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Thermogenesis

Bryan C. Bergman and James O. Hill

Introduction

This section deals with thermogenesis, which we define as energy expenditure (EE) above resting metabolic rate (RMR) not associated with physical activity. Other sections in this volume deal with both RMR and physical activity individually, and therefore these subjects will not be addressed. As defined for discussion in this section, thermogenesis can be produced from diet, drugs, and cold exposure. This section will discuss factors that may enhance thermogenesis, followed by a discussion of potential implications of thermogenesis in determining total energy expenditure (TEE), and how modulations in thermogenesis may influence the obesity epidemic now facing the United States and other countries.

Thermic Effect of Food

The thermic effect of food (TEF) is the acute increase in metabolic rate above resting metabolic rate after meal ingestion which can last for up to six hours (Figure 37.1). The TEF has also been called dietary-induced thermogenesis (DIT), but this term is less specific and could refer to the chronic effect of overfeeding on thermogenesis, which will be discussed in a later section. Thermic effect of food accounts for approximately 7 to 10% of daily EE under mixed meal conditions,[2,3] and thus could be an important determinant of daily EE. Factors which influence TEF are controversial, largely because of methodological differences between studies and questions about the applicability of laboratory studies to real-life situations.[4] Investigators often do not monitor TEF for sufficient time to quantitate the full effect of a meal on EE, which may explain much of the disagreement between studies.[1] IT is influenced by many variables, including meal size and frequency, meal composition, age, gender, obesity, and previous exercise.

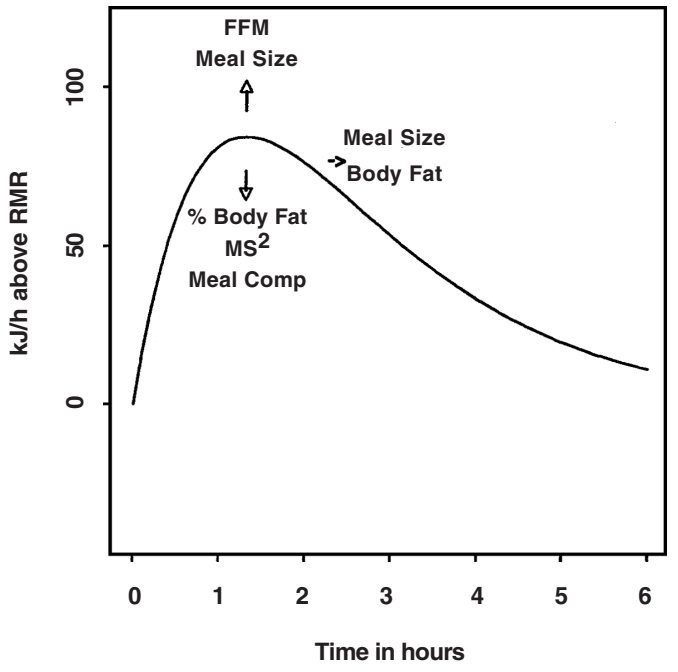

FIGURE 37.1
An illustration of how the TEF (thermic effect of food) curve shifts depending on subject and meal characteristics. Meal size and fat-free mass (FFM) tend to increase the peak; subject's body fat and meal size squared (MS^2) tend to lower the peak; meal size and subject's body fat tend to move the time of the peak further out. There is some evidence that increased fat in the meal may decrease the peak. Illustrated curve equation: $175.9 \times T \times e^{-T/1.3}$, where *T* is time and *e* is the base of the natural logarithm. RMR, resting metabolic rate. Reprinted with permission from: Reed, G. W. and Hill, J. O. Measuring the thermic effect of food. *Am J Clin Nutr* 63: 164-9, 1996.

Meal Size and Frequency

It should not be surprising that meal size is positively correlated with magnitude of TEF, due to increased energy requirements necessary to digest, transport, and store the greater energy load (Figure 37.1).[1] Increasing meal size enhances TEF in young women,[5] adult non-obese women,[6] and lean and obese men.[7,8] The greater the number of kcalories consumed during a meal, the more dramatic the increase in TEF.

The effect of meal frequency on TEF is unclear. Enhanced TEF has been reported when a meal is consumed in one bolus compared the same meal consumed at 30-minute intervals over a 3-hour period,[9] and is unchanged when a meal is consumed as one meal compared to two smaller meals.[10] The potential absolute change in TEF comparing an isocaloric load consumed as one meal or several meals is small, and is not likely to significantly affect daily EE. Thus, any role of meal pattern in overall energy balance is not likely due to differences in TEF.

