The first day was used to measure baseline controls, and the second day, at least a week later to measure energy expenditure using the above mentioned ephedrine/methylxanthines mixture, administered three times a day with each meal.

The results of this acute study indicated that the ephedrine/methylxanthines mixture is twice as effective as ephedrine alone in increasing fasting metabolic rate. Measurements on 24-h energy expenditure showed that the mixture did not affect the lean subjects, however it did cause an 8% increase in 24-h energy expenditure in the subjects predisposed to obesity. The authors concluded that the predisposed group had a decrease in the thermogenic response to food intake. In other words, there seems to be a defect during diet

induced thermogenesis (DIT). The activity of the SNS appears to be suppressed in obese individuals as indicated by the results of this study. Thus, drugs capable of stimulating the SNS such as the mixture used in this study can increase the metabolic rate and offset the defective DIT. The energy expenditure was not affected by the mixture in the lean subjects most likely because of a negative feedback inhibition of thermogenesis as described by the authors. Therefore, it appears that this feedback loop is absent in obese or post-obese subjects since the ephedrine/methylxanthine mixture tends to normalize any reduced sympathetic drive that contributes to a defective DIT. Thus, the role of the ephedrine/methylxanthines mixture is to compensate for any decreased thermogenic response.

In a subsequent study Dulloo and Miller (1987) investigated the effects of aspirin as a promoter of ephedrine induced thermogenesis. This study involved obese mice which were given one of the following treatments: ephedrine, aspirin, or ephedrine/aspirin. Aspirin alone had no effect on energy balance and body composition, but ephedrine increased energy expenditure by 9% and reduced body fat by 50%. In the dual combination body fat was reduced by more than 75%, and energy expenditure was doubled when compared to ephedrine alone. Thus, aspirin works much in the same way as methylxanthines in that it aids the actions of ephedrine (Appendix 1). Thus, this study provides sufficient evidence to indicate that equivalent combinations in humans may be effective in treating obesity.

In another preliminary study Pasquali et al. (1987) conducted a double blind study on 46 obese patients (14 males, 32 females). There were three treatment groups: a) ephedrine 150 mg/day, b) ephedrine 75 mg/day, and c) placebo. In addition all patients

received a 1000-1200 kcal diet. The treatments lasted for three months, and measurement of BMI was done once a month. Although this study failed to show statistical significance, the group receiving the 150 mg of ephedrine showed greater weight loss compared to the other treatment groups.

Dulloo and Miller (1989) wrote a review article to summarize the early developments in the field. They concluded that "A reduced release of norepinephrine (NE), rather than insensitivity to the neurotransmitter, has been implicated in the thermogenic defect of the obese."

Astrup (1989) in a editorial article indicated that "the thermogenic increase after a meal has a facultative component that is unrelated to the processing of nutrients and is mediated by the sympathoadrenal system", thus further indicating that an improper functioning SNS plays a role in decreasing metabolism which can lead to obesity. Therefore, drugs which can mimic the SNS will increase sympathetic tone, and produce heat.

Based on the fact that some subjects experience side effects when using ephedrine, Mancini et al. (1990) conducted a study to determine the effects when a lower dosage of ephedrine was taken with caffeine and aminophylline. A double blind randomized study was performed on 42 obese women matched for age, weight, and BMI in two groups. Twenty-two women received the treatment consisting of 22 mg of ephedrine, 20 mg of caffeine, and 50 mg aminophylline. 19 women received the placebo. Both groups also consumed a hypocaloric diet. The study lasted for 8 weeks, however 7 subjects interrupted the study: 2 for side effects (insomnia and dyspepsia) and 5 for poor compliance. Despite this, the ephedrine/methylxanthine group showed a 4.5 kg $\pm$ 3.7 weight loss compared to

the placebo group which had a 2.2 kg ± 2.8 weight loss. Therefore, this study indicated that ephedrine at a dose of 22 mg appears not only safe, but with the addition of the methylxanthines promotes weight loss in obese women. No male subjects were used.

Pasquali et al. (1992) conducted a study to determine the effects of chronic administration of ephedrine during very low calorie diets on energy expenditure, protein metabolism and hormone levels on obese subjects. The study involved 10 subjects (5 males, 5 females) in a randomized, double blind, crossover design. The study lasted for 6 weeks with the treatment group receiving 50 mg of ephedrine during weeks 2 and 5, the other group received the placebo. The results indicated that the ephedrine treatment produced a significant decrease in daily urinary nitrogen excretion. In addition, the fasting resting metabolic rate fell significantly in both treatment groups, but to a lesser extent during the administration of ephedrine. Thus, once again it appears that ephedrine is able to partially prevent the fall in resting metabolic rate. Furthermore, evidence that indicates an improved nitrogen balance as indicated in this study is desirable in that obese people want weight loss to be fat and not muscle. Therefore, ephedrine seems to be able to maintain muscle mass in obese subjects.

Earlier, a study mentioned some of the side effects that can occur during treatment with an ephedrine/methylxanthine mixture. Astrup et al. (1992) performed a study to specifically look at the effects and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine and placebo in obese subjects on an energy restricted diet. In a randomized, double blind study, 180 obese patients (25 males, 155 females) were treated with diet (4.2 MJ/day) and either ephedrine/caffeine (20/200 mg), ephedrine (20 mg), caffeine (200 mg) or placebo three times a day for 24 weeks. Only 141 patients completed

the study, drop-outs were equal among treatments. Weight loss was highest for the ephedrine/caffeine group (16.6 ± 6.8 kg vs. placebo 13.2 ± 6.6 kg). Several side effects were present, but transient and after 8 weeks were similar to those in the placebo group. The most common side effects were insomnia, tremor, and dizziness during treatment with the ephedrine/caffeine mixture. Nevertheless, once again this dual combination was effective in stimulating weight loss in obese patients. The dual combination appears to be relatively safe for the most part as side effects are present, but only transient.

The first study to use a double blind, placebo controlled testing of ephedrine and caffeine, separately and in combination was conducted by Astrup and Toubro (1993). They found that an ephedrine/caffeine (20/200 mg) mixture had a greater effect on thermogenesis than the 10/200 mg and 20/100 mg combination respectively. They also showed that the 20/200 mg mixture exerted a supra-additive thermogenic response whereas the other combinations seemed to be only additive. Separately, caffeine increased lipid metabolism, but ephedrine had no effect. Clearly, this study is consistent with others in terms of generating increased metabolism when taking a dual combination of ephedrine/caffeine when compared to each drug separately. Thus, the optimal well tolerated mixture seems to be 20 mg of ephedrine and 200 mg of caffeine.

At this point several studies indicate that the dual combination of ephedrine and caffeine promoted weight loss in obese individuals. Both Dulloo and Miller (1986) and Astrup et al. (1992) found positive results with an ephedrine/caffeine mixture. On the other hand, Pasquali et al. (1987) showed that the ephedrine/caffeine (50/100 mg) mixture did not have an additive effect in terms of weight loss when compared to ephedrine alone. This study was done on 22 obese women who were given one of three treatments for 4 months

in addition to a low calorie diet. The treatments were as follows along with the calculated weight loss: placebo group lost 7.56 ± 4.8 kg (n=7), ephedrine (50 mg) group lost 10.2 ± 3.3 kg (n=6), and ephedrine/caffeine (50/100 mg) group lost 9.2 ± 4.2 kg (n=7). Clearly, there was a greater mean weight loss, but not statistically different ($p>0.05$) when compared to the drug groups using ephedrine alone. Most likely any apparent discrepancies can be attributed to the different experimental designs. Regardless, this study indicates that more studies need to be done to determine the full effect of an ephedrine/caffeine mixture particularly on obese men as most studies to date have been done on women or women and a few men. Furthermore, as indicated earlier, obesity is a higher health risk for men. Thus, more studies need to focus in this area.

The study which initiated the present proposal was conducted by Daly et al. (1993), who investigated the efficacy and safety for treatment of human obesity of an ephedrine, caffeine, and aspirin combination. In a randomized, double blind, placebo controlled trial lasting for 8 weeks, 24 obese men and women were given either a mixture of 75-150 mg of ephedrine, 150 mg of caffeine, and 330 mg of aspirin or the placebo. Weight loss was 2.2 kg for the drug group vs. 0.7 kg for the placebo ($p<0.05$). Diet was not restricted in this study, but all subjects received nutrition counseling. 6 subjects continued with the drug treatment for 7 to 26 months. At the end of five months 5 subjects lost an average 5.2 kg whereas the no intervention group gained 0.03 kg. The sixth subject lost 31.7 kg during this five month period and an overall weight loss of 58.8 kg at the end of the 26 month period while incorporating a diet and exercise routine. No important side effects persisted during treatment, and any that did were transient. Thus, as indicated at the recent international symposium on obesity (Colorado, USA, Oct. 1996) true weight loss only

occurs with a diet and exercise program as exemplified by the above mentioned subject. With the addition of thermogenic drugs such as ephedrine and caffeine, it seems highly likely that any defect in metabolism seen in exercising populations can be corrected.

In a follow-up study Toubro et al. (1993) looked at the acute and chronic effects of an ephedrine/caffeine mixture on energy expenditure and glucose metabolism. This study was a continuation of the study by the same authors discussed earlier. In an open follow-up trial 127 obese patients (20 males, 107 females) were given an ephedrine/caffeine (20/200 mg) mixture three times a day for 24 weeks. Prior to administering this treatment, subjects were given a 2 week washout period to determine any withdrawal symptoms that could have occurred from the previous 24 week double blind, placebo controlled study. At the end of the follow-up study all subjects showed an additional weight loss of 1.1 kg ($p=0.02$). Thus, at the end of 50 weeks the ephedrine/caffeine combination was effective in improving and maintaining weight loss. However, adverse drug reactions were reported by 102 patients during the follow-up study. The majority of the symptoms (75%) occurred during the first few weeks with the lowest being in the ephedrine/caffeine and placebo groups. Only 2% of symptoms lasted for 16 weeks; all others disappeared with time. The most common central nervous system (CNS) symptoms were tremor, agitation, insomnia, increased sweating and nervousness. Some patients complained of tachycardia and palpitations. Nevertheless, these symptoms were similar to those found by other researchers as indicated earlier. In addition, no clinically relevant withdrawal symptoms were observed. In conclusion, this dual drug combination seems safe. However, more studies are needed.

Clearly, most of the studies looking at the effects of an ephedrine/caffeine mixture in obese subjects have been done on women on hypocaloric diets for short periods of time.

