Review Article
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Nonshivering thermogenesis revisited: sympathetic and non-sympathetic contributions

Abstract

Factors of diet and environment contribute to complementary, additive mechanisms that influence the magnitude of diet induced thermogenesis generated in man and animals. Both short terms sympathetically mediated and longer acting thyroidal mediated pathways have been identified and appear to function in a metabolically coordinated fashion to facilitate biochemical and physiologic pathways of energy balance implicating multiple organs and peripheral tissues during periods of over- and under-nutrition. In a congenic lean rodent model known to express parameters of environmentally and diet induced mediated thermogenesis, thyroidal and sympathetic contributions each contributed to approximately 50% of the relative increase in VO2 in quietly resting animals after consuming a high energy palatable diet as determined in the presence vs. absence of α-methylparatyrosine, a sympathoplegic chemical agent. In contrast, in the obese phenotype of the corpulent and other rodent strains, both sympathetic and thyroidal contributions to adaptive thermogenic mechanisms are impaired in response to both nutritional and environmental challenge, contributing to a greater efficiency of energy metabolism and body fat accretion. Thus, the purpose of the present review is to approximate the qualitative distribution between the two primary factors linked to the physiologic process resulting in the expression of diet induced thermogenesis in a normally lean phenotype of rat, the LA/Ntul//-*cp*.

Keywords: nonshivering thermogenesis, obesity, cafeteria feeding, congenic LA/Ntul//-*cp* rats

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Introduction

The thermogenic effects of diet and environment contribute to the modulation of the metabolic rate and of elements of energy expenditure and energy balance in man and animals.[1,2] The highly palatable Café feeding diet approach has often been applied as a reliable and reproducible method to induce overfeeding and stimulate the adaptive process of diet induced thermogenesis (DIT) in normally lean and obese strains of rodents.[3] Because thermogenesis in mammalian organisms consists of both obligatory and adaptive processes, it is important to be able to discriminate between the origins of the various thermogenic mechanisms to determine the relative contributions of each compartment. Discovery of the relative contributions can potentially be of significance in dietary planning and weigh management protocols. Both the obligatory and the adaptive thermogenic responses may be modulated at least in part via hormonal actions including noradrenaline, thyroid hormones, insulin, glucocorticoids and other factors, all of which can be partially modulated by dietary and environmental stimuli and to contribute to overall mechanisms contributing to parameters of energy balance.[2–8] Since up to 45% to 60% of the obligatory component has often been generally attributed to the maintenance of the basal metabolic rate in lean tissues and the biochemical work that is obligated to maintain that compartment of energy expenditure (EE), and is linked at least in part to actions of thyroid hormones.[8] It is important therefore to categorize the remaining components of energy expenditure. Circulating thyroid hormone-mediated actions may increase or decrease in proportion to circulating hormone concentrations and availability during periods of over- and undernutrition and during environmental challenges to variable ambient temperatures in lean animals. However, numerous studies indicate that aspects of Thyroid hormone metabolism and actions may be impaired in the obese phenotype of several rodent strains.[9,10] Thyroid hormone actions are mediated via nuclear receptors, in concert with processes of gene expression in peripheral tissues, where at least some aspect of the impaired thermogenic responses may be attributed. Overall, the three main compartments of energy expenditure may be divided into obligatory energy expenditure related to lean body mass (45-60%), muscular work or exercise mediated (~30%) and adaptive responses (~10%).[8]

An additional component of unclear proportions is dependent on the magnitude of neural actions mediated by the sympathetic nervous system, which has been associated with fast responses including those of brown adipose tissue, while thyroidal mediated actions usually engage adaptive biochemical pathways in liver and other tissues that typically can persist for longer durations.[5,6,11] The additional contributions to thermogenesis of an additive nature may also be related to biochemical processing via energy dependent biochemical pathways associated with the specific dynamic actions (SDA) or thermic effect of foods (TEF) during their digestive and metabolic sequela, and which vary based on the quantities, frequency and specific macronutrient and non-nutrient composition of the digestive.8 The purpose of the present review was to examine and quantify the sympathetic and non-sympathetic contributions to non-shivering thermogenesis as determined by pharmacotherapeutic ablation via administration of a loading dose of α-methylparatyrosine (α-MPT, 250 mg/kg BW, i.p.) of the sympathetic component in a congenic lean phenotype of the LA/Ntul//-*cp* strain of rats.[12,13] Studies were conducted following a minimum of a 21 day regimen of Café feeding in which the experimental diet-induced increases in both caloric intake and weight gain in addition to the predicted increases in nonshivering thermogenesis. The sympathetic blockade resulted in partial but not complete normalization of resting metabolic rates in Café fed rats and was without immediate effect of circulating thyroid hormone parameters in normally fed animals. While the magnitude of change on metabolic rate due to factors related to the specific thermic effect of foods (formerly called the SDA of meals) was not determined in the current studies, other studies in this strain were consistent with