Meal Composition

Macronutrient composition of the meal influences the magnitude of TEF. Meals containing a high percentage of protein invoke a greater TEF compared to isoenergetic meals with a

high percentage of carbohydrate,[11-14] which are more thermogenic than a meal containing a greater percentage of fat,[13,15-17] although there is data to the contrary.[6] Additionally, higher fiber content in isoenergenic- and macronutrient-matched meals may result in enhanced TEF compared with low fiber meals.[18]

An important question to consider is whether alterations in TEF can modulate daily EE. If a high-protein diet increases TEF compared to a high-carbohydrate or high-fat diet, it is possible that high protein diets may increase daily EE, which may explain some of the anecdotal success of high-protein diets for weight loss. However, Westerterp et al.[17] found that changes in TEF from alterations in macronutrient content did not significantly affect daily EE determined by whole room calorimetry. Moreover, others have also reported isoenergetic high-carbohydrate and low-carbohydrate diets did not change TEE measure by whole room calorimetry.[19,20] Therefore, because TEF is such a small percentage of TEE, alterations in TEF induced by changes in macronutrient composition do not appear to increase daily EE, and thus will not enhance weight loss or weight maintenance.

Age, Gender, and Obesity

Effects of age on TEF are unclear, as few studies have examined this directly. From TEF data on 471 subjects, Tataranni et al.[21] reported no overall relationship between the magnitude of TEF and age in men and women, and in women alone, and only a slight negative relationship between age and TEF in men alone. Moreover, other studies have found decreased TEF in older, compared to younger men,[22] but no relationship between age and TEF in women.[23] While there may be a small decrease in TEF in men but not women with increasing age, the absolute change in EE is small, and therefore not likely to impact weight stability in older individuals. More studies are needed to elucidate mechanisms of why TEF decreases with age in men, but not women.

Gender does not seem to change the magnitude of thermogenesis in response to a meal.[21,24] Potential alterations in TEF with menstrual cycle phase are unclear, as investigators have reported increased TEF during luteal phase,[25] decreased TEF during luteal phase,[26] and no change in TEF with menstrual cycle phase.[27] Additional studies are needed to more clearly elucidate whether menstrual cycle phase, or alterations in sex steroid hormones via utilization of birth control pills, have an effect on TEF.

The role of reduced TEF in the etiology of obesity remains controversial. Some report that obesity is associated with decreased TEF compared to age-matched control subjects,[28-33] but others report data to the contrary.[8,12] Potential factors influencing confounding results for effects of obesity on TEF have been reviewed by de Jonge and Bray,[34] who suggested that obesity does decrease TEF. Additionally, obese type II diabetic men[29] have lower TEF compared to age-matched obese men, and insulin-resistant lean men exhibit decreased TEF compare to insulin-sensitive lean men.[35] However, when obese subjects lose weight, TEF is either partially normalized[36] or not different from age-matched lean subjects.[37,38] These data suggest that alterations in TEF are a result of the obese state and not a predisposing factor promoting accumulation of adiposity.

Effects of Exercise on TEF

Acute exercise prior to meal ingestion has been reported to increase TEF in normal-weight men and women,[5,39] or not change TEF in lean men.[35] The magnitude of enhanced TEF

post exercise is quantitatively small, with enhanced EE of 4.5 kcal/hr for 4 hours reported by Nichols et al.[39] and 5 and 6 kcal/hr for 2 hours reported by Young[5] with a 630 and 1260 kcal meal, respectively. Mechanisms for elevations in TEF following exercise are unclear, as further research is necessary to elucidate mechanisms responsible for enhanced TEF. Due to the small absolute increase in TEF post exercise, meal consumption after exercise is not likely to increase whole-body EE or help promote weight loss or maintenance.

In obese subjects, enhanced post-exercise TEF occurs following an acute one-hour bout of cycle ergometry.[32,35] After exercise, TEF was elevated 3.3 and 7.6 kcal/hr for 3 hours in insulin-sensitive and non-insulin-sensitive obese men, respectively. While TEF was elevated after exercise in obese men, values were lower than lean men with similar insulin sensitivity.[35] Thus, dampened TEF is a consequence of obesity both at rest and immediately following exercise.

The literature is also unclear with respect to effects of chronic endurance exercise training on TEF. Investigators have reported endurance exercise training to both decrease,[40] and increase TEF[41] by 30% (4.5 kcal/hr for 2 hrs) in men and rats.[42] Additionally, enhanced TEF has been reported in obese and diabetic men following 12 weeks of cycle ergometer training.[29] While TEF was not normalized compared to age-matched lean subjects, these data suggest that chronic endurance exercise training may increase TEF. Thus, while most data suggest that chronic endurance exercise training increases TEF, the absolute change relative to daily EE is small.

Thermogenesis with Chronic Overfeeding

The previous discussion of TEF has not dealt with potential alterations in RMR with chronic dietary alterations such as overfeeding. The literature is unclear as to the effect of overfeeding on RMR. Some investigators have reported enhanced RMR during overfeeding in humans,[43-46] while an equal number have not shown an effect.[47-51] This confusion is not due to diet composition, as there does not appear to be a relationship between macronutrient composition of overfeeding and alterations in RMR.