This prompted Astrup et al. (1995) to address the need for more long-term studies especially on obese males. Furthermore, these authors indicated that pharmacological treatment should only be considered in patients where diet and behavior modification have failed. They proposed that only patients who suffer from obesity related complications such as (cardiac malfunction, hypertension/stroke, diabetes, renal disease, gall bladder disease, pulmonary disease, osteoarthritis, high cholesterol, and severe psychological burden), as well as abdominal fat distribution (android pattern typical of obese men), and critical weight loss for surgery should use drug therapy.

Finally, Horton and Geissler (1996) conducted a study to determine whether or not aspirin potentiates the greater post-prandial thermogenesis induced by ephedrine with caffeine. Three groups of 10 (lean, predisposed to obesity, and obesity were given either a 1050 kJ liquid meal, meal plus 30 mg of ephedrine and 100 mg of caffeine, or meal plus ephedrine, caffeine and 300 mg of aspirin. Pre and post metabolic rates via indirect calorimetry were measured. The results showed that in all three groups aspirin did not further potentiate the acute thermic effect of ephedrine and caffeine with a meal. These results are consistent with those found by previously cited authors.

Beginning with the study by Dulloo and Miller (1986), many studies indicate that the combination of ephedrine/caffeine stimulates a thermogenic response in the body which results in weight loss. However, results are not conclusive as indicated by Pasquali et al. (1987), who found no additive effect with the addition of caffeine to ephedrine. However, this was most likely due to different experimental design. Regardless, most studies indicated positive results with this combination especially when ephedrine is administered alone, but studies done on males are lacking. Furthermore, some researchers have found adverse side

effects while taking these drugs, the most common symptoms include insomnia, dizziness, and tremor. Withdrawal symptoms include headache, tiredness, and hunger among others. Thus, this combination must be used with caution. Nevertheless, for the most part these symptoms associated with this drug treatment are transient and tend to subside with adaptation, and unfortunately so does the weight loss effect. Finally, no study has been done which looks at the effects of an ephedrine/caffeine mixture in obese humans without controlling for diet and exercise. Such a study should be conducted because it would offer a more realistic approach to weight loss.

III. METHODS

SCREENING AND SELECTION OF SUBJECTS

Potential subjects were selected by screening all 105 respondents from a newspaper and poster advertisement for overweight individuals wishing to participate in a new research study (Appendix 2). A telephone interview was conducted with all respondents, who were then asked a series of questions based on the following guidelines. The inclusion criteria were that subjects must have a BMI>27 kg/m^2, be between the ages of 20-55 years, have family doctor approval, and must sign the informed consent form (Appendix 3). The exclusion criteria included: a) hypertension (DBP>110 mm Hg), b) severe psychiatric or somatic disease, c) any possible contraindication to trial treatment, d) evidence of alcohol or drug abuse, e) treatment with drugs known to produce obesity, f) treatment with methylxanthines 1 month prior to start of the study, g) weight loss of more than 8 kg in the previous two months, h) chronic caffeine users, and I) current smokers. Based on the interview and doctor approval, 20 subjects agreed to take part in the study. All subjects gave informed consent. The study was approved and a certificate was given by the University of British Columbia, Office of Research Services and Administration, Clinical Research Ethics Board (Appendix 4).

EXPERIMENTAL DESIGN

This study was a randomized, double blind, cross-over, 2 x 3 factorial repeated measures design. Factor 1 was condition (treatment or placebo), and factor 2 was order of condition (treatment-washout-placebo or placebo-washout-treatment). Pre, mid, and post-test measurements of weight, body mass index (BMI), resting metabolic rate (RMR), waist to hip ratio (WHR), and sum of girths were measured at the Buchanan Exercise Physiology Lab, UBC.

Twenty obese subjects were assigned randomly to either a treatment group (n=10), and given an ephedrine/caffeine (20/200 mg) mixture or the placebo group (n=10) three times a day before a meal. The l (-) ephedrine hydrochloride was provided by Roberts Pharmaceutical Canada Inc., Mississauga, Ontario. The caffeine citrate and the placebo (calcium carbonate) were provided by Wiler Fine Chemicals Ltd., London, Ontario. Treatment was for 8 weeks in both groups. After the initial 8 week period both groups were given the placebo as part of a 2 week wash-out period. In other words the control group continued with the placebo treatment and the experimental group began the placebo treatment. After this 2 week period the crossover took place. Total length of the study was 18 weeks (8 wks ephedrine/caffeine + 2 wks washout (PLACEBO) + 8 wks placebo) or vice-versa. Subjects were asked to maintain their normal daily routine while the study was in progress (e.g. if not exercising at the start of the study they were expected not to start during the study). Food intake and exercise were not controlled; however, because the main purpose of this study was to determine the amount of weight loss possible while using the drug treatment, it was important that any fluctuations in these factors be documented.

Thus, subjects were asked to monitor their diet and exercise reporting on any major changes in diet, exercise, and health that may have occurred.

Six (1 male and 5 females) of the 20 subjects who enrolled in the study failed to complete all requirements. One lost interest while on the placebo, 1 encountered food poisoning, and 4 did not attend follow-up appointments. Of the 14 remaining subjects 5 were males and 9 were females.

During each of the three visits, subjects were measured on all variables as well as interviewed on their general well being. Notes were made by the researcher as to any difficulties that the subjects may have experienced.

Compliance was assessed by recording the number of capsules remaining in the vials. Each subject was instructed to bring the vials during each follow-up appointment. The researcher counted and recorded the missed dosages, and assumed that all other dosages not in the vial were consumed by the subjects.

PROCEDURE

All dependent variables (weight, RMR, BMI, WHR, and girths) were measured by the researcher along with a certified lab technician in the Buchanan Exercise Physiology Lab. The subjects were tested on three occasions for each variable (pre, mid and post-test). Subjects were asked to arrive at the testing location in the morning after an overnight fast, to minimize time of day effects.

PROTOCOL

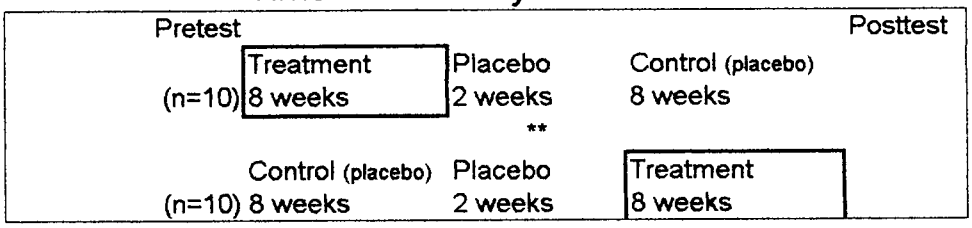
Figure 1 represents a summary of the research protocol. The study was carried out over a period of 7 months from May to December 1998. Subjects were entered into the 18 week study as soon as approval was granted. Each subject who obtained doctor approval was initially seen by the researcher at the Buchanan Exercise Science Lab at UBC. The subjects were asked to present themselves with loose clothing so that anthropometric measurements could be recorded. Subjects were also asked to have been in a fasting state for at least 12 hours so that RMR could be recorded accurately.

Figure 1. Outline of Research Design

Two Factor Design, Repeated Measures on one Factor
(2 x 3) factorial design, repeated measures on the second factor

TABLE OF OBSERVATIONS		**Factor 1**: CONDITION	
		Treatment (T)	Placebo (P)
Factor 2:	(n=10) T-C		
Order of Condition	(n=10) C-T		

Timeline of Study Flow Chart



** After treatment all dependent variables will be measured

(Measurement will take place on three occasions: pre, after treatment, and post)

MATERIALS

The equipment used in this study included a steel anthropometric tape measure, Mettler Toledo Model 2136 Scale, Ohio, USA, and Vmax/$V_{6200\ AUTOBOX}$ by Sensor Medics, USA.

Reliability was influenced by many factors, thus all equipment was frequently calibrated and all measurement sites were carefully marked in order to increase consistency. Measures of resting metabolic rate may have had serious reliability problems in that subjects were required to come in on an overnight fast and remain motionless for up to one half hour so that the body was at the lowest resting rate possible prior to measurement on the Vmax. Nervous or tense subjects were more likely to move during measurement and thus the researcher carefully omitted these values during the analysis.

REST METABOLIC RATE

Upon arriving in the morning, subjects were placed in the supine position for a half-hour in order to begin the RMR measure. It was essential that the subjects were in a totally relaxed state, yet not sleeping. The Vmax/v6200 by Sensor Medics, USA was used to measure RMR. This was done by measuring the oxygen consumption (VO_2) during a 5 min period after 25 mins of motionless rest (the amount of oxygen consumed per minute is equal to the difference between the amount of oxygen inspired and the amount of oxygen expired). Thus, a mouth piece was placed into the subject's mouth connected to a tube, which was connected to the Vmax mixing chamber. The Vmax was used to measure O_2 and CO_2 concentrations, RMR was calculated by multiplying the amount of oxygen inspired in liters per hour by 4.8 kcal/l using a nonprotein respiratory exchange ratio (R) =

0.80 (Lusk, 1928). Resting metabolic rate was recorded as kcal/hour. The 4.8 kcal/l value was used for all subjects as this is the amount of energy that is liberated as heat when 1 liter of oxygen is utilized in the oxidation of a diet containing a mixture of proteins, carbohydrates, and fats at an R= 0.80. The average VO_2 reading over the last 5 minutes of a 30 minute test was taken to be the true resting value.

ANTHROPOMETRIC MEASUREMENTS

All subjects were weighed wearing workout clothing and without shoes on a Mettler Toledo Model 2136 Scale, Ohio, USA. Height without shoes was measured once during the study, on the first testing day using a wall-mounted calibrated stadiometer. The BMI (body weight in kg divided by the square of the height in meters) was calculated for each subject.

Waist to hip ratio was measured with a steel anthropometric tape measure. The subjects were asked to stand erect for this measurement. Using the tape measure the researcher performed a measure on the *waist* (measured at the most noticeable level of waist narrowing which was located approximately half-way between the coastal border and the iliac crest), and *hip* (measured at the level of greatest posterior protuberance-about the level of the symphysis pubis). The mean of six measures was used as the actual value.

The girth measures consisted of arm, waist, gluteal, and calf (Appendix 5). Using a steel anthropometric tape measure the researcher performed three measures on each site. The mean of the three measures was taken as the actual value. Subjects stood erect during all measurements. Limb girths were taken on both sides of the body.

