Diet-induced thermogenesis: fake friend or foe?

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Abstract
Diet-induced thermogenesis (DIT) is energy dissipated as heat after a meal, contributing 5–15% to total daily energy expenditure (EE). There has been a long interest in the intriguing possibility that a defect in DIT predisposes to obesity. However, the evidence is conflicting; DIT is usually quantified by indirect calorimetry, which does not measure heat. Using gas exchange, indirect calorimetry measures total post-prandial EE, which comprises heat energy produced from brown adipose tissue (BAT) and energy required for processing and storing nutrients. We questioned whether DIT is reliably quantified by indirect calorimetry by employing infrared thermography to independently assess thermogenesis. Thermogenic activity of BAT was stimulated by cold and by a meal that induced a parallel increase in energy production. These stimulatory effects on BAT thermogenesis were inhibited by glucocorticoids. However, glucocorticoids enhanced postprandial EE in the face of reduced BAT thermogenesis and stimulated lipid synthesis. The increase in EE correlated significantly with the increase in lipogenesis. As energy cannot be destroyed (first law of thermodynamics), the energy that would have been dissipated as heat after a meal is channeled into storage. Post-prandial EE is the sum of heat energy that is lost (true DIT) and chemical energy that is stored. Indirect calorimetry does not reliably quantify DIT. When estimated by indirect calorimetry, assumed DIT can be a friend or foe of energy balance. That gas exchange-derived DIT reflects solely energy dissipation as heat is a false assumption likely to explain the conflicting results on the role of DIT in obesity.

Energy expenditure
Food intake stimulates energy expenditure, a phenomenon commonly referred to as diet-induced thermogenesis (DIT) (Fig. 1). It is also termed the thermic effect of food or the specific dynamic action of food. Depending on the nutrient load and composition, the energy expenditure increases by about 10–15%, peaking between 1 and 2h before returning gradually to baseline after 8h.

DIT is one of three major components of daily energy expenditure (EE), the other two being REE and physical activity. On average, REE accounts for 60–70%, physical activity for 10–20% and DIT for 5–15% of total daily EE. Despite having the lowest contribution to daily EE, there has been a long interest in its metabolic significance and the intriguing possibility that a defect in DIT predisposes to obesity.

This paper presents a review of what DIT is by taking the reader through concepts and methods for quantifying energy and energy forms pertinent to human metabolism, which are critical to the understanding of its physiological significance in energy homeostasis.
Methods for measuring energy production

The measurement of heat energy plays a pivotal role in the study of energy homeostasis. The generation of heat is a sine qua non of the energy metabolism of substrates and proportional to energy expenditure and, therefore, metabolic rate (Kenny et al. 2017).

The chemical energy of a nutrient liberated by oxidation is in part lost as heat and in part transferred to a variety of high-energy compounds, such as ATP (Silva 2006). Approximately 60, 67 and 68% of the energy value of protein, glucose and fat respectively are converted to ATP during oxidative metabolism; the rest is lost as heat (Ferrannini 1988).

Heat energy is also produced in UCP-containing tissues such as brown adipose tissue (BAT) the function of which is to protect against hypothermia (Cannon & Nedergaard 2004, Thuzar & Ho 2016). Thus, the amount of body heat is produced from chemical energy required to support tissue function and from specialized heat-generating UCP-rich tissues. The consumption of oxygen links metabolism and heat production, underpinning the use of direct and indirect calorimetry as major complementary methods for measuring energy production.

Direct calorimetry

Direct calorimetry estimates energy expenditure by measuring heat dissipation from the body (Kenny et al. 2017). Because the amount lost equals the amount that is produced at steady state, direct calorimetry is a measurement of heat production (Ferrannini 1988, Kenny et al. 2017). Its usefulness is dependent on purpose, circumstance and context. In the resting state, almost all the energy produced is in the form of heat. However, it underestimates the amount of energy required to perform physical work such as exercise (Webb 1988 #3651). Although muscular contractions of exercise increases heat production, the energy required for physical work itself is derived from chemical energy (through the use of ATP), which is not measured by direct calorimetry. Thus, metabolic heat production represents the amount of energy dissipated as heat, which is not

Energy

Energy is the capacity for doing work. It exists in many forms such as light, heat, sound, gravitational, electrical, chemical and nuclear energy. The most pertinent forms of energy in the living body are heat and chemical. Heat is the energy form for maintaining a constant body temperature in mammalian life. This is tightly regulated, and hormones play a critical role in the regulation of thermogenesis (Hampf et al. 2006, Silva 2006, 2011).