While the response of RMR to overfeeding is unclear, the effect on TEF is less ambiguous. Overfeeding increases TEF due to the greater total amount of food consumed, as TEF is determined by energy content of the diet.[8] However, it is less clear if TEF to a given energy load is increased during overfeeding. Overfeeding has been reported to enhance TEF during an isoenergetic meal before and after overfeeding in some,[47,51] but not all studies.[49]

The notion of "luxoconsumption" originally proposed by Neumann,[52] and revisited by Miller et al.,[53] where excess ingested energy is "wasted" to minimize weight gain, has not been proven. Several investigators have determined all aspects of energy balance during overfeeding and accounted for the vast majority of ingested energy. They measured enhanced TEF due to a greater total volume of food consumed, facultative energy requirements of excess energy storage, and increased cost of activity due to greater total body weight.[44,49,50] However, 85 to 90% of excess energy consumed is stored and not oxidized.[50] Thus, overfeeding may enhance TEF to an isoenergetic challenge, and potentially increase RMR. However, there is no evidence for "luxoconsumption" in overeating humans, where excess ingested energy is dissipated as heat and not stored.

Cold-Induced Thermogenesis

During cold exposure, the first method of maintaining body heat is shunting of blood from the periphery to the body core to reduce heat loss. As body temperature drops slightly, shivering is initiated to generate heat through contraction of pilo-erectile muscles in the skin, followed by involuntary contraction of skeletal muscle. Chronic cold exposure may lead to cold acclimatization and the development of non-shivering thermogenesis (NST), where other body tissue begins to produce heat which replaces shivering thermogenesis. While NST is well documented in rodents, its role in human thermoregulation during chronic cold exposure is less clear.

Cold exposure in rats results in increased rates of heat production due, in part, to increased sympathetic nervous system activity.[54] Enhanced norepinephrine release[55] and concentration[56] persist for the duration of cold exposure, and serve to increase brown adipose tissue (BAT) thermogenesis for maintenance of body temperature. BAT is a mitonchondrially dense specialized tissue for heat generation found in rodents and animals which hibernate. Heat is generated from uncoupling of oxygen consumption to the phosphorylation of ADP to ATP such that oxygen is consumed, but ATP is not produced. The metabolic energy is released as heat instead of captured in high-energy phosphate bonds.

Norepinephrine is thought to be a vital component to the development of cold tolerance, as daily injections of norepinephrine improve cold tolerance in animals which had never before been exposed to cold.[57] Acute exposure of rats to cold results in loss of body weight, and initiation of energetically inefficient shivering thermogenesis for warmth.[58] However, continued exposure results in normalization of weight as animals eat more when shivering abates due to enhanced activity of BAT for heat production.[58,59]

Humans, however, respond much differently than rats when exposed to cold. There has been little evidence to suggest that humans have the capacity for BAT thermogenesis. Humans have a small amount of BAT, and compared to rodents this tissue is less active. Thus, compared to rodents, humans exhibit different adaptive mechanisms to tolerate cold exposure. Following cold acclimatization, humans tolerate lower core body temperature during cold exposure without enhanced thermogenesis seen in the rat model.[59] As a result, humans acclimatized to cold shiver less during a cold challenge, and adaptive heat production is reduced. One study has shown that it is possible to induce NST through chronic cold exposure in humans;[60] however, others have not replicated this result, as shivering thermogenesis was maintained after cold acclimatization with no evidence for NST.[48] Cold acclimatization is largely an academic question, as it generally does not occur in humans except under extreme circumstances. Normally, human behavior can be changed to get out of the cold or alter the microenvironment to prevent a drop in body temperature.[61]

Over-the-Counter Weight Loss Stimulants

There are numerous products on the market and natural substances in foods and beverages which may increase whole-body EE. While many products claim to have thermogenic properties, the extent to which these drugs enhance EE is often tenous. An added difficulty when assessing thermogenic properties of substances, especially those marketed as an over-the-counter stimulants, is the large variety of different concentrations available to

the consumer, both between different products and between batches of one individual product. Additionally, supplements exhibit great variability in drug bioavailability, especially when the stimulant in question is consumed with other foods and/or drugs. Here we will attempt to cover the main thermogenic substances on the market, as well as potential summation or synergy when using these drugs in combination.

Caffeine

Caffeine is a stimulant of EE in both rats and humans. Caffeine ingestion alone has been reported to increase EE by 3 to 7% for up to three hours.[62-64] Dulloo et al.[63] reported that a single 100 mg caffeine dose increased resting metabolic rate by 3 to 4% over 150 minutes in both lean and post-obese humans. Thus, caffeine ingestion may have utility in enhancing daily EE for weight loss. However, some investigators have not observed increased EE with caffeine ingestion alone,[65] likely due to small dose administration, as caffeine's effects on thermogenesis are dose dependent.[66] The mechanism of action of caffeine's stimulatory effect on EE may be a result of the energy cost of enhanced lipolysis from phosphodiesterase inhibition and/or antagonism of adenosine action.[67] In addition to thermogenic properties of caffeine ingested alone, caffeine also increases TEF when consumed with a meal in both young and old men and women.[68] Additionally, caffeine ingestion with a meal partially normalizes the attenuated TEF observed in post-obese subjects.[63]