DATA ANALYSIS

To examine the effects of ephedrine and caffeine, 20 subjects participated in this study, but only 14 subjects completed all the requirements. Descriptive statistics were used to analyze baseline data for all 20 subjects which included age and height. Three Independent t-tests were used to assess any difference between those subjects who completed the study (n=14) and those that did not (n=6). The t-tests were done on baseline age, height and weight.

To investigate the changes in weight, RMR, WHR, BMI, and girths a 2 (condition) x 3 (order of condition) repeated measures (RM) on the second factor analysis of variance (ANOVA) was used on each variable. The alpha level was set at $\alpha = 0.01$ because five ANOVAs were used. Using five ANOVAs increases the likelihood of making a type I error, therefore lowering the alpha level decreases the risk of making any error. The rationale for using the above alpha level is based on the Bonferroni inequality, which states that the probability of occurrence of one or more events can never exceed the sum of their individual probabilities. Marginal means and descriptive statistics were also used to help interpret the findings. Furthermore, Orthogonal Contrasts were used where statistical significance was achieved at the desired alpha level. Mauchly's Test of Sphericity was used to determine if all RM ANOVAs performed in this study met the assumption of sphericity, which was set at an epsilon parameter ($\varepsilon > 0.700$). All RM ANOVAs met the assumption except for girths thus the Greenhouse-Geisser test was used to determine the level of significance of this variable.

Pearson Product-Moment Correlations (PPMC) were used to measure the degree to which the five dependent variables were linearly related. High positive correlations were

expected. Pearson correlations were also done to measure the rank order of the relations. The same rank order of the Pearson correlations for the three RM (baseline, treatment, and placebo) indicates that time and order of condition were not a factor during this study. These correlations were done pairwise.

Pearson Product correlations were also calculated on weight for the three RM, in order to determine if order of condition had an effect on the results. Finally, a Pearson Product correlation was calculated for baseline weight and the difference of baseline minus treatment. This was done in order to determine if subject baseline weight affects weight loss during treatment-i.e. do subjects that weight more lose more weight? All statistical analyses used the Statistical Package for the Social Sciences (SPSS) 8.0 for windows (SPSS Inc. Chicago, USA. 1997)

LIMITATIONS OF THE STUDY

Analysis of data collected allowed inferences to be made regarding: 1) the amount of weight loss achievable during a short time period without controlling for diet and exercise, 2) the impact the treatment had on RMR, 3) the safety of the treatment dosage by monitoring the side effects and, 4) determining where the weight loss occurred by analyzing girth measurements.

Limitations of this study are:

1) The small sample size (n=14), in particular only 5 male subjects. Therefore, there is an increased likelihood of making a type II error.

2) Not able to accurately assess where the weight loss occurred. Girths and BMI are known to be highly variable.

3) Monitoring subject compliance; it is difficult to be certain that the subjects actually took the treatment capsules.

4) Determining if subjects followed all the research requirements i.e. were diet and activity levels held constant throughout the study?

IV. RESULTS

SUBJECTS' CHARACTERISTICS

Fourteen of the twenty subjects completed the study. Of the six who failed to complete the study, one female withdrew while on placebo because of lack of interest, another female dropped out because of food poisoning, and the remaining four subjects were excluded because of missed follow-up appointments.

Table I displays a summary of the subjects' baseline characteristics. The subjects, six males and fourteen females ranged in age from 20 to 52 years with a mean of 38.3 years. The Body Mass Index ranged from 26.7 kg/m^2 to 45.0 kg/m^2 with a mean of 33.7 kg/m^2. The weight ranged from 73.9 to 125.7 kg with a mean of 99.7 kg.

There were no significant differences between subjects who completed the study (n=14) and those who did not (n=6) in age (p=0.926) mean ± SD, 38.4 ± 9.3 and 38.0 ± 9.7 years, height (p=0.883), 172.1 ± 7.5 and 171.4 ± 11.2 cm and weight (p=0.695) 100.8 ± 19.8 and 97.2 ± 14.7 kg, respectively. All other analyses only include those subjects who completed the study.

Five, 2 (condition) x 3 (order of condition) ANOVAs with repeated measures on the second factor were performed on five variables: bodyweight, RMR, WHR, BMI, and sum of girths. There were no significant condition x order of condition interactions for each of the five variables analyzed ($p > 0.001$), thus only interpretation of the two main effects will be discussed.

Table I. Baseline data of obese subjects participating in the study

Subject #	Sex	Age (years)	Height (m)	Weight (kg)	RMR (kcal/h)	WHR	BMI (kg/m^2)	Girths (cm)
1	M	24	166.4	108	93.6	1.01	39.0	322.8
2	F	52	169.5	93.9	65.4	0.84	32.7	306.4
3	F	42	164.0	73.9	64.8	0.74	27.5	262.0
4	M	37	180.0	118.2	90.7	0.94	36.5	315.9
5	F	51	162.8	75.4	na	0.77	28.5	255.3
6	F	36	175.0	84.6	68.3	0.81	27.6	265.2
7	M	41	169.0	110.0	na	0.96	38.5	309.8
8	F	38	165.0	101.0	73.4	0.79	37.1	316.6
9	M	24	191.0	111.9	93.0	0.91	30.7	288.1
10	F	38	175.5	125.7	83.5	0.83	40.8	345.2
11	F	45	167.5	88.2	80.6	0.83	31.4	281.7
12	F	45	175.0	85.0	72.9	0.82	27.8	266.1
13	F	44	190.5	114.8	78.3	0.71	31.6	312.8
14	M	43	176.0	89.8	88.7	0.98	29.0	274.8
15	F	42	164.5	82.5	68.0	0.87	30.5	273.7
16	F	34	172.0	116.9	95.7	0.79	39.5	330.6
17	M	44	172.5	134.0	103.1	1.10	45.0	340.2
18	F	43	175.5	114.7	77.2	0.77	37.2	321.8
19	F	23	167.5	75.0	65.4	0.81	26.7	263.2
20	F	20	158.0	91.1	73.2	0.83	36.5	306.5
Mean		**38.3**	**171.9**	**99.7**	**79.8**	**0.86**	**33.7**	**297.9**
S.D.±		*9.1*	*8.5*	*18.0*	*11.9*	*0.1*	*5.3*	*28.4*

Table II. outlines the Pearson Product Correlations between the measured variables at baseline. The high correlations indicate that regardless of order of condition, the rank order of the relationships of all variables remained constant. Therefore, time was not a factor in this study.

SUBJECTS' COMPLIANCE

Fourteen subjects completed the study, but only 3 subjects (1, 6, and 19) took all the treatment dosages which consisted of 378 capsules (168-ephedrine/caffeine and 210-placebo). Five subjects took all of the required ephedrine and caffeine capsules, whereas 4 subjects took all of the placebo capsules. Subject 12 missed all of the washout (placebo) capsules (Table III).

SIDE EFFECTS

Table IV outlines the types of side effects experienced by the subjects during the study. In general, the majority of subjects reporting side effects were affected mainly during the first two weeks while taking the ephedrine and caffeine treatment. Nineteen symptoms were reported, the most common side effect was insomnia followed by headaches. Three subjects did not report any side effects while on the ephedrine and caffeine treatment.

Six symptoms were reported by 4 subjects while taking the placebo, the most common being cramps and loose stool. Subsequently, 4 subjects reported seven symptoms during the washout period, the most common being headaches and tiredness.

BODY WEIGHT

On average, subjects lost more weight (2.8 ± 2.4 kg) during ephedrine and caffeine treatment (Figure 2) than during placebo treatment (Figure 3) with an average gain of (0.5 ± 1.1 kg).

There was no significant difference in the condition factor ($F=0.388$, $p=0.545$) however, there was a significant difference in the treatment factor as measured by body weight change during baseline, treatment, and placebo ($F=11.16$, $p=0.001$). The marginal means were mean ± SE, 100.8 ± 5.5, 98.1 ± 5.2, and 100.2 ± 5.4 kg for weight measured at baseline, treatment, and placebo, respectively. Using orthogonal contrasts it was determined that there was a significant difference in body weight change during the ephedrine and caffeine treatment ($F=21.147$, $p=0.001$).

Using Pearson Product Correlations, subjects on average demonstrated a high relationship between body weight at baseline and body weight after treatment ($r=0.992$, $p=0.01$), and body weight at baseline with body weight after placebo ($r=0.995$, 0.01). Correlation of body weight after treatment and body weight after placebo ($r=0.993$, $p=0.01$), indicates that order of condition or time was not a factor in the changes in body weight seen during the treatment with ephedrine and caffeine. Conversely, using Pearson Product Correlations between body weight at baseline and baseline body weight minus body weight after treatment ($r=.380$, $p=0.180$) demonstrated that the change in body weight during ephedrine and caffeine treatment was dependent on the individual subjects and not their weights at baseline values.

Table II. Pearson Product Correlations of all variables measured at baseline (n=14)

		Baseline weight	Baseline RMR	Baseline WHR	Baseline BMI	Baseline Girths
Baseline Weight	Pearson		.851**	.648*	.903**	.903**
	sig. (2-tail)		.000	.023	.000	.000
Baseline RMR	Pearson			.875**	.733**	.653**
	sig. (2-tail)			.000	.007	.021
Baseline WHR	Pearson				.627*	.514
	sig. (2-tail)				.029	.087
Baseline BMI	Pearson					0.970**
	sig. (2-tail)					.000
Baseline Girths	Pearson					
	sig. (2-tail)					

** Correlation is sig. at the 0.01 level (2-tailed)

* Correlation is sig. at the 0.05 level (2-tailed)

