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Editorial Comment

Energy balance, cancer and the sympathetic nervous system

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The body derives its energy from the oxidation of foodstuffs: carbohydrate, fat and protein. Heat is released and external work performed. Energy expenditure can be measured by indirect calorimetry (oxygen consumption, CO_2 production); combined with measurements of urinary nitrogen excretion the technique allows net substrate oxidation to be calculated. It does not, however, give any indication of abnormalities in intermediary metabolism. Indirect calorimetry measurements can also be affected by factors other than substrate oxidation, such as disturbances in respiratory patterns, by abnormalities of acid base balance and by body temperature. Substrate metabolism is determined by existing substrate stores, by recent food intake, by body composition [1] and by 'stress' such as trauma, sepsis or exercise [2,3].

The so-called 'basal' or resting metabolic rate (i.e. metabolic rate measured at rest in a thermoneutral environment in the postabsorptive state — usually after an overnight fast) normally accounts for 60–75% of total energy expenditure. Basal expenditure represents the energy cost of the basic life functions such as the work of breathing and the beating heart; most of the energy is expended in the maintenance of cell membrane potentials. Energy is otherwise expended in muscle contraction and in the digestion and assimilation of food, so-called dietary induced thermogenesis (DIT).

In the neonate and (in the rat) another mechanism of heat production is nonshivering thermogenesis [4]. This functions as a means of thermoregulation. Its anatomical basis is in brown adipose tissue (BAT) found in the perirenal fat and in the great vessels around the heart. Brown adipose tissue contains large numbers of 'uncoupled' mitochondria which, instead of harnessing the energy produced by the oxidation of energy substrates such as adenosine triphosphate, release it as heat [5]. The process is under the control of the sympathetic nervous system and in man is considered not to function beyond the age of 6 months, although the subject has been controversial [6]. In the rat the sympathetic activity involved in the control of BAT is pivotal in the control of energy balance (body weight). It is mediated by an atypical beta (beta 3) receptor. This beta 3 receptor stimulates thermogenesis (energy expenditure) and thus, controls energy balance in the face of wide variations in food intake, so-called 'facultative' thermogenesis. Such a mechanism is thought not to occur in man, although one study has shown a weight loss in obese subjects treated with a beta 3 agonist [7]. Another one, however, failed to do so [8].

Dietary induced thermogenesis in man has traditionally been considered the energy cost of digestion and assimilation of food. Following a protein meal, and with intravenous (i.v.) amino acids, the site of the increased metabolism is the liver. The probable cause is increased rates of gluconeogenesis and ureagenesis [9]. However, following carbohydrate ingestion the increase in metabolic rate does not appear to be in the splanchnic region at all [10]. Glucose induced thermogenesis is sympathetically driven, at least in part, probably via the action of insulin on the hypothalamus [11]. Intravenous infusion of glucose and insulin increases sympathetic activity and a proportion of the rise in energy expenditure can be blocked with a beta blocker; the effect appears to be largely beta-1 [12,13]. Glucose ingestion alone stimulates adrenaline secretion and adrenaline infusion increases metabolic rate [14]. Arterial levels of adrenaline found after glucose ingestion are higher than those known to stimulate metabolism [14]. The thermogenesis observed with adrenaline infusion is mediated via beta-1 and beta 2 receptors in approximately equal proportions. The site of heat production appears to be skeletal muscle although adipose tissue may also have a role [15,16].

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Part of the normal metabolic rate appears to be sustained by sympathoadrenal activity, possibly secondary to the ongoing effect of the dietary intake on sympathoadrenal mechanisms; starvation is associated with a decline in sympathetic nervous activity [17]. Welle and colleagues [18] showed that 6 to 10 days of nadolol, a non-selective beta blocker reduced resting metabolic rate by 7%. The effect of beta blockers on DIT has been variable. Propranolol does not inhibit the thermic effect of a pure carbohydrate meal given orally [19,20] but it does inhibit the thermic effect of mixed (protein containing) meals, even those rich in carbohydrate [21,22].

So what of energy expenditure (and weight loss) in cancer? An elevation in resting expenditure occurs in some cancers but not all. It has been described in lung [23], gastric [24], pancreatic [25], sarcoma [26], hepatocellular cancer [27] and acute lymphatic leukaemia [28], but only in a proportion of these patients. It is found, for example, in only 50% of patients with non-small cell lung cancer (NSCLC) [29]. Metabolic rate in weight losing patients with cancer of the colon [30] and oesophagus [31], and in metastatic breast cancer and metastatic melanoma, where weight loss is not a feature, is normal. In some instances hypermetabolism [32] can be explained by loss of peripheral tissue and a relative preservation of the metabolically more active visceral tissue, but again not in all [33]. The metabolic abnormalities often associated with malignancy include increased Cori cycle activity (lactate recycling) [34], an acute phase protein (inflammatory) response [35] and elevated rates of gluconeogenesis [36] and whole body protein turnover [37]. Removal of the tumour in some instances has resulted in normalisation of a previously elevated energy expenditure [38,39] as has a response to chemotherapy [28,40].