Not all population groups exhibit similar increases in thermogenesis following caffeine consumption. Thermogenic effects of caffeine appear to be similar in men and women,[68] and in habitual and non-habitual consumers of caffeine.[69] However, older men and women tend to exhibit less of an increase in thermogenesis when compared to young controls.[70] Caffeine-stimulated thermogenesis may also be attenuated in endurance-trained subjects compared to sedentary control subjects.[69] Differences in the magnitude of caffeine-induced thermogenesis in obese compared to lean individuals is unclear. Some investigators reported less of an effect of caffeine to increase thermogenesis in obese compared to lean women,[71] while others reported no difference in the thermogenic response to caffeine in lean and obese women.[72,73]

Following repeated administration of caffeine, Dulloo et al.[63] reported that the net increase in daily EE in post-obese subjects was roughly half that observed in lean controls. This study found that 100 mg of caffeine ingested at 2-hour intervals for 12 hours promoted an 11 and 8% increase in EE in lean and post-obese subjects, respectively, during that 12-hour period, with no effect of caffeine on subsequent 12-hour EE (Figure 37.2).[63] Caffeine administration repeated for 12 hours resulted in an increase in daily EE of 150 kcal/day in lean, and 79 kcal/day in post-obese subjects. Thus, this study suggested that caffeine consumption throughout the day may have utility in promoting weight loss or weight maintenance. However, the effects of caffeine supplementation on weight loss in obese subjects during an energy-restricted diet were evaluated in a 24-week double-blind trial by Astrup et al.[74] These authors reported no significant difference in weight loss during 200 mg caffeine supplementation administered three times per day compared to placebo in obese subjects (Figure 37.3). Subjects supplemented with caffeine reported side effects which included dizziness, headache, and insomnia which abated after eight weeks, with no effects on systolic or diastolic blood pressure or heart rate. Thus, these data suggest that caffeine alone in combination with energy restriction offers no benefit for added weight loss compared to placebo control. Considering the small effect of caffeine to stimulate thermogenesis, it is not surprising that caffeine ingestion alone does enhance weight loss via enhanced thermogenesis. However, based on data from Dulloo et al.,[63] caffeine supplementation may be needed more times per day than performed by Astrup

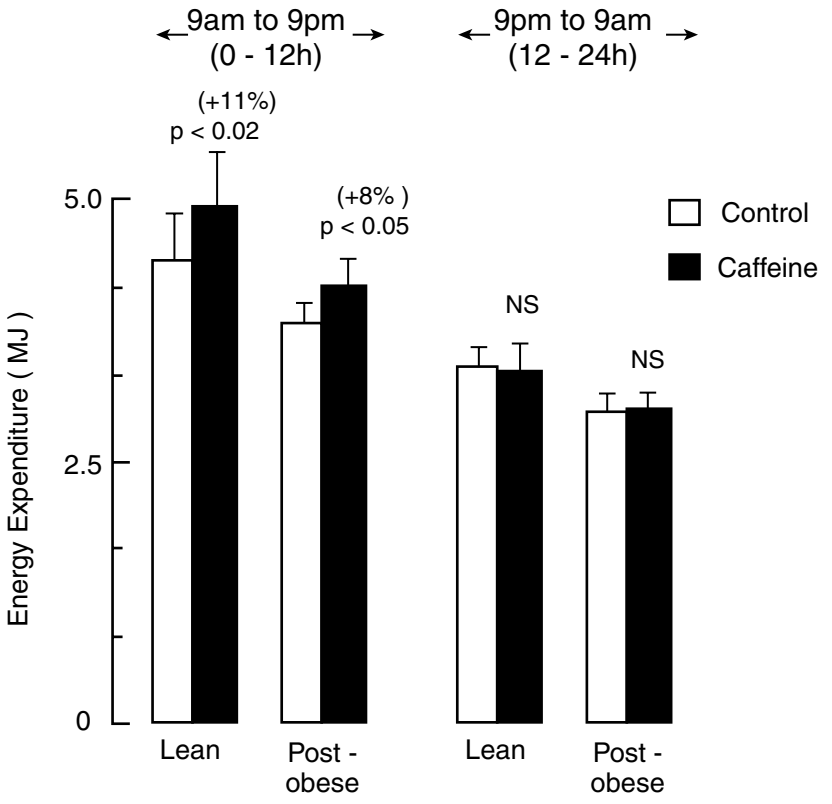

FIGURE 37.2
Energy expenditure compartmented into the first 12-h d period (0 to 12 h) and the subsequent 12-h night period (12 to 24 h) in lean (n = 5) and postobese (n = 6) subjects during a control study (open bars) and during administration of caffeine. Vertical bars represent the SEM values. The probability level for significant differences is for paired data. MG values can be converted to kcal by multiplying them by 239. Reprinted with permission from: Dulloo, A. G., Geissler, C. A., Horton, T., Collins, A., and Miller, D. S. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. *Am J Clin Nutr* 49: 44-50, 1989.

et al.[74] to significantly increase daily EE. If true, repeated caffeine supplementation for 12 hours during the day may be useful in promoting enhanced EE for weight loss. While not discussed in this section, caffeine ingestion may be beneficial for assisting weight loss via appetite suppression, regardless of effects on thermogenesis.