FIGURE 2. SUBJECTS' CHANGE IN BODY WEIGHT USING EPHEDRINE AND CAFFEINE

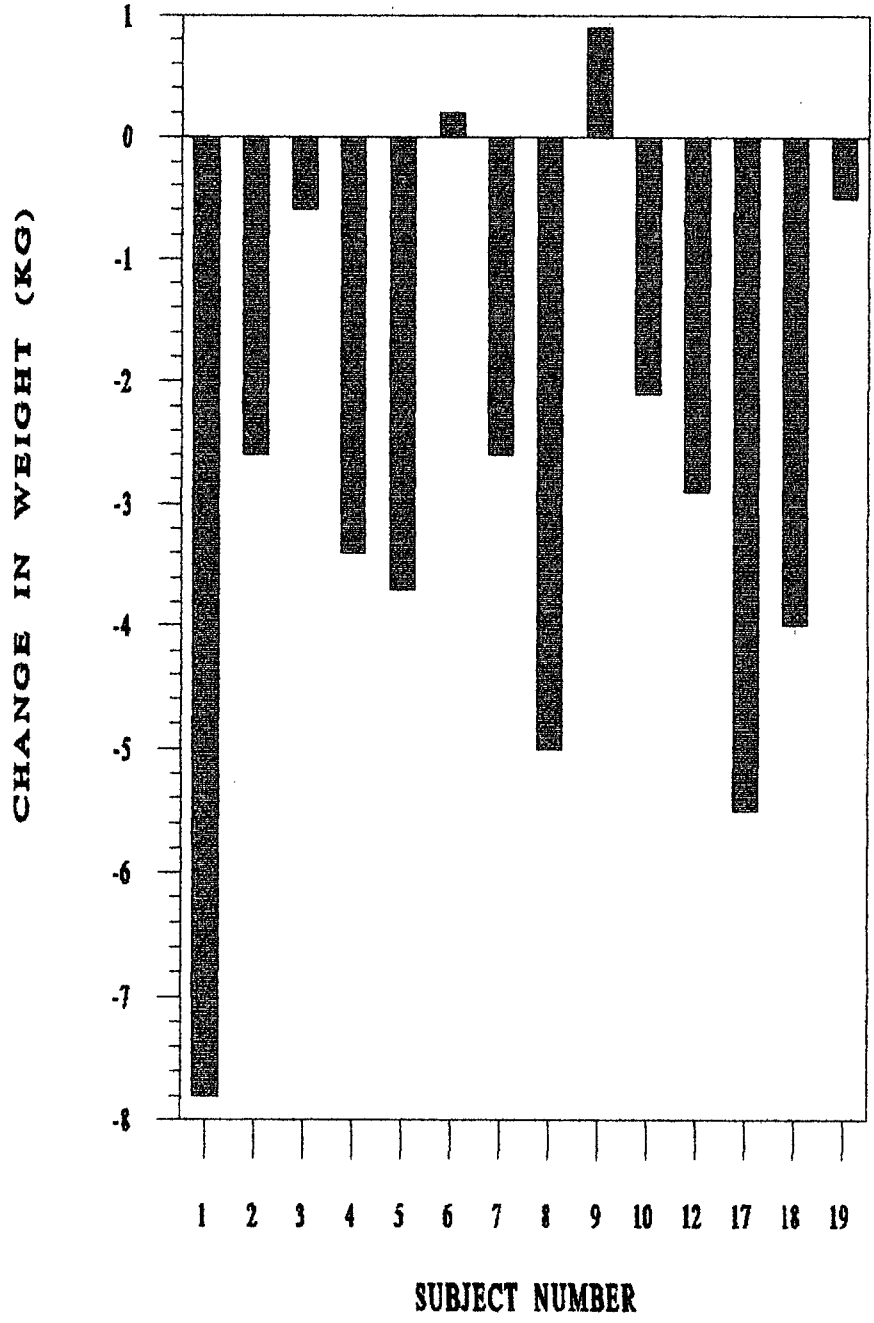


FIGURE 3. SUBJECTS' CHANGE IN BODY WEIGHT COMPARING 8 WEEKS OF TREATMENT VS 8 WEEKS OF PLACEBO

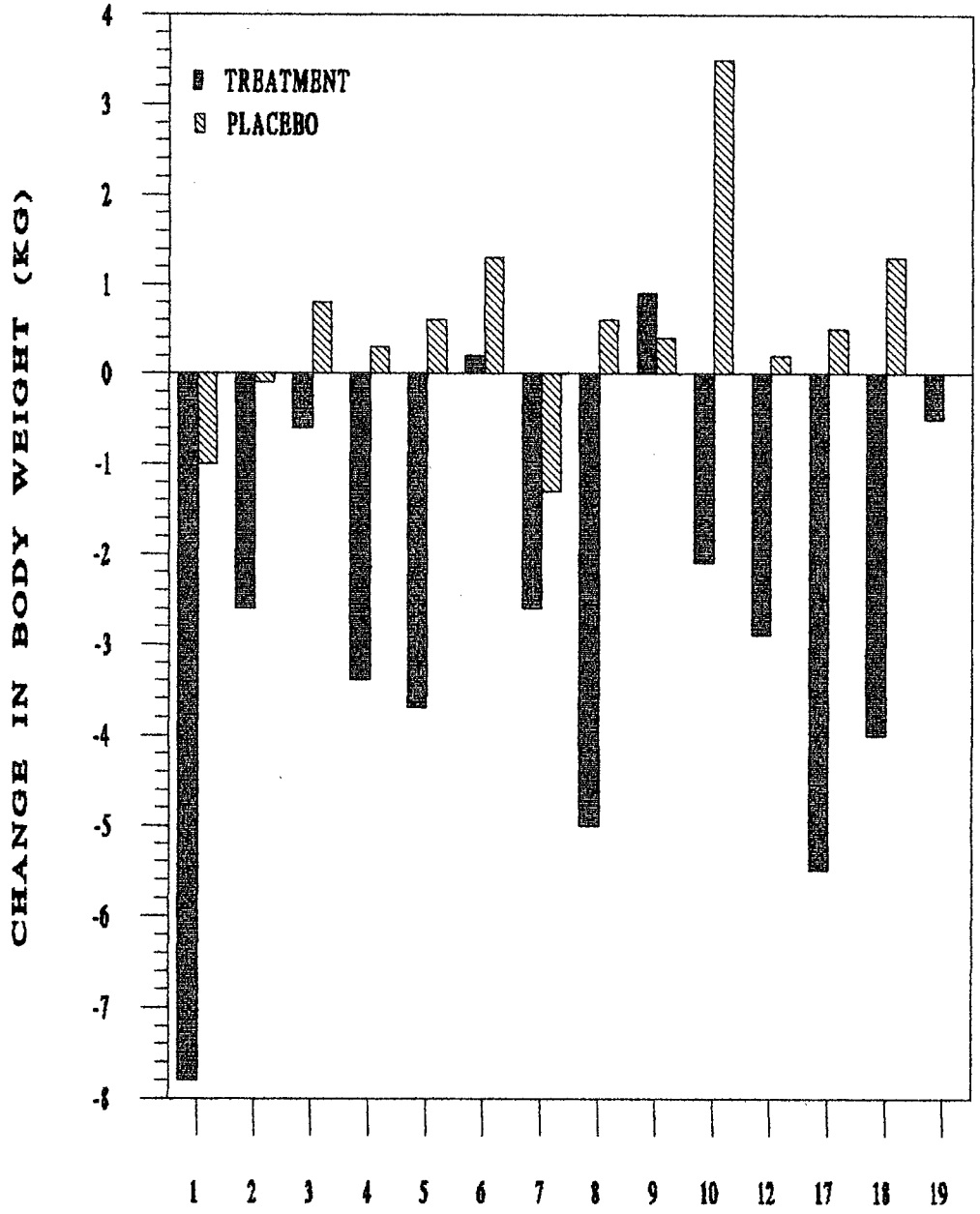


Table III. Subjects' compliance reported as number of missed dosages.

Subject Number	Ephedrine/Caffeine	Placebo	Washout
1	0	0	0
2	39	8	0
3	8	4	2
4	9	30	0
5	37	21	0
6	0	0	0
7	1	0	0
8	3	5	0
9	0	11	5
10	0	10	0
12	8	28	42
17	18	37	7
18	22	36	6
19	0	0	0
Mean	10.4	13.6	4.4
± SD	13.6	14.0	11.1

Table IV. Side effects

	Number of subjects		
Side effect	Ephedrine/Caffeine	Placebo	Washout
Cramps	3	2	0
Euphoria	1	0	0
Tremor	1	0	0
Chest Pain	1	0	0
Nausea	1	0	1
Insomnia	4	0	0
Tachycardia	2	0	0
Headache	2	1	2
Irritability	1	0	1
Frequent Urination	2	0	1
Dizziness	1	0	0
Tiredness	0	1	2
Loose Stool	0	2	0

Subject 1 lost the greatest amount of weight (7.8 kg) whereas subjects 6 and 9 did not lose any weight during the ephedrine and caffeine treatment. Subjects 1, 2, and 7 lost weight during the placebo treatment in addition to the ephedrine and caffeine treatment.

RESTING METABOLIC RATE

Table V outlines the changes in RMR during the repeated measure trials. The average baseline value was mean ± SD, 79.8 ± 11.9 kcal/hr, 85.8 ± 13.0 kcal/hr for treatment, and 82.1 ± 13.3 kcal/hr for placebo (Figure 4).

There was no significant difference in the condition factor ($F=1.85$, $p=0.203$) as well as the order of condition factor ($F=4.38$, $p=0.027$). However, the RMR increased by 7.6 % during ephedrine and caffeine treatment and 2.9% during placebo treatment compared to baseline values.

WAIST TO HIP RATIO

There was no significant difference in WHR in terms of condition ($F=0.689$, $p=0.423$). In addition, there were no significant differences during treatments ($F= 2.758$, $p=0.084$). The marginal means were mean ± SE, 0.86 ± 0.03 for baseline, 0.85 ± 0.03 for treatment, and 0.85 ± 0.03 for placebo.

BODY MASS INDEX

Figure 5 outlines the absolute changes in BMI for the group during the study. There was a significant order of condition or repeated measures effect ($F=10.97$, $p=0.001$). The marginal means were means ± SD, 34.0 ± 5.9 kg/m^2 for baseline, 33.0 ± 5.4 kg/m^2 for treatment, and 33.8 ± 5.9 kg/m^2 for placebo. Orthogonal contrasts indicated that the ephedrine and caffeine treatment had a significant effect ($F=20.77$, $p=0.001$). There were no significant differences in condition ($F=.672$, $p=.428$).

GIRTHS

There were no significant differences in sum of girths for both factors. The condition factor was not significant ($F=0.049$, $p=.829$). The order of condition was not significant at the desired alpha level, however it was significant at a reduced alpha level ($F=5.45$, $p= 0.027$). The marginal means, means ± SE, were 298.4 ± 8.6 cm for baseline, 292.9 ± 8.0 cm for treatment, 296.4 ± 8.2 cm for placebo (Table V). Figure 6 outlines the subjects' change in girths during the two treatments.