only modest impact related to the SDA in chow fed animals, likely equivalent to an estimated mean of approximately 3 to 5% decrease in RMR in normally fed vs fasted animals.[14]

Administration of the β-adrenergic agent norepinephrine can activate both glucose mobilization from glycogen stores and adrenergic activation of brown adipose tissue, and an increase in both glucose-mediated and BAT mediated thermogenesis.8,15,16 Peripheral sensitivity to the membrane associated actions of insulin are an essential element in glucose uptake in skeletal muscle and in both white and brown adipose tissue, and insulin resistance has been linked to impaired BAT thermogenesis on obese-diabetic rats.[15,16,17] BAT is heavily vascularized in addition to being broadly innervated by sympathetic neurons, and exogenous administration of adrenergic agents with stereospecific β3receptor affinity is similarly effective in activating biochemical pathways of BAT thermogenesis.6 Thus, the physiologic effects of noradrenaline administration resemble in part the responses elicited during cold induced activation of glucose mobilization and BAT thermogenic activity and are independent of shivering induced components of thermogenesis occurring in the skeletal muscle of mammalian organisms in direct response to early cold acclimatation. Danforth et al.[8,17] have reported that infusion of glucose can increase energy expenditure independent of adrenergic stimulation during the quietly resting state.[8,17] In insulin resistant obese rodent models including both the Zucker fatty rat and the corpulent rat, parameters of nonshivering thermogenesis and nutritionally induced alterations in plasma thyroid hormones including T3 were impaired, consistent with insulin resistance imposing a regulatory role in the efficiency of energy expenditure when adjusted for differences in body surface area among lean and obese phenotypes of the strains.[9,10] Measures of protein turnover including both biosynthesis and degradation of tissue proteins, a combined function of thyroidal, insulinogenic and glucocorticoid actions were decreased in the obese phenotype of pre-obese corpulent rats, consistent with impaired epigenetic expression of protein turnover among the obese phenotype. At a reported 4 high energy phosphate bonds consumed per peptide bond formed in muscle tissues, this represents a significant potential contribution to the conservation of energy expenditure during expression of the obese phenotype.[4] Thus multiple physiologic and biochemical systems including both obligatory and adaptive processes likely combine to determine the net energy expenditure, with both thyroidal and sympathetic-mediated processes facilitating the net result and contributing , each in their own domain to the epigenetic expression of the obese phenotype.[4]

Administration of noradrenaline readily stimulates BAT tissues, resulting in marked increases in VO2, a measure of thermogenesis, with corresponding increases in plasma glucose mobilization from glycogen, and in cellular glucose uptake of BAT and peripheral tissues.[5–8,15–17] The above responses are impaired in the obese phenotypes of the obese rat strains at least in part secondary to insulin resistance in peripheral tissues, in addition to additional hormonal dysregularities that may contribute to the impaired thermogenic responses and further contribute to impaired glucose uptake and metabolism.[4,18] Measures of protein turnover represent the most energetically expensive processes of peripheral tissues, at 4 high energy phosphate bonds per peptide bond forms, and have also been shown to be diminished by 50% or more in the obese phenotype, thereby further contributing to the expression of the obese state.[4]