Chemical energy exists as ATP or as high-energy bonds in storage form of glycogen and lipids. ATP drives cellular function and work performance. According to the law of conservation of energy, energy can be converted from one form to another but cannot be destroyed. In the living organism, the chemical energy of food is converted to heat and to various energy-rich intermediaries through complex biochemical processes referred to as energy metabolism. Once produced, heat is lost to the environment and cannot be harnessed for mechanical work.

History

The French physiologist Antoine Lavoisier (1743–1794) is credited with seminal work linking respiratory chemistry to physical work and nutrition (Karamanou et al. 2013). Using an ice calorimeter, he demonstrated that combustion and respiration are the same thing. He observed that heat produced during respiration occurred with the consumption of oxygen and production of carbon dioxide. Oxygen consumption, pulse rate and respiratory rate increased during work. He observed that the consumption of air (oxygen) at rest in a fasted state increased in a cold environment and after a meal. These vital experiments connecting external respiration and internal combustion provided the fundamentals to the science of respirometry.
directed to performing external work (Kenny et al. 2017). To be effective, a calorimeter must be a closed system to ensure that all of the heat produced from metabolism is measured, and no transfer of energy occurs between the calorimeter and its surroundings (Webb et al. 1988). Direct calorimetry is not widely used because the specifications require a highly sophisticated system which is costly and technically challenging.

**Indirect calorimetry**

Indirect calorimetry measures energy production from gas exchange. It is the most widely used method for quantifying rates of energy production estimated from the amount of oxygen consumed. The amount of carbon dioxide produced gives an indication of the type of substrate utilized from which energy production is calculated using the caloric equivalents of macronutrients. The basic principles are well established as are assumptions underlying the stoichiometry of macronutrients. These assumptions and equations will not be covered in this review but are very well reviewed elsewhere (Frayn 1983, Ferrannini 1988, Swyer 1991).

The post-prandial metabolic rate measured by indirect calorimetry is almost universally referred to as energy expenditure. A component of this is chemical energy channeled into nutrient stores that occurs after a meal. For clarity and consistency, the energy measured by indirect calorimetry will be referred to as energy expenditure from this point of the review.

Indirect calorimetry does not measure heat. As heat energy is a component of total energy, its contribution to total energy expenditure varies with the situation under study, for example, between rest and exercise. In careful studies comparing energy measurements by indirect and direct calorimetry, Webb et al. (1988) reported that heat energy accounted entirely for the oxidative metabolic energy produced at rest. During walking, the energy required to perform external work was not entirely captured by direct calorimetry. Even though heat production increased during and in proportion to the level of physical work, the energy expenditure measured by metabolic gas exchange was greater than that of heat dissipated from exercise (Webb et al. 1988). Thus, respirometry captures the total energy quantum of exercise representing the sum of mechanical and heat energy that are derived from chemical energy.

**Comparison of indirect and direct calorimetry**

Indirect and direct calorimetry measures different aspects of energy expenditure from different outcome measures. They do not measure the same energy or form of energy. Indirect calorimetry measures energy expenditure based on oxygen consumption and carbon dioxide production. This energy may be heat, mechanical and chemical energy but this method is unable to distinguish between the components and their magnitude. The magnitude of the components varies between fast and fed states or between rest and exercise. Direct calorimetry estimates energy expenditure by measuring heat dissipation from the body. The extent to which heat production accurately reflects total energy production is also influenced by the conditions of study.

Several studies both in humans and rodents have compared energy measurements between direct and indirect calorimetry (Kaiyala & Schwartz 2011, Kenny et al. 2017). It is unsurprising that discrepancies occur because the methods measure different things under different experimental condition using methodologies that differ in accuracy and precision (Kaiyala & Schwartz 2011). Thus, claims that one method is superior to the other cannot be substantiated and should be greeted with skepticism (Speakman 2014). As discussed earlier, when used and compared under well-defined conditions, such as rest and exercise (Webb et al. 1988), the results obtained from both techniques may not be identical but are coherent.