Figure 4. Subjects' RMR Comparing 8 weeks of Treatment vs. 8 weeks of Placebo

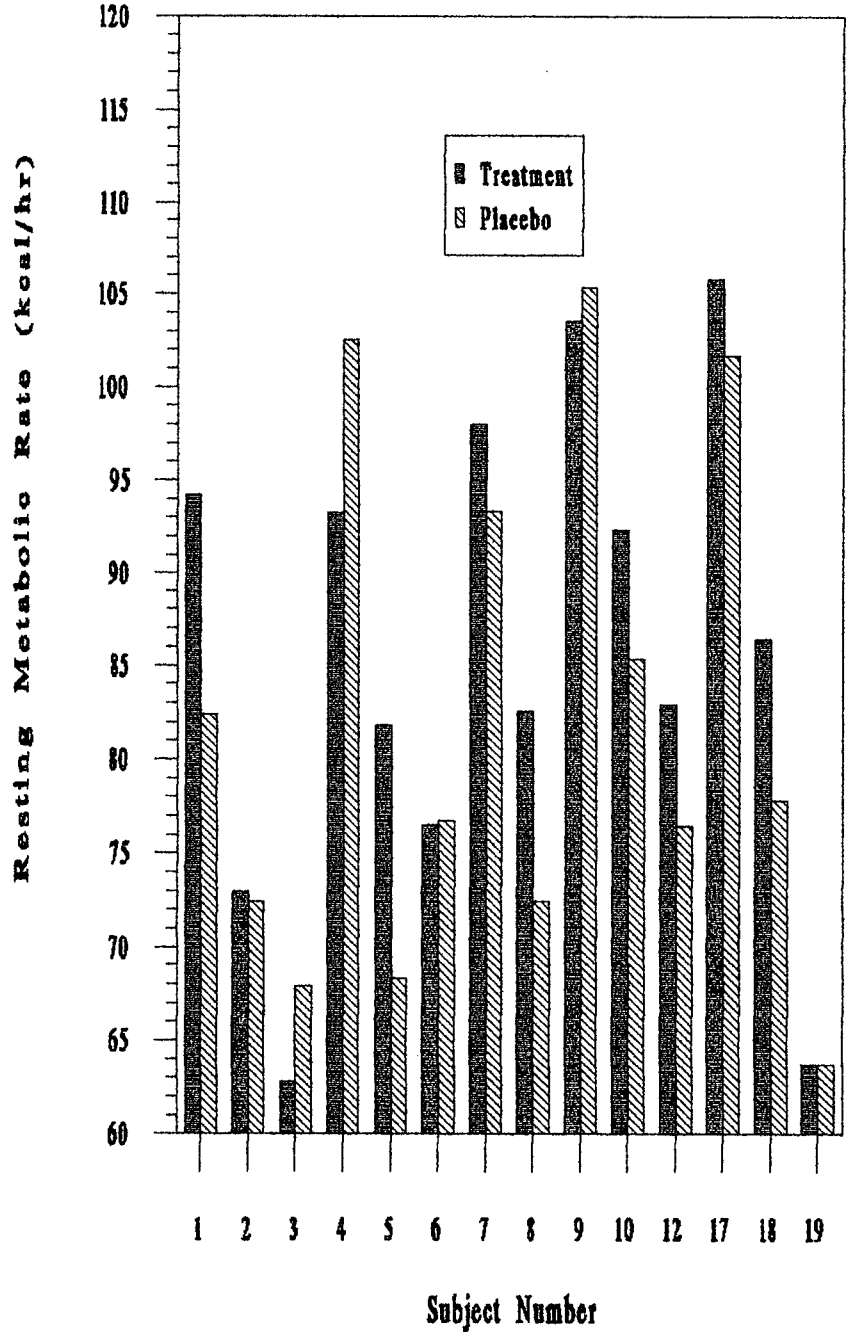


Table V. General data at baseline, after treatment, and after placebo for all subjects.

			BASELINE					TREATMENT					PLACEBO				
Subject	Age	Height	Weight	RMR	WHR	BMI	Girths	Weight	RMR	WHR	BMI	Girths	Weight	RMR	WHR	BMI	Girths
#	years	cm	kg	kcal/hr			Total cm	kg	kcal/hr			Total cm	kg	kcal/hr			Total cm
1	24	166.4	108	93.6	1.01	39.0	322.8	99.2	94.2	0.9	35.8	294.5	107	82.4	0.94	38.7	310.4
2	52	169.5	93.9	65.4	0.84	32.7	306.4	91.3	72.9	0.84	31.8	296.5	91.2	72.4	0.83	31.7	293.6
3	42	164.0	73.9	64.8	0.74	27.5	262	74.1	62.8	0.76	27.6	257	74.7	67.9	0.75	27.8	262.4
4	37	180.0	118.2	90.7	0.94	36.5	315.9	114.8	93.2	0.95	35.4	310.7	115.1	102.5	0.94	35.5	308.9
5	51	162.8	75.4	na	0.77	28.5	255.3	72.3	81.8	0.77	27.3	249.9	76	68.3	0.79	28.7	256.9
6	36	175.0	84.6	68.3	0.81	27.6	265.2	84.8	76.5	0.81	27.7	271.3	86.1	76.7	0.81	28.1	268.3
7	41	169.0	110	na	0.96	38.5	309.8	106.1	98	0.94	37.1	310.2	108.7	93.3	0.94	38.1	310.7
8	38	165.0	101	73.4	0.79	37.1	316.6	96	82.6	0.8	35.3	306.8	96.6	72.4	0.8	35.5	307.5
9	24	191.0	111.9	93	0.91	30.7	288.1	113.2	103.6	0.88	31	291.5	112.3	105.4	0.87	30.8	296.5
10	38	175.5	125.7	83.5	0.83	40.8	345.2	123.6	92.3	0.82	40.1	340.8	127.1	85.3	0.81	41.3	345.8
12	45	175.0	85	72.9	0.82	27.8	266.1	82.1	82.9	0.81	26.8	261.2	82.3	76.4	0.83	26.9	262.7
17	44	172.5	134	103.1	1.10	45.0	340.2	129	105.8	1.08	43.4	330	134.5	101.7	1.1	45.2	336.3
18	43	175.5	114.7	77.2	0.77	37.2	321.8	112	86.4	0.73	36.4	317.8	116	77.8	0.72	37.7	328.2
19	23	167.5	75	65.4	0.81	26.7	263.2	74.5	63.7	0.81	26.6	262	74.5	63.7	0.81	26.6	261.4
MEAN	**38.4**	**172.1**	**100.8**	**79.3**	**0.86**	**34.0**	**298.5**	**98.1**	**85.5**	**0.85**	**33.0**	**292.9**	**100.2**	**81.9**	**0.85**	**33.8**	**296.4**
SD	9.3	7.5	19.8	13.2	0.10	5.9	31.1	18.9	13.4	0.09	5.4	28.7	19.9	13.8	0.10	5.9	29.9

Figure 5. BMI After Treatments (F=10.97, p=0.001)

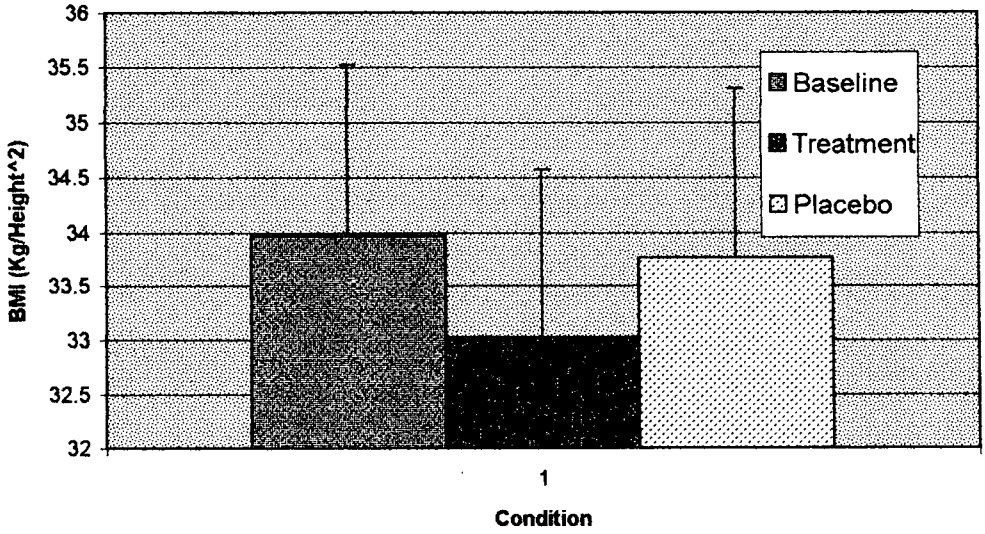
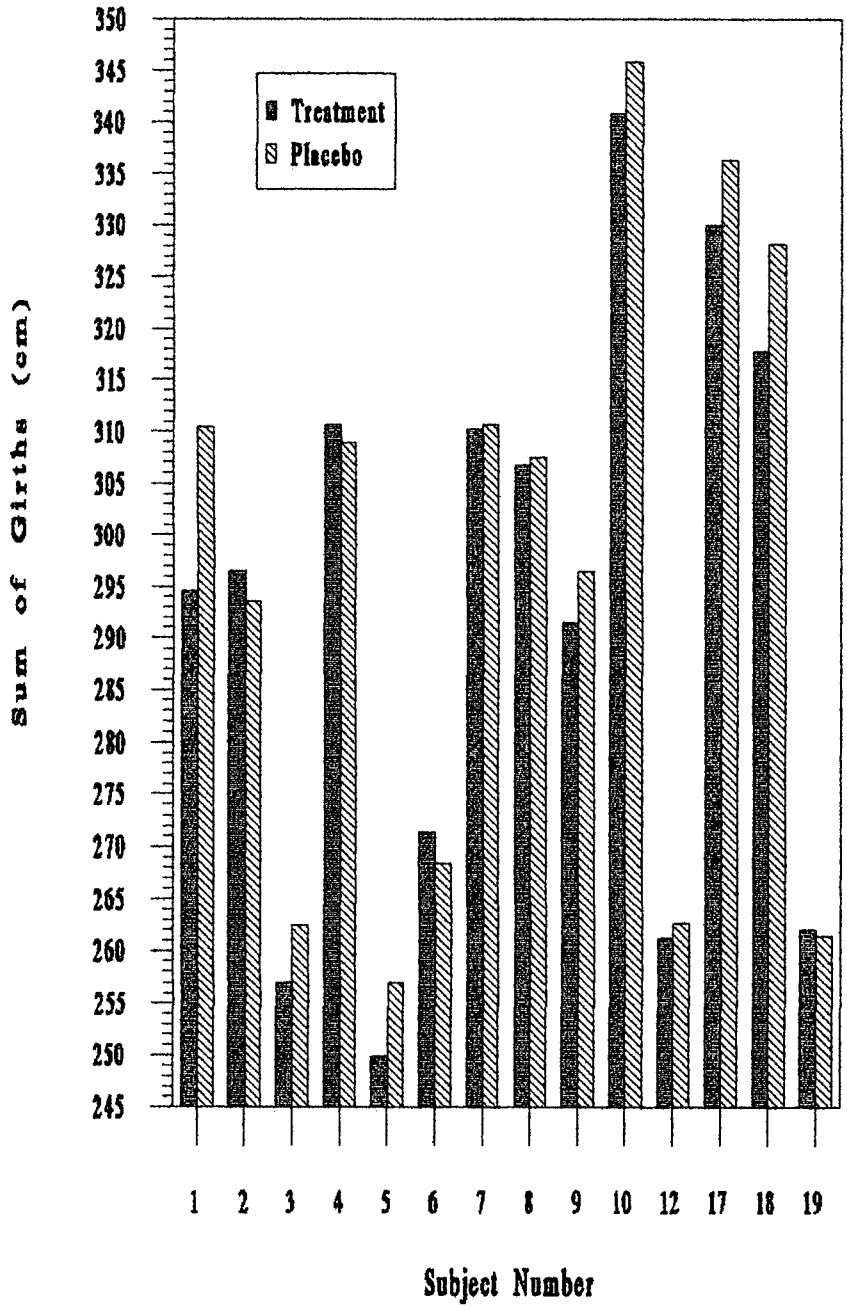


