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β-Adrenoceptor activity and resting energy metabolism in weight losing cancer patients

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Abstract

This study was aimed at comparing the blocking of β-adrenoceptor activity to changes in the resting energy metabolism of 10 cancer patients with progressive weight loss due to solid malignant tumours. Resting energy expenditure (REE) as well as whole body carbohydrate and fat oxidation were investigated and related to plasma substrate levels (glucose, glycerol, free fatty acids (FFA)) before and after 5 days of oral administration of specific β1 receptor blocker (atenolol, 50 mg/day) and non-specific β1,β2-adrenoceptor (propranolol, 80 mg/day) blockade. The administration order of the drugs was random, and a 3-day washout period was used in all individuals between the provision of the first and the second drug in order to minimise the risk of carry-over effects. Resting measurements in the morning after an overnight fast were performed by indirect calorimetry. Atenolol treatment reduced REE by 77 ± 14 kcal/day and propranolol by 48 ± 13 kcal/day, respectively ($P < 0.05$ versus pretreatment values). Whole body oxygen uptake and carbon dioxide production were decreased similarly by both atenolol and propranolol treatment ($P < 0.05$). Carbohydrate oxidation was increased by atenolol and decreased by propranolol, whilst fat oxidation was decreased by atenolol and unchanged by propranolol. The decrease in REE, accounting for the decline in heart rate, was significantly more pronounced following treatment with propranolol compared with atenolol ($P < 0.05$). Atenolol and propranolol had no effect on blood glucose, plasma glycerol and FFA. We conclude that wastage in cancer patients is in part explained by increased β_1 and β_2-adrenoceptor activity, in part secondary to elevated cardiovascular activity as a result of anaemia, loss of cardiac contractile capacity and altered host metabolism.

Keywords: Cachexia; Indirect calorimetry; β-adrenoceptor