Appetite is often depressed particularly in patients with an acute phase response [41], so there is often uncertainty as to the relative contributions that a raised expenditure and a depressed intake have to weight loss. A depressed dietary intake, for example, is thought to be a major factor in the weight loss reported in normometabolic gastric and colon cancer [42] and hypermetabolic pancreatic cancer. Research efforts have concentrated on the measurement of the resting energy expenditure (REE) as it accounts for 60–75% of the total energy expenditure. However, weight maintenance in the presence of hypermetabolism may also be achieved by compensatory decreases in physical activity [33], akin to the situation in patients with acquired immunodeficiency syndrome [43]. Measurement of total energy expenditure (TEE) in cancer has only received limited study but low levels of physical activity were recently reported in patients with small cell lung carcinoma (SCLC) [44].

Dietary induced thermogenesis in patients with cancer and an elevated metabolic rate is normal [45,46] although one study reported an increase in glucose induced thermogenesis in patients with newly-diagnosed SCLC [47]. In children with malignant disease there is some indirect evidence for activation of brown adipose tissue [48], whilst in adults an autopsy study showed an increase in BAT stores in cachectic patients compared with age-matched controls [49].

The metabolic abnormalities in cancer are not dissimilar to those seen in sepsis and trauma where the hypermetabolism and weight loss is associated with the acute phase response — elevated rates of protein turnover gluconeogenesis, and triglyceride/free fatty acid cycling [50]. The site of the increased heat production is in the splanchnic circulation; the increased heat production from muscle is negligible [51]. Beta blockers have been used to reduce hypermetabolism in burn injury [52].

Lundholm and colleagues have for many years argued that the elevation in energy expenditure in cancer patients is due to an increase in sympathetic nervous activity (partly secondary to anxiety and stress) [53] and in particular, its effect on the heart [54]. They argue that the patients compensate for the anaemia and weight loss with an increased sympathetic drive and that these patients also demonstrate an increased sensitivity to adrenergic agents. Uncomplicated malnutrition is associated with decreased noradrenaline turnover [17] so this could represent a type of 'denervation' sensitivity.

The complexity of the neuroendocrine and the immune systems make it difficult to distinguish precisely the relative roles of the adrenergic and inflammatory pathways on the hypermetabolism in cancer. Interleukins (IL-6 and TNF) stimulate the neuroendocrine system and increase catecholamine production [55]. In turn, catecholamines have been shown to stimulate production of the acute phase proteins by the liver. This is mediated by a beta receptor as catecholamine stimulation of the acute phase response is inhibited by propranolol [56]. Anaemia may be secondary to an inflammatory response but it may stimulate hypermetabolism via an adaptive increase in adrenergic activity [57].

Pharmacological attenuation of the acute phase protein response (APPR) has produced quite significant metabolic effects; in patients with irresectable pancreatic cancer treatment with the cyclo-oxygenase inhibitor ibuprofen (1.2 g for 7 days) resulted in a fall in resting energy expenditure of 5.5% and a fall in C-reactive protein (CRP) [58]. Recently, Wigmore and colleagues [59] suppressed the inflammatory response in patients with pancreatic cancer using n-3 fatty acids and slowed the rate of weight loss. Food intake went up, CRP concentrations dropped but there was no change in energy expenditure.

In this issue, Lundholm's group (pp. 330–334) have examined the effect of beta blockade on energy

expenditure in a variety of cancers [60]. Their patients all had lost weight (10% on average). Energy expenditure is reported, but not in relation to any predicted standard or to any control group, so it is uncertain as to whether or not they are 'hypermetabolic'. Metabolic rate however was depressed by beta blockade; 6.1% by atenolol (a specific $beta_1$ blocker) and by 4.1% with propranolol (a non-specific $beta_1$ $beta_2$ blocker). This difference between the two drugs was significant. It is also the opposite to what has been observed in normal individuals where the decrease in resting metabolism with a non-specific blocker is usually twice that seen in the normal individual with a specific $beta_1$ or $beta_2$ blocker [15]. Most of their patients appear to have had an ongoing acute phase response as judged by an elevated erythrocyte sedimentation rate, although no data are obviously available for protein turnover nor do they report any figures for nitrogen excretion. It is not possible either to rule out the possibility that the beta blockade might have had an effect on splanchnic metabolism. Kahl [56] showed that an acute phase protein response could be inhibited with propranolol. The decline in metabolic rate they report is comparable to that described with ibuprofen and is similar to that seen with beta blockade in normal individuals. The significance is uncertain. The values reported (48 ± 13 and 77 ± 14 kcal/day) correspond to the accretion of 0.5–1.0 kg fat tissue or 2–3 kg of muscle tissue over 4–6 months.

Beta blockade could be a useful therapeutic agent in cancer cachexia; in theory it inhibits the metabolic effects of the increased catecholamine activity. It decreases REE as well as attenuating production of the acute phase proteins in the liver, and triglyceride and free fatty acid cycling. Hypermetabolism, however, is only part of the cancer cachexia syndrome and we should consider what other effects these agents may have on cancer patients. They are likely to excarcebate the fatigue which is common [61] and they are unlikely to achieve comparable improvements in energy balance to those seen with anti-inflammatory medication which increase both dietary intake and attenuate REE. Lundholm's group have themselves shown that such a therapy can be associated with prolonged survival [62]. Despite reducing REE in burn trauma [52] they have not achieved widespread use because of their undesirable cardiovascular effects. Whether they can produce the same improvement in survival that this group showed with indomethacin remains to be seen.

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