Figure 6. Subjects' Girths Comparing 8 weeks of Treatment vs. 8 weeks of Placebo.



V. DISCUSSION

In the present study twenty obese subjects participated in a weight loss study using a mixture consisting of 20 mg l-ephedrine hydrochloride and 200 mg caffeine citrate t.i.d. for eight weeks without controlling for diet and exercise. The primary advantage of having subjects eat and exercise at their own discretion closely resembles a normal lifestyle; humans cannot be expected to follow very low calorie diets and strict exercise regimes for life. The primary objective was to determine the amount of weight loss achievable during a short time period in those who had experienced difficulty losing weight through lifestyle changes alone. Another objective was to confirm the safety of taking such a mixture to treat obesity. Major findings were that 1) subjects found the treatment tolerable, and completed the study, 2) side effects self reported by subjects were minimal and transient, 3) body weight was significantly reduced when compared to the placebo, 4) resting metabolic rate increased during treatment, 5) waist to hip ratio, body mass index, and sum of girths all decreased, but not significantly while on ephedrine and caffeine. The following discussion will outline the major findings of the study under the following categories: 1) subjects' characteristics at baseline; 2) subject compliance and side effects; 3) changes in body weight during treatments; 4) resting metabolic rate and energy expenditure; and 5) effects of treatment on secondary variables (WHR, BMI, and girths).

SUBJECTS' CHARACTERISTICS AT BASELINE

Twenty subjects were recruited for this study, but only 14 subjects completed all the requirements (Table I). There were no significant differences between those that completed the study and those that did not for age, weight, and height. In fact, baseline data was similar for the two groups. The mean baseline weight of those completing the study was 100.8 ± 19.8 kg, and 97.2 ± 14.7 kg for those that did not.

Every effort was made to recruit as many males as possible, but like most similar studies females are more inclined to participate. Five males of the six that began completed the study. The average weight (99.7 ± 18.0 kg) of all subjects and BMI (33.7 ± 5.3 kg/m^2) falls within the range expected for an obese group i.e. having a BMI>27-30 kg/m^2. International classification has a BMI of >27 kg/m^2 as being obese, whereas the Canadian criterion has a BMI>30 kg/m^2 as being obese. Furthermore, a WHR>0.85 for women, and 1.0 for men along with a BMI>27-30 kg/m^2 are also Canadian criteria for assessing obesity. Most subjects met all these criteria however, Subject 19 only had a BMI of 26.7 kg/m^2, but was included because of this subject's desire to lose weight.

Girths were measured at four sites (arm, waist, gluteal, and calf), however, no comparisons could be made because girth measurements were not recorded in any previous study reviewed in the literature. On the other hand WHR has been documented in one study by Daly et al. (1993). The average WHR in their study was 0.88 ± 0.03 which is similar to that found in the present study, 0.86 ± 0.04.

The RMR recorded at baseline was 79.8 kcal/hr. This value was greater than the baseline values found by Pasquali et al. (1987) 56.1 kcal/hr, and Horton and Geissler

(1996) 73.5 kcal/hr. However, a higher value is to be expected because the previous studies' subjects' body weights were 83.9 and 85.5 kg, respectively. In addition, both of these studies were done on female subjects only, therefore a lower RMR would be expected because of less lean body mass in females. Factoring out the males in the present study lowers the RMR to 74.4 which is similar to the that found by Horton and Geissler (1996). Regardless, RMR measures can vary greatly particularly when females are menstruating or experiencing other biological fluctuations. Furthermore, it was noted that several subjects had difficulty in remaining motionless for the entire duration of the RMR measurements. Any movement could increase the reading as may have been the case in the present study. Although analysis was done very carefully, and inflated values were discarded and not used in calculations, errors may still have existed.

Finally, different RMR measurement protocols were used in the previous studies, which could result in different interpretations. Nonetheless, the RMR values at baseline found in this study are similar to those found by others. It appears that the subjects in this particular study are similar to those in previous studies.

SUBJECT COMPLIANCE AND SIDE EFFECTS

Fourteen out of twenty subjects completed the study. All the subjects who failed to complete the study presented with valid reasons. However, none of the reasons presented had anything to do with the study treatment of ephedrine and caffeine. All subjects remained motivated throughout the study except for one particular subject. One subject quickly became disinterested when results were not immediate as is the case with many people who want to reduce their weight, and in doing so look for the so called "magic

bullet" which does not yet and probably will never exist. Moreover, this particular subject was on the placebo treatment at the time.

The second subject who failed to complete the study had an unfortunate incident with food poisoning and as a result was hospitalized for over a week and unable to eat. This subject was on the treatment at the time, and therefore dropped from the study. However, this subject did indicate that once the food poisoning passed, she would like to have resumed with the study.

The remaining four subjects simply failed to make their follow-up appointments and therefore they were dropped from the study as well. Included in this group was one subject who presented herself for baseline measurements, but never returned for any of the follow-up appointments. The others showed up for one of the two scheduled follow-ups.

There was greater compliance with the ephedrine and caffeine (10.4 $\pm$ 13.6 capsules) than the placebo (13.6 $\pm$ 14.0 capsules) assessed by recording the number of capsules returned to the lab during follow-up appointments (Table III). It was assumed that all other capsules, not returned to the lab were consumed by the subjects. The majority of subjects took all of the washout capsules. Previous studies have not reported on the number of missed dosages, which is particularly important when assessing body weight in short term trials. Even with a relatively high missed dosage rate for a short study, body weight change was still significant. If all subjects had taken all of the treatment dosages one would expect an even greater change.

The side effects in the present study were similar to, but occurred less frequently than those reported by other studies (Table IV). The most common side effects were insomnia and cramps while on the ephedrine and caffeine. Mancini et al. (1990) and

Astrup et al. (1992) also reported that insomnia was the most common side effect while taking this mixture. Three subjects reported cramps in the present study, this may be due to caffeine's diuretic effect, hence excessive water loss decreases electrolyte balance resulting in muscle cramping. Other side effects in the present study included headaches, tachycardia and frequent urination.

Only three subjects did not complain of any side effects during treatment with ephedrine and caffeine. However, most subjects complained of one or two side effects only. Slightly more subjects (86%) in the present study complained of at least one side effect whereas a study conducted by Astrup et al., (1992) found that only (60%) of subjects reported at least one side effect on a similar dose.

During the placebo treatment very few side effects were reported as was expected. Only four subjects experienced any symptoms, the most common being cramps and loose stool. Withdrawal symptoms were also very minor; However, only one of the six analyzed did not report a symptom. Five subjects reported symptoms, the most common were headache and tiredness. Only one other study in the literature has recorded withdrawal symptoms. Headaches and tiredness were the most common symptoms followed by hunger (Astrup et al., 1992). In the present study only one subject reported an increase in appetite.

For the most part the treatment was well tolerated, side effects that occurred did so during the first two weeks only, and none of the subjects reported side effects after the initial two weeks of treatment. Therefore it appears that the treatment dosage is safe and side effects are only transient as reported in other studies (Astrup et al., 1992; Toubro et al., 1993).

CHANGES IN BODY WEIGHT DURING TREATMENTS

There are several studies in the literature that look at the effects of ephedrine (Pasquali et al., 1985); ephedrine and caffeine (Dulloo and Miller, 1986; Mancini et al., 1990; Toubro et al., 1993); and ephedrine, caffeine and aspirin (Dulloo and Miller, 1987; Daly et al., 1993) to stimulate thermogenesis, particularly diet-induced thermogenesis (DIT), and energy expenditure (EE) via the sympathetic nervous system (SNS) in the treatment of obesity. However, all of these previous studies either controlled for diet, exercise or both. No study has examined the effects of and ephedrine and caffeine combination in the treatment of obesity without controlling for diet and exercise, which was the purpose of the present study.

It has been demonstrated that ephedrine has the ability to mimic norepinephrine and thus stimulate metabolism (Dulloo, 1993) and promote weight loss through the oxidation of fat (Appendix 1). Furthermore, ephedrine also has the ability to stimulate protein synthesis as reported by Pasquali et al. (1992) who found that 50 mg of ephedrine t.i.d. significantly improved the nitrogen balance as well as increasing EE.

On the other hand, caffeine has been shown to act as a promoter by preventing the inhibitory effects of adenosine on the release of norepinephrine (Appendix 1). Increased norepinephrine release will increase thermogenesis and ultimately weight loss. When ephedrine and caffeine are combined there is a supra-additive synergism on thermogenesis (Dulloo and Miller, 1989; Astrup et al., 1991).

The ability to stimulate the SNS with natural chemicals such as ephedrine and caffeine has sparked considerable interest over the past decade and many pharmaceutical companies have been investigating synthetic drugs to do the same. One such drug,

dexfenfluramine, a serotonergic stimulator was found to produce weight loss mainly through appetite suppression in addition to thermogenic stimulation. However, in comparing the effects of dexfenfluramine and ephedrine/caffeine Breum et al. (1994) showed that the ephedrine/caffeine combination produced a greater weight loss (8.3 ± 5.2 kg) than the dexfenfluramine (6.9 ± 4.3 kg) during a 15 week study. Side effects were similar in both groups.