**DIT and obesity**

The possibility that differences in the thermogenic response to food are a causative factor for obesity was first proposed over 100 years ago (Wang & Strouse 1924). This attractive hypothesis has stimulated enduring interest that has produced continuing controversy. de Jonge and Bray (1997) reported in their review that 29 of 49 studies found the ‘thermic effects of food’ (DIT) to be lower in obese than in lean subjects. They concluded that factors such as variability in study design, meal size and age may have obscured DIT as a discriminant. A 2016 review addressing whether obesity is associated with altered energy expenditure concluded that ‘there is insufficient evidence to support the theory of an altered DIT in obese individuals’ (Carneiro et al. 2016). A thoughtful commentary on a pathogenic role of thermogenesis in obesity highlighted other issues that could contribute...
to the controversy (Kaiyala & Schwartz 2011). These included whether appropriate corrections had been made for differences in lean and even fat mass within the study groups (Kaiyala & Schwartz 2011). Among other factors considered was the role of the gut microbiome in obesity (Turnbaugh et al. 2009) and being mainly anaerobic, their contribution to whole body energy expenditure (Turnbaugh et al. 2006) is not measured by indirect calorimetry (Kaiyala & Schwartz 2011).

This review redresses the controversy differently by questioning the conceptual and methodological validity of DIT: whether the energy expended after a meal and estimated by indirect calorimetry is wholly heat energy lost to the environment. This review looks critically at the methodology and assumptions underlying the principles and practice of indirect calorimetry, the law of thermodynamics and recent work placing a different interpretation of previous data.

What is DIT?

Food evokes an acute and transient increase in energy expenditure commonly termed DIT (Jequier 1985, Tataranni et al. 1995).

Components of DIT

The food-induced increase in energy expenditure is made up of two components: an obligatory component required for the digestion, transport and storage of nutrients and a facultative component of heat production (Acheson et al. 1984, Jequier & Schutz 1988) (Fig. 1). The proportion of energy required for digestion and transport is negligible compared to that required for nutrient storage (Vernet et al. 1986, Flatt 1995). Five percent of the energy from a glucose load is required for storage as glycogen and 24% for storage as triglycerides indicating the substantial energy cost of nutrient storage (Ferrannini 1988). Thus, the food-evoked increase in energy expenditure is principally the sum of heat and storage energy, that is, heat loss only account for a portion of the energy produced in the immediate hours following a meal.

Terminology

The food induced-stimulation of energy expenditure is almost universally measured by indirect calorimetry. As discussed earlier, indirect calorimetry does not measure heat production (thermogenesis) but rather energy expenditure based on gas exchange. All studies reviewed above (de Jonge & Bray 1997, Carneiro et al. 2016) are based on indirect calorimetry. The authors have assumed that what was measured is solely heat energy, when in fact heat constitutes only a portion of the energy evoked by food. Thus, assumed DIT derived from gas exchange is an inaccurate estimate of heat energy dissipated after a meal.

To avoid ambiguity, the following terminology is used from this point of the review: post-prandial energy expenditure and not DIT to define the rise in energy after a meal; thermogenesis to denote the generation of heat.

In order to determine the thermogenic component to post-prandial energy expenditure, an independent method for assessing heat energy is required such as direct calorimetry. Unfortunately, this time-honored method for measuring heat energy is very rarely used in human metabolic studies because of expense and technical requirements. Infrared thermography is a valuable and reliable method for mapping thermal contours of organs in animals and humans. Several laboratories have investigated and validated its use for detecting the functional activity of BAT against PET/CT isotopic imaging (Symonds et al. 2012, Jang et al. 2014). We have employed infrared thermometry (IRT) and indirect calorimetry to investigate the extent to which thermogenesis contributes to whole body energy production using glucocorticoids as a model of perturbed energy metabolism.