Ephedrine

Ephedrine is a sympathomimetic agent which increases energy expenditure by enhancing norepinephrine release from sympathetic nerve endings with stimulation of all three beta receptor subtypes.[75] Ephedrine administration alone via intravenous injection has been reported to increase resting energy expenditure by 16% in dogs[76a] and 17% in obese premenopausal women.[76] Moreover, chronic oral ephedrine administration in female subjects induced a sustained 10% increase in resting metabolic rate compared to pretreatment values.[77] Similarly, chronic administration of ephedrine alone to mice increased EE by 9% and induced an 18% decrease in body weight.[78] Chronic ephedrine supplementation may increase the magnitude of enhanced EE compared to acute ephedrine administration.[79]

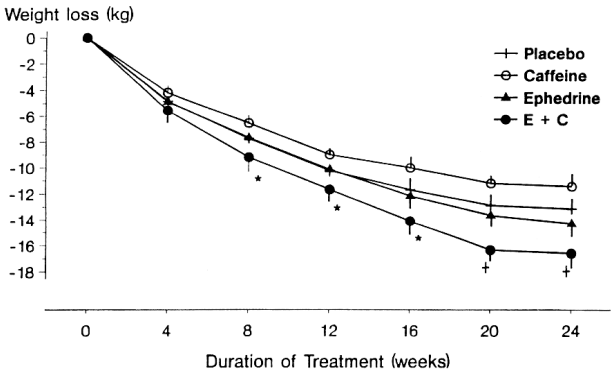

FIGURE 37.3
Changes in body weight of diet plus placebo, caffeine (C), ephedrine (E) or E + C. Means ± SEM are presented. E + C versus placebo: *P<0.04 †P<0.01. Reprinted with permission from: Astrup, A., Breum, L., Toubro, S., Hein, P., and Quaade, F. The effect and safety of an ephedrine/caffeine compound compared to ephedrine, caffeine, and placebo in obese subjects on an energy restricted diet. A double blind trial. *Int J Obes Relat Metab Disord* 16: 269-77, 1992.

These data suggest that chronic ephedrine administration may be a useful adjunct to promote weight loss in obese individuals.

Despite evidence suggesting ephedrine alone can increase RMR, experimental evidence is lacking for ephedrine supplementation alone in enhancing weight loss when combined with energy restriction. Astrup et al.[74] reported that ephedrine supplementation of 20 mg three times per day during energy restriction for 24 weeks did not enhance weight loss compared to placebo (Figure 37.3). Subjects reported significantly more side effects compared to caffeine-only supplementation, which also did not enhance weight loss, with symptoms including insomnia, tremor, and dry mouth most prevalent for the first four weeks of treatment. Additionally, Pasquali et al.[80] reported no enhancement of weight loss with two doses of ephedrine compared to placebo during a three-month intervention.

While evidence suggests ephedrine administration alone does not enhance weight loss compared to placebo, several studies have investigated ephedrine combined with other potentially thermogenic agents on RMR and weight loss. A combination of ephedrine and caffeine administration is more effective in enhancing thermogenesis compared to either caffeine or ephedrine alone,[81] with above additive synergism observed at a dose of 20 mg ephedrine and 200 mg caffeine.[82,83] Additionally, data suggest that addition of ephedrine and caffeine to an energy-restricted diet enhances weight loss in obese women compared to caffeine or ephedrine administered separately during isocaloric energy restriction,[74] or compared to energy restriction alone.[84] Astrup et al.[71] reported supplementation with ephedrine plus caffeine during a 6-month energy-restricted diet enhanced weight loss by 3.4 kg compared with placebo, caffeine alone, or ephedrine alone (Figure 37.3). Similarly, Dulloo and Miller[81] reported that daily administration of 22 mg ephedrine, 30 mg caffeine, and 50 mg theophylline to post-obese subjects decreased energy intake by 16% and increased EE 8%. These data are corroborated by animal studies reporting decreased body weight during eight weeks of daily ephedrine and caffeine supplementation due to decreased energy intake and increased EE in monkeys.[85] These data suggest that ephedrine plus caffeine supplementation decreases appetite and enhances TEE, which may be beneficial for weight loss practices in the obese.