Recently the Food and Drug Administration (FDA) has removed dexfenfluramine from the market after reports of patients experiencing abnormal echocardiograms and rare heart valve defects. Therefore, the present study was conducted to further document safety and the amount of weight loss achievable using an ephedrine and caffeine mixture without controlling for diet and exercise.

In an eight week double-blind, placebo controlled, cross-over study in 14 obese subjects, weight loss was significantly greater for the ephedrine/caffeine treatment (2.8 ± 2.4 kg) compared to the placebo treatment which had a gain of (0.5 ± 1.1 kg) $p<0.001$ (Figure 2). These are the first results to document a change in body weight using the ephedrine/caffeine treatment without controlling for diet and exercise which has not been established. The advantage of this type of control is that subjects are more closely reflecting a normal lifestyle in terms of diet. The main disadvantage of this type of control is that the researcher has no way of knowing if subjects changed their diet or exercise levels during the study. Therefore, future studies should have subjects report in a diary the foods consumed and activities performed. In addition, subjects should be recalled every week to closely monitor changes in diet. For instance, only three factors lead to weight loss -

decreased diet, increased exercise, and effect of treatment (ephedrine/caffeine). Furthermore, a fourth factor which could lead to weight loss is water loss. Caffeine is a well known diuretic and therefore part of the weight loss measured in this study may be attributed to water loss and not fat. Regardless, Astrup et al. (1992) using the same mixture as the present study reported 4.5 kg more body fat lost with treatment when compared to placebo. Therefore water loss would appear to be a minor portion of the observed change in body weight. Several studies have shown significant weight loss while using the treatment dosages and reduced diet that could not have been from water loss alone (Mancini et al., 1990; Astrup et al., 1992; Toubro et al., 1993).

Individual weight loss varied among the group (Figure 3). Two subjects failed to lose weight while on the treatment. In fact they both gained weight. One subject, despite taking all of the dosages experienced a 0.2 kg gain in bodyweight while on the treatment. There are three possible explanations for this, the first being that this subject may have a genetically high threshold for ephedrine and caffeine and thus would require a larger dose to increase thermogenesis. The second reason may be that the subject might have adapted to a low calorie diet and thus not enough of a negative caloric deficit existed to induce a change in body weight. The last reason is that the subject may not have taken the dosages after all.

During the placebo treatment, subjects either stayed at the same weight or gained. Three subjects lost weight during the placebo treatment (Figure 3). Several factors could be responsible for these findings: (i) subjects may have decreased their diet and or increased their exercise levels, (ii) two of the three subjects who lost weight during the placebo

treatment received the placebo treatment first, (iii) the other subject may have experienced a carry-over effect from the ephedrine and caffeine treatment.

It appears that the combination of ephedrine (20 mg) and caffeine (200 mg) t.i.d. used in this study and others is sufficient enough to induce weight loss without the use of a hypocaloric diet. Unfortunately, after SNS stimulation with ephedrine and caffeine, there appears to be a 'rebound' effect, hence subjects who began with the placebo treatment gained 0.2 ± 0.9 kg whereas subjects taking the placebo after ephedrine/caffeine stimulation gained 0.8 ± 1.3 kg.

RESTING METABOLIC RATE AND ENERGY EXPENDITURE

The present study failed to find any statistical significance in RMR values with the two different treatments. However, the RMR did increase from 79.3 ± 13.2 kcal/hr at baseline to 85.5 ± 13.4 with ephedrine and caffeine. The RMR at the end of the placebo treatment was 81.9 ± 13.8, $p=0.027$. Although the present study did not show a significant increase in metabolic rate during ephedrine and caffeine treatment, the relative rise (7.6%) is consistent with the increase (8.0%) found by Dulloo and Miller (1986). However, their study used a combination containing 22 mg of ephedrine, 30 mg of caffeine and 50 mg of theophylline. In another study by Horton and Geissler (1996), RMR increased by 20.0% from the baseline value using a treatment consisting of a 252 kcal meal, 100 mg caffeine, and 30 mg of ephedrine measured at 160 minutes post-treatment.

The RMR values in the present study are not able to explain all the changes observed in body weight. However, the changes in body weight may have been because of

increased percentage of lean mass and a decrease in fat mass. Dulloo and Miller (1987) found that ephedrine administered to mice increased EE by 9%, but more importantly reduced body weight and body fat by 18% and 50%, respectively. The same may have been true in the present study. Another possible explanation may be that the subjects in the present study increased their lean body mass and decreased their fat mass regardless of the change in RMR. As indicated above ephedrine has the ability to increase protein synthesis by beta-3 receptor stimulation. Future studies should use dual energy x-ray absorptiometry (DEXA) scans in order to measure the relative change in lean body mass and fat mass.

EFFECTS OF TREATMENT ON SECONDARY VARIABLES (WHR, BMI, AND GIRTHS)

Although the overall purpose of this study was to measure the amount of body weight change while using ephedrine and caffeine, it was also important to determine where the body weight change occurred. In other words, did subjects gain lean mass, lose fat mass or both? Therefore, WHR, BMI and sum of girths were measured.

WHR

There was no significant change in WHR ($p=0.084$). Waist to hip ratio was the same during treatment with ephedrine/caffeine and placebo (0.85). The baseline WHR was 0.86. Because of the short duration of this study (8 weeks) significant change in WHR was not expected, because this study had both male and female subjects, each having a unique fat distribution pattern. The males tend to have an android or central distribution of fat whereas females tend to have a gynoid or peripheral distribution. In other words changes

that may have occurred in one subject might have been masked by others. Nevertheless, the most likely explanation for a lack of change in the WHR may be because the fat loss was evenly distributed. For example, if one was to lose 2 cm around the gluteal and 2 cm around the waist, the WHR would not change much, but a reduction in body weight or fat definitely would occur. This was the case with most subjects in this study because of the large changes in sum of girths.

BMI

As expected, there was a significant change in BMI during treatment (Figure 4). The baseline value was 34.0 kg/m^2, 33.0 kg/m^2 after treatment, and 33.8 kg/m^2 after placebo, $p<0.001$. Mancini et al, (1990) using a slightly different mixture along with a low calorie diet for 8 weeks measured a -1.90 kg/m^2 change in BMI in the treatment group and -0.9 kg/m^2 change in the placebo group. The present study only had a -1.0 kg/m^2 change after treatment, but a 0.8 kg/m^2 gain after placebo. In other words weight loss is almost always guaranteed when using SNS stimulants and low calorie diet. Unlike the previous study, this study saw a increase in BMI when subjects were on the placebo. This can be explained by the fact that the SNS is not being stimulated, and therefore the theorized defect in DIT is no longer being corrected. The end result is weight gain as was observed in the present study.

Although the present study was able to document a significant change in BMI, it does not, however, indicate where the change occurred. Was it because of a decrease in fat mass, change in lean mass, both or water loss. Because of the known actions of ephedrine and caffeine on the SNS, it was most likely a combination of all three factors (Dulloo,

1993; Astrup and Toubro, 1993; Astrup, 1995). Once again future studies need to look at where the change in body weight occurs using instruments such as DEXA.

GIRTHS

There was no statistical difference in girths during the treatments ($p=0.027$). However, the sum of girths decreased from 298.5 ± 31.1 cm at baseline to 292.9 ± 28.7 cm after treatment, and increased to 296.4 ± 29.9 cm after placebo. Although the change was not statistically significant, it indicates that the majority of the change in bodyweight can be attributed to fat loss.

Once again, the present study was able to demonstrate that when ephedrine and caffeine are removed, the stimulating and the DIT correcting properties are also removed. Hence, girths increased almost back to baseline values after the placebo treatment.

VI. CONCLUSIONS

In an 8 week, randomized, double-blind, placebo controlled, cross-over design, 14 obese subjects were administered a mixture consisting of 20 mg ephedrine and 200 mg of caffeine t.i.d. The results of this study provide preliminary evidence that stimulation of the SNS with ephedrine and caffeine promotes changes in body weight without controlling for diet and exercise. The change in body weight was -2.8 $\pm$ 2.4 kg during treatment with ephedrine and caffeine, and a gain of 0.5 $\pm$ 1.1 kg during placebo treatment ($p<0.001$).

The ephedrine and caffeine treatment was safe and generally well tolerated. All the side effects occurred within the first two weeks of treatment. The most common side effects were: insomnia and cramps. There were minimal withdrawal symptoms, the most common being headaches and tiredness.

The results of this study appear to be important in the treatment of obesity, particularly to those who are unable to exercise because of their current weight. A reduction in weight with the use of metabolic stimulants could allow obese individuals to reduce their weight to a level that would make them more mobile so that exercise could be accomplished. In addition, a reduced body weight would also reduce the risk of many other diseases associated with obesity.

Because of the small sample size in this study, the results should be confirmed in more studies with a larger group of subjects for a longer duration, and with more detailed measures of body composition. Dual energy x-ray absorptiomerty scans would have been appropriate, this would have provided accurate measures of body fat and thus able to

determine what percentage of the measured weight loss was water loss. Such studies should also look at specializing specific treatments for individuals incorporating diet and exercise programs. Future studies should also look at reducing dosages for subjects who experience side effects. These studies should focus on using the right dosage based on the metabolic profile of the subjects.

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APPENDIX 1

Definitions and Mechanisms

DEFINITIONS & MECHANISMS

Sympathomimetic Drug

Ephedrine: a chemical which mimics the actions of activation of the SNS, an adrenergic agent similar to NE. Ephedrine is a β-agonist found in many over-the-counter preparations used for treating bronchial disorders and asthma.

Methylxanthine Drug

Caffeine: a chemical stimulant which acts to aid sympathomimetics drugs by acting as an adenosine receptor antagonist. Caffeine inhibits cAMP phosphodiesterase. Caffeine is one of the most widely used drugs in the world.