Glucocorticoids and post-prandial energy expenditure

Obesity is a common adverse effect of glucocorticoid treatment, the causes of which are not completely understood. Glucocorticoids promote differentiation of preadipocytes into mature white adipocytes (Cristancho & Lazar 2011) and stimulate appetite (Christ-Crain et al. 2008). In animals, glucocorticoids impair BAT function (Moriscot et al. 1993); however, there is a paucity of information on their effect on humans. Based on in vitro evidence that glucocorticoids inhibit the response of cultured human brown adipocytes to adrenergic stimulation (Barclay et al. 2015), we postulated that they inhibit BAT function and reduce the thermogenic contribution to and attenuate energy expenditure following a meal.

We investigated the effects of a 15 mg daily dose of prednisolone for a week on BAT function in response to cooling and to a standardized meal in a double-blind
placebo cross-over design (Thuzar et al. 2017). BAT function was assessed by fluoro deoxyglucose (FDG) update with PET/CT and by measuring the skin temperature overlying supraclavicular BAT depots using infrared thermography. Prednisolone significantly reduced FDG uptake into BAT. Over a 2-hour period of cooling, supraclavicular temperatures fell to a greater degree during prednisolone treatment (Fig. 2A). Thus, prednisolone significantly reduced the metabolic and thermogenic activity of BAT in response to cooling.

During the meal study, food evoked a significant increase in energy expenditure as expected. This increase in post-prandial energy expenditure was enhanced by prednisolone (Fig. 3A). The stimulation of energy expenditure could be interpreted as a beneficial effect on energy balance. However, this is not consistent with the obesogenic effects of glucocorticoids. Moreover, the apparent enhancement of post-prandial energy expenditure is in a direction opposite to that expected from a concurrent inhibition of BAT activity. Indeed, IRT confirmed that the post-prandial stimulation of BAT thermogenesis was all but abrogated by prednisolone (Fig. 2B). In summary, prednisolone suppressed the metabolic activity of BAT, reduced cold-induced thermogenesis and enhanced post-prandial energy expenditure despite reducing thermogenesis.

Prednisone had not only diminished the thermogenic contribution to total energy production but also increased the absolute magnitude of post-prandial energy expenditure (Fig. 3A), increasing the non-thermogenic component. Can the latter represent the energy cost of storage? Indeed, lipogenesis was stimulated during prednisolone treatment (Fig. 3B) with the rate of lipid synthesis significantly correlated to energy expenditure after the meal (Thuzar et al. 2017). In short, the enhancement of the non-thermogenic component of energy production by prednisolone is explained by the energy cost of the synthesis of lipid. These findings are in accordance with the first law of thermodynamics that energy cannot be destroyed but can be transformed from one form to another. The energy that would otherwise have been dissipated irreversibly as heat is channeled into storage energy as lipid. In the setting of glucocorticoids, the internal energy fluxes following a meal are misrepresented by the term DIT.

**Implications**

These findings have important messages for the field of nutrition and energy metabolism.

1. The term DIT is conceptually misleading. In the context of indirect calorimetry, it wrongly connotes that the measured energy produced after a meal is entirely thermogenic.
2. Post-prandial energy expenditure represents the sum of heat energy which is lost and chemical energy which is stored after a meal.

3. The magnitude of post-prandial thermogenesis (true DIT), traditionally believed to be as much as 10–15% of total daily energy expenditure, is an overestimation that warrants re-evaluation that warrants re-evaluation by techniques independent of gas exchange.

Conclusion

The widely held assumption that DIT is accurately measured by indirect calorimetry has brought confusion and misconception to the field. The science of nutrition in relation to the thermogenic effects of macronutrients requires a thorough re-evaluation. Is the thermogenic hierarchy of protein, carbohydrate and lipid correct? The incorrect assumption that post-prandial energy expenditure is entirely thermogenic is a likely explanation for the controversy on a pathogenic role of ‘DIT’ in obesity. When measured by gas exchange, the term DIT should be abandoned and consideration be given to the following as alternatives: diet-induced energy production or diet-induced energenesis. The time has come for a renaissance of direct calorimetry to provide an accurate measure of thermogenesis (Kenny et al. 2017). Assumed DIT derived from gas exchange lurks as a fake friend and foe of energy balance. Heat and energy are not synonymous. Indirect and direct calorimetry are required to unpick their contributions to energy homeostasis.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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