Ephedrine supplementation has also been combined with aspirin, which doubled ephedrine's thermogenic action in mice[78] and enhanced ephedrine stimulation of TEF in obese, but not lean women.[86] Aspirin acts only to enhance the thermogenic effects of ephedrine,

as chronic aspirin administration alone had no effect on energy balance in mice.[78] However, addition of aspirin to an ephedrine and caffeine mixture does not further potentiate TEF induced by ephedrine and caffeine alone in lean and obese women.[86] The drug combination of ephedrine, caffeine, and aspirin taken before meals for two months has been reported to induce weight loss without controlled energy restriction in a double-blind experiment in obese humans.[87]

These data suggest that administration of caffeine and ephedrine in combination, with or without aspirin, may increase daily EE and enhance weight loss during energy restriction. The increase in metabolic rate is small and may promote weight loss from appetite suppression when these drugs are used in combination.[84,85]

Nicotine

Anecdotal evidence suggests that smoking either increases metabolic rate, decreases appetite, or both, as weight gain frequently occurs with smoking cessation. Many investigations support the former, as resting EE in men has been found to increase 5% for one hour after smoking 2 cigarettes in 20 minutes (.8 mg nicotine yield),[88] 3.3% over a 3-hour period after smoking 4 cigarettes (3.2 mg nicotine yield),[62] 6.5% over 2 hours following nicotine nasal spray administration,[89] and 6% increase in RMR in male habitual smokers after smoking 2 cigarettes in 20 minutes.[90] While an increase in RMR may be advantageous for weight loss or weight maintenance, the absolute increase in EE from nicotine administration is not convincing. Collins et al.[62] reported the most dramatic increase in RMR (6%) for 3 hours after smoking 2 cigarettes in 20 minutes. However, the absolute increase in EE was only an additional 12.5 kcals over the 3-hour period, which is unlikely to promote substantial weight loss, even if smoking was maintained throughout the day. DIT is not enhanced following nicotine administration via nasal inhalation at 15 micrograms/kg body weight.[89] Additionally, habitual smoking does not appear to influence nicotine-induced thermogenesis in men.[90] Thus, data are lacking to suggest nicotine administration, either from cigarette smoking or nasal spray inhalation, may have weight loss effects via enhancement of EE.

Nicotine may be more potent in appetite suppression than in enhancement of EE. Miyata et al. [91] reported that systemic nicotine infusion decreased body weight in rats via reductions in energy intake, with the most dramatic effects on reduction in meal number. Gender differences were not observed for the alterations in meal size and number and body weight reduction during nicotine administration in rats.[92] Increased concentrations of serotonin and dopamine were found in the lateral hypothalamus following nicotine administration, which suggested that nicotine may exert anorectic effects in part by alterations in these brain neurotransmitters. Appetite supressive effects of nicotine are not as clear in humans. Perkins et al.[93] administered nicotine via nasal spray inhalation at three doses and then monitored subsequent meal size following an overnight fast. Suprisingly, the authors reported meal caloric intake was increased following nicotine administration in both men and women compared to placebo controls. However, the same authors reported that nicotine reduced appetite in men during a subsequent meal test when nicotine was administered following consumption of a morning meal.[94] More studies are needed to determine if nicotine is an anorectic agent in humans.

Only one study investigated gender differences in thermogenic effects of nicotine, where nicotine was administered via nasal spray inhalation.[89] Nicotine was administered once every 30 minutes for 2 hours at 20 micrograms nicotine/kg for each dose. Nicotine increased resting EE in men, but not women. Since nicotine intake is associated with lower body weights in both men and women, the authors speculated that nicotine exerts anorectic effects in women via more dramatic appetite suppression compared to men.

Obviously, cigarette smoking should not be used to promote weight loss, due to well documented health risks caused by smoking. However, since smoking cessation should be a health goal for the population, understanding the expected alterations in appetite and/or RMR following nicotine withdrawl will be vital to attenuate weight gain often reported with smoking cessation. The literature suggests that clinicians and health professionals may expect a slight decrease in RMR, potentially as dramatic as 6% in chronic smokers, upon cessation of smoking.[62] Assuming that smoking only occurs during waking hours, 8 hours sleep/night, a caloric equivalent for oxygen of 4.85 kcal/L O_2, and RMR of 3.5 ml/kg/min; a 6% decrease in RMR in a 70 kg individual would be predicted to decrease EE by only 70 kcal/day. While the accumulation of 70 kcal/day positive energy balance may promote slight weight gain, this simple calculation suggests that enhanced appetite following smoking cessation may be more powerful for promoting weight gain, and thus behavioral therapy may be indicated to help control energy intake.

Prescription Drugs for Weight Loss

Several prescription medications are currently available to physicians to enhance weight loss. Two of these medications, sibutramine and fenfluramine, are systemic agents which are putatively thought to only affect appetite. Orlistat, a pancreatic lipase inhibitor, is not systemic and thus is unlikely to have thermogenic action. The potential thermogenic role of both sibutramine and fenfluramine for enhancing weight loss is discussed here.

Sibutramine

Sibutramine is a serotonin and norepinephrine reuptake inhibitor[95] which enhances weight loss compared to placebo both with[96,97] and without[95] behavior modification. However, thermogenic effects of sibutramine are less clear. Studies in rats suggest that sibutramine increases resting EE via beta adrenergic stimulation of BAT.[98] However, human data suggests that sibutramine increases resting metabolic rate,[99] or does not change RMR or TEF.[96,97] Several investigators have reported that sibutramine attenuates the decline in RMR that occurs during weight loss.[100,101] Thus, effects of sibutramine on thermogenesis in humans are unclear; however, evidence indicates that sibutramine does decrease appetite and/or increase satiety, which promotes weight loss.[99,100]

Fenfluramine

Fenfluramine is a serotonin-releasing agent and reuptake inhibitor[102] which enhances weight loss compared to placebo in both rats[103] and humans.[104-106] Effects of fenfluramine on thermogenesis are not clear, and there appear to be species differences which further cloud data interpretation. Investigations on rats suggested fenfluramine promotes a transient decrease in energy intake, with maintenance of weight loss via enhanced TEF, as there were no changes in resting energy expenditure.[103,107] Others, however, reported that fenfluramine decreased energy intake throughout the treatment period[108] in rats. In humans, fenfluramine appears to act as an appetite suppressant, with decreased energy intake compared to placebo reported for treatment groups.[105] Most investigators report unchanged RMR and TEF following fenfluramine treatment in humans.[105,109-111] However, enhanced TEF has been reported in humans following acute administration of fenflu-

ramine in men.[112] Thus, fenfluramine appears to have little, if any, thermogenic action, with enhancement of weight loss in humans predominately via appetite suppression.

Uncoupling Proteins and Thermogenesis

Uncoupling proteins (UCP) are proteins located in the inner mitochondrial membrane. These proteins dissipate the proton gradient by allowing proton leaking across the inner mitochondrial membrane. This results in a disassociation of respiration from ATP production, with the result of an increase in heat production.[113] Thus, oxygen is consumed and heat is produced but there is no ATP synthesis. UCP are an exiting area of research, as they may be potential weight loss drug targets to promote a less efficient metabolism and subsequent increase in TEE.

The first uncoupling protein, now termed UCP1, was isolated from BAT in 1978 by Heaton and colleagues,[114] subsequently purified by Lin et al.[115] in 1980, and molecularly cloned in 1985.[116] UCP1 is only found in BAT, and the inhibition by purine nucleoside di- and tri-phosphates and stimulation by free fatty acids was initially described in isolated BAT mitochondria.[117] Humans exhibit minimal BAT, therefore alterations in BAT thermogenesis cannot explain changes in whole-body energy expenditure or the propagation of the current obesity epidemic.

Since the discovery of UCP1, proteins with similar homology have been identified. UCP2 is expressed in most tissues, and exhibits 55% homology with UCP1 based on initial cloning in 1997.[118,119] There was considerable excitement over the discovery of UCP3 in skeletal muscle, BAT, and heart in 1997, as it was thought to be a potential regulator of thermogenesis which could partly explain susceptibility to, or development of obesity. However, excitement abated after publications reported UCP2 and 3 mRNA responded unintuitively following various perturbations, suggesting that UCP2 and 3 are not regulators of thermogenesis *in vivo*. Fasting increased UCP2 and 3 mRNA expression in rats[120-122] and in lean and obese humans[123] during a time when whole-body EE was decreased,[124] suggesting that UCP2 and 3 were not involved in altering thermogenesis in response to dietary intervention. However, food restriction downregulated UCP3, but not UCP2 mRNA expression in skeletal muscle.[120,121,125,126] Data showing upregulation of UCP3 mRNA in response to conditions associated with enhanced lipid oxidation,[120-123] in addition to results which have shown upregulation of UCP3 mRNA in rats during intralipid and heparin infusion,[127] suggest a role of UCP3 in fat metabolism and not thermogenesis. It is important to consider that mRNA expression does not necessarily represent alterations in protein content due to post-transcriptional regulation of the mRNA transcript. Thus, measures of protein content and activity are necessary to fully elucidate the potential role of UCP2 and 3 in thermogenesis. However, initial research suggests that they do not behave similarly to UCP1 in BAT and thus may not determine susceptibility to obesity.

UCP Up-Regulation and Knockout Experiments

Knockout mice for UCP1 cannot maintain body temperature during cold exposure, confirming the role of BAT in determining NST.[127] Interestingly, UCP1 knockout mice are not

obese, which suggests that UCP1 is not a determinant of obesity.[128] Recent reports indicate that UCP3 knockout mice are also not obese, and they do not show alterations in fatty acid oxidation, exercise tolerance, or cold-induced thermogenesis.[129,130] These knockout mice do exhibit more tightly coupled mitochondria (state 3/state 4 ratio) as well as reduced production of reactive oxygen species. Thus, these data suggest that neither UCP1 nor 3 solely determine metabolic rate or body weight regulation.

Thermogenesis and Obesity

There is no strong evidence that alterations in thermogenesis contribute to obesity. Thermogenesis, excluding resting metabolic rate and physical activity, only contributes roughly 10% to total daily EE. Thermic effect of food is the majority of this 10% of TEE, which has been reported to be slightly decreased in obese compared to lean subjects in some,[28,29-33,131] but not all studies.[8,12] More importantly, it is not known whether alterations in TEF promoted the obese state, or whether the obese state promotes alterations in TEF. Insight into this question arises from investigations on subjects before and after weight reduction. When subjects are studied after weight loss, TEF is either not different from age-matched lean subjects[38] or partially normalized,[36] suggesting that decreased TEF is a result of weight gain, and not a causative factor in the development of obesity. Therefore, it is unlikely that alterations in thermogenesis can explain the increased prevalence of obesity today.

Thermogenesis, NEAT, and Alterations in Daily Energy Expenditure

Thermogenesis induced by drugs, food consumption, or cold exposure is of questionable importance in determining TEE due to their transient nature and the relatively small effect on increasing whole body oxygen consumption. However, fidgeting behavior has recently been described and may contribute significantly to enhance whole-body EE.[132] Levine et al.[132] quantitated EE during 8 weeks of overfeeding 1000 kcal/day in 16 non-obese men. They coined the term Nonexercise Activity Thermogenesis (NEAT) to account for EE not associated with physical activity or TEF. The authors reported that changes in NEAT predicted resistance to fat gain during overfeeding, while no relationship was observed between fat gain and changes in TEF or RMR (Figure 37.4). This NEAT exhibited marked intra-individual variability and may partially explain why some individuals are more susceptible to obesity than others.

Currently, we don't have a conclusive idea of what determines the magnitude of NEAT, or why there is up to tenfold variability in NEAT from person to person.[132] However, NEAT is an interesting avenue for future research which may suggest possible lifestyle interventions or drug targets which could potentiate NEAT and promote greater whole-body EE. One should not discount the importance of energy expended by NEAT activities. Levine et al.[133] recently reported on the energetics of gum chewing, a component of NEAT. The authors reported that gum chewing increased energy expenditure by 11 kcal/hour, a 20% increase over RMR. If gum chewing occurred during the waking hours throughout

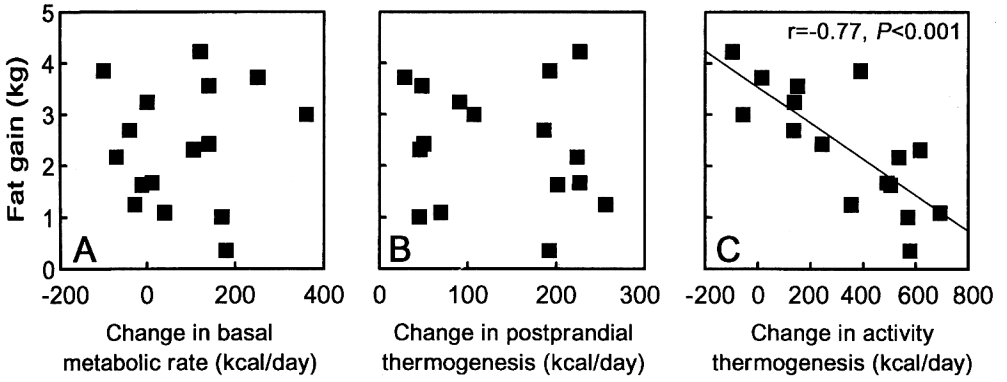

FIGURE 37.4
The relation of the change in (A) basal metabolic rate, (B) postprandial thermogenesis, and (C) activity thermogenesis with fat gain after overfeeding (27-33). Exercise levels and the thermic efficiency of exercise were unchanged with overfeeding, so that changes in activity thermogenesis represent changes in NEAT. Reprinted with permission from: Levine, J. A., Eberhardt, N. L., and Jensen, M. D. Role of nonexercise activity thermogenesis in resistance to fat gain in humans [see comments]. *Science* 283: 212-4, 1999.

the day with no other lifestyle changes, the authors predicted weight loss of up to 5 kg body weight in one year. Thus, NEAT activities increase EE only slightly, but may have important implications for long-term energy balance.

Thermic effect of food has the largest influence in dictating changes in whole-body EE excluding physical activity and NEAT. However, diet composition is the most influential moderator of TEF, more so than age, gender, or weight.[11-17] Thus, differences between individuals in TEF are mostly due to alterations in macronutrient composition of the diet (see "Meal Composition" under TEF) and have very small effects on changing whole body EE. It is therefore unlikely that alterations in TEF are responsible for changes in daily EE in most people. Rather, the amount of planned physical activity far exceeds any small increment in thermogenesis induced by drugs, cold, or diet in determining daily EE.

Conclusions

Thermogenesis, as defined in this section, is an increase in whole body EE above RMR which is not due to physical activity. Meal consumption increases EE, called TEF, which accounts for up to 10% of daily EE and therefore is the most important element in determining thermogenesis. Over-the-counter stimulants such as caffeine, ephedrine, and nicotine are also important in enhancing thermogenesis and reducing appetite, and may be beneficial in enhancing weight loss during energy restriction. Cold exposure also can induce thermogenesis to maintain body temperature. But in humans, this process is largely unimportant except under extraordinary circumstances, as behavior can be changed to alter our microenvironment to prevent prolonged cold exposure necessary to induce shivering and non-shivering thermogenesis observed in rodents. Alterations in thermogenesis are also unlikely to play a major role in the development of obesity and the growing problem of obesity around the world, since thermogenesis is a relatively minor determinant of whole-body EE.

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