Ephedrine & Caffeine

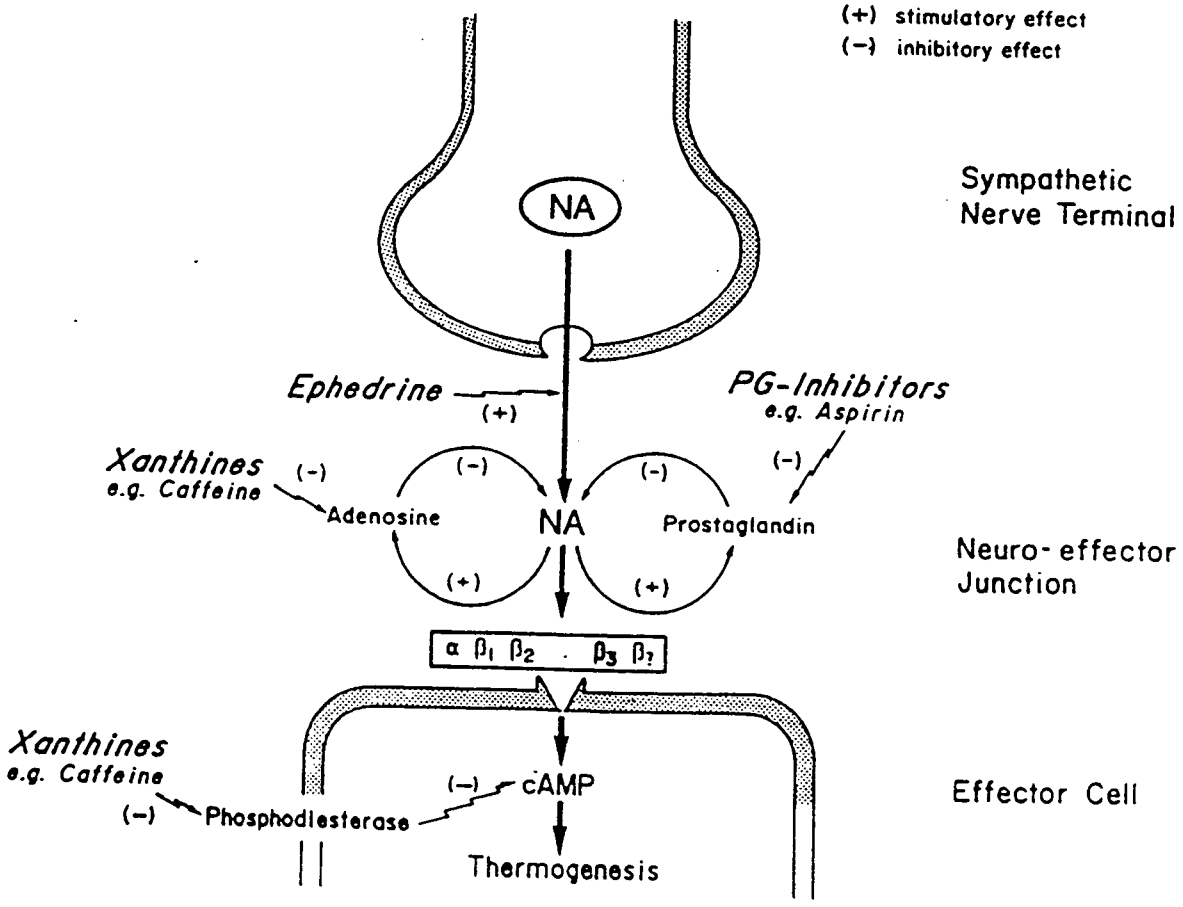
Together these drugs are thought to improve fat loss by dual action:

1) a central suppression of appetite

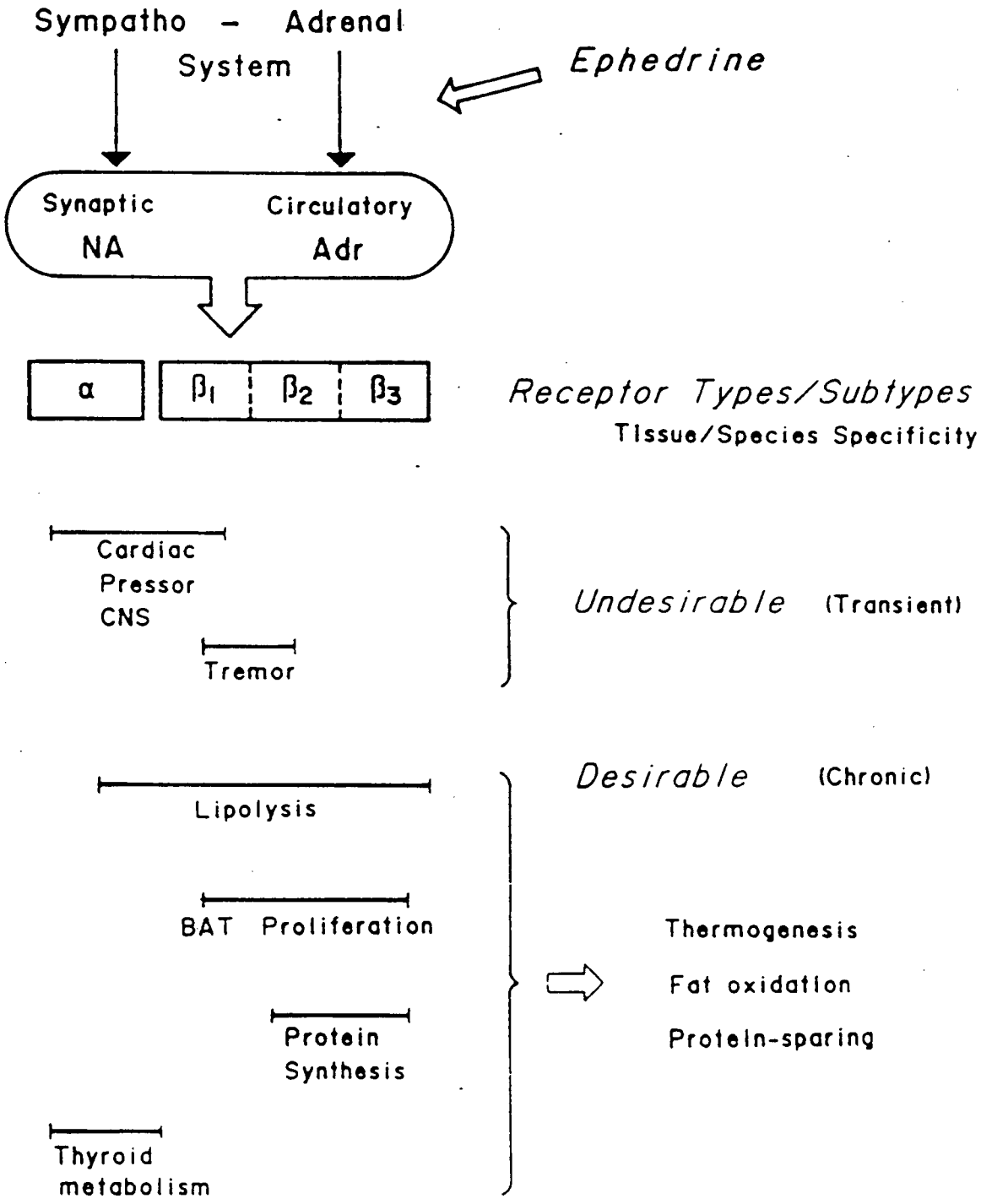
2) peripheral stimulation of energy expenditure covered by fat oxidation (Dulloo & Miller, 1986; Astrup et al., 1992)

The actions of Ephedrine and Caffeine on the Sympathetic Nerve Terminal

Hypothetical mechanisms to explain the potentiation of the thermogenic effects of ephedrine by caffeine and aspirin. The SNS is modulated by NE released from the sympathetic nerve terminal which acts on the effector cell to generate heat. Ephedrine is thought to increase NE release at the sympathetic nerve terminal. Adenosine and prostagladins act as co-modulators in the neuro-effector-junction and act as inhibitors in a negative feedback loop when the level of NE increases. Therefore, caffeine and aspirin are thought to act as promoters and prevent the inhibitory effects of adenosine and prostagladins. Thus, more heat can be produced (From AG Dulloo, 1993).



The actions of ephedrine on the adrenoceptors (From AG Dulloo, 1993).



APPENDIX 2

Newspaper Advertisement and Poster

APPENDIX 3

Consent Form

At the end of 8 weeks, once all 56 packets are taken you will be asked to come into the Buchanan Exercise Science Lab and have a series of measurements taken. In addition you will pick up 70 new packets.

Because this study is a cross-over, meaning that if you were taking the drug treatment during the first 8 weeks you will be taking the placebo capsules for the next 10 weeks or vice versa. Once again you will be asked to maintain a log.

The total length of the study is 18 weeks (8 weeks ephedrine/caffeine + 10 weeks placebo) or vice-versa, depending on which treatment you received first.

In addition to taking the capsules you will first have a series of harmless tests done on the day before you begin treatment, after the treatment, and again after the study is completed. These tests will take place in the morning and will last for about 2 hours. These tests may include a scan, and several measurements of the body.

The scan is known as DEXA (Dual energy x-ray absorptiometry) and works much like a x-ray. There is very little radiation given off; no more than a normal x-ray. You will lie down face up on a flat padded surface and a low intensity x-ray beam will scan over your entire body(head to toe). You will spend approximately 30 minutes under the scan. This procedure is safe and you will not feel anything.

The measurements of the body include height, weight, girths, and skinfolds. The skinfolds will be taken form the chest, stomach, and leg. You may experience a little pinch as the skin is grasped by the researcher. However, this measure only takes a few seconds and is virtually harmless.

You will spend a total of 6 hours during the entire study being tested in the lab. Two hours before the treatment begins, two hours after the initial 8 weeks, and two hours at the end of the study.

Exclusions: If you have hypertension (DBP>110 mm Hg), severe psychiatric or somatic disease, any possible contraindication to trial treatment, evidence of alcohol or drug abuse, treatment with drugs known to produce obesity, treatment with stimulants 1 month prior to start of the study, weight loss of more than 8 kg 2 months prior to start of the study, chronic caffeine use, and smoke you will not be able to participate in the study.

Consent: I understand that my participation in this study is entirely voluntary and that I may refuse to participate or withdraw from the study at any time without any consequences whatsoever.

I have received a copy of this consent for my own records.

I consent to participate in this study.

Subject Signature Date

Witness Signature Date

Investigator's Signature Date

APPENDIX 4

Certificate of Approval

APPENDIX 5

Girth Techniques

Girth Techniques

Arm: 90 degree angle at the shoulder. Measurement to be taken at the peak of the bicep muscle.

Waist: at the level of the most noticeable waist narrowing located approximately half-way between the costal border and the iliac crest.

Gluteal: at the level of the greatest posterior protuberance.

Calf: at the greatest circumference with the subject standing on a box, and weight evenly distributed on both feet.