Materials and methods

To determine the relative contribution of sympathetic activity to nonshivering thermogenesis following overnutrition, pharmaceutical ablation was generated in individually housed animals, groups (n- 6 rats/group) of young adult lean LANtul//-cp rats were offered a Purina chow diet (CHOW) or the same diet plus a daily Café supplement ad libitum from 10 until 24 weeks of age as describes previously.[12,13] The sympathoplegic drug α-methylparatyrosine (α-MPT) was administered to groups (250 mg α-MPT/kg BW, i.p.) to ablate sympathetic (SNS) activity or a sham injection of 0.154 M NaCl given, and measures of plasma T3, urinary vanilmandelic acid (VMA) and of fasting resting thermogenesis (VO2) were obtained at thermal neutrality (30°C) before and after the α-MPT or sham administration. Data were analyzed via ANOVA and Student-Neuman-Keuls subset identification. The measures of VO2 were determined via indirect calorimetry as described previously by Tulp et al, and expressed as ml oxygen / kg BW -0.75 to correct for differences in body size as outlined by Klieber and others.[3,7,19,20] Measures of urinary vanilmandelic acid, a terminal metabolite of norepinephrine, as an indicator of daily sympathetic activity were determined in 24 hour urine collections as described previously.[12,13] Measures of T3 were determined by radioimmunoassay as described previously.4 This study was approved by the Institutional Bioethics, Animal Care and Use Committee (Protocol 2015/11).

Results

The Café diet resulted in a 67% increase in body weight (BW) and a ~25% increase in VO2 following café overfeeding, while only a 40% increase in BW and no additional increase in VO2 occurred in CHOW fed or sham treated rats. The growth and VO2 responses of the sham group were similar to those of the ad libitum controls as predicted. Sympathetic ablation with α-MPT was associated with modest decreases in body temperature and < 15% decrease in VO2 in the café treated group, but when the RMR data were corrected to isothermal conditions the net decrease in CHOW fed rats averaged only 3% and was without additional effect in the sham group. Serum T3 concentrations increased by >90 % and excretion of urinary catecholamine metabolites as vanilmandelic acid (VMA) >250% following the café diet (p=<0.05), but measures of the VMA excretion were virtually nil following the sympathetic α-MPT-induced ablation (Table 1).

Table 1 Mean changes in thermogenic parameters in café fed rats

Group	n	Weight Gain, g	Vo2	T3	VMA	α-MPT +	Core temp
Control	5	90	8.5	50	140	37.9	-
+α-MPT			7.5	51	nil	36.5	-1.39%
Café	5	139		12.5	95	385	38.1
+α-MPT			9	-	nil	37.5	-0.52%
Sham	5	92		8.1	51	143	37.5
+α-MPT			8,2	-	nil	37.6	+0.13

Data are mean changes, n=5 rats/treatment group. α-MPT administered at 150 mg/kg BW, i.p. 24 hours before α-MPT measurements obtained. Measures of VO2 obtained at thermal neutrality (30°C) and expressed as ml O2/kg BW -0.75.

Initial body weights were C=222± 9 g, Café = 221±10 and Sham +228±11 grams BW respectively in the three groups;

(-) = not determined. VMA expressed as µg urinary vanilmandelic acid released / 24 hours; T3 expressed a ng/dl.

Summary and discussion

In studies of nuclear T3 receptor occupancy and of peripheral half-life kinetics of T4 and T4, the authors observed that the peripheral half

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life of T4 was significantly prolonged, while the half life of T3 was similar in both lean and obese animals.[21] In addition, Young observed that while T3 receptor density was similar in both lean and obese phenotypes, T3 receptor affinity was decreased in the obese phenotype in young adult corpulent rats.[22] In addition, measures of T4-5'-deiodinase and T3 neogenesis were decreased in the obese phenotype, thereby implications for both endogenous tissues and nuclear factions to contribute to overall mechanisms of energy balance.[21–24] Both caffeine and the adrenergic activator ephedrine resulted in increases in nonshivering thermogenesis in man and animals, although likely via different biochemical mechanisms.[25] Ephedrine acts as an adrenergic agent, while caffeine and its primary metabolite, paraxanthine are selective inhibitors of cAMP phosphodiesterases, a broad class of cytoplasmic isoenzymes, thereby extending the actions of cAMP and cGMP on energy linked cellular activities including both calcium and potassium translocation in smooth muscle, where they can promote muscle relaxation.[25–27] Thus, the effects of caffeine on BAT thermogenesis although prominent, act in an indirect manner and with a half-life that persists somewhat longer than the direct actions of adrenergic agonists.[26]

It has been widely reported that a major proportion of the process of nonshivering thermogenesis in rodents occurs via rapid activation of brown adipose tissue which functions under neural-generated stereospecific β3-adrenergic sympathetic control.[5,6,24,28] BAT contains abundant β3 adrenergic receptors, virtually unique to brown adipose tissue. Following adrenergic stimulation, the thermogenic process is biochemically mediated by actions of uncoupling protein-1 (UCP1), which is also unique to the BAT tissue, and results in rapid heat generation via a phosphorylytic uncoupling reaction of high energy phosphate bonds which liberate releasable heat that is subject to peripheral dissipation rather than storage as chemical energy.11 The heat generated can then effectively be dissipated as body heat loss rather than storage as lipid or other forms of energy metabolism, and results in measurable increases in both resting and norepinephrine stimulated thermogenesis. Brown adipose tissue contains abundant specialized mitochondria distributed through the cytoplasmic compartment of the brown adipocyte, surrounded by numerous small locules of lipid as a readily available energy source. The numerous small lipid locules provide a relatively greater surface area than that which occurs in white adipocytes due to their single large lipid droplet. This fundamental difference in lipid droplet size thereby enables BAT cells to facilitate a more efficient and rapid lipid mobilization, and thereby provide quick source of metabolizable energy for the surrounding mitochondria.[29] While adipocytes from both white and brown adipocytes utilize glucose for immediate intracellular needs, in white fat cells the primary functions leads to lipogenesis and energy storage, while in brown adipocytes the primary functions are to coordinate energy expenditure via generation of heat energy in the highly vascularized tissue.

In addition to most peripheral tissues, brown adipose tissue is also an active site of T4-5'deiodinase activity, resulting in generation of T3 for both endogenous and peripheral thyroidal activities.[24] The BAT deiodinase activity is responsive to both nutritional and environmental stimuli, thereby assisting in maintaining peripheral hormonal levels and central feed-back regulation for thyroid hormones. Therefore, while the circulating thyroid hormone concentrations can provide a useful assessment of hypothalamic and thyroidal parameters, they are unable to determine the efficiency and magnitude of cellular actions, where the various parameters of day-to-day energy balance are based. When circulating levels of T3 including free T3 remain elevated, tissue energy requirements become increased via nuclear-induced increases in cellular metabolism and somewhat interdependent of the relative activity of brown adipose tissues. The increases in circulating T3 are linked to BAT and other peripheral tissues primarily by an enhancement of adrenergic receptor affinity, which may result in an exaggerated metabolic response when present. Moreover, administration of a 10X dose of exogenous T3 but not T4 to the obese phenotype of the corpulent rat strain resulted in weight loss toward normalization, and which weight was regained rapidly when the animals were switched to a 10X dose of exogenous T4 instead of T3.[21,23] Thus, the process of diet and environmentally induced thermogenesis necessarily implicates both thyroidal and sympathetic actions, in addition to insulinogenic actions on glucose uptake in peripheral tissues, which in concert bring about the nutritionally and environmentally induced adaptations constituting the phenomena of adaptive, diet-induced thermogenesis in man and animals.[30]

Conclusion

In conclusion, these observations indicate that the SNS-mediated contribution component to DIT under conditions of thermal neutrality following prolonged Café overfeeding contribute approximately 50% of the diet induced thermic response, and the remaining adaptive proportion linked to non-SNS-mediated processes including thyroidal and SDA/TEF-related activities. In contrast under normal long-term CHOW feeding the SNS component may be as little as 3 % of the thermic response under conditions of thermal neutrality. Thus, the total thermic response of DIT in normally lean animals likely represents a combination of short acting SNS and longer acting epigenetically mediated non-SNS mechanisms, including a likely significant element of thyroidally mediated contributions originating at the nuclear receptor level of expression. In contrast, and not reported in the present communication, in the obese phenotype where the epigenetic expression of obesity likely implicates thyroid hormone mediated actions including nuclear T3 receptor occupancy and affinity events, the resting, environmental and adrenergic stimulated elements of resting metabolism become decreased under ordinary circumstances od diet and environment. The nuclear mediated thyroidal events combine to result in a greater efficiency of hormonally mediated energy metabolism and storage, and an in expression and development of the obese stigmata soon after weaning.

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Conflicts of interest

The author declares that there is no conflict of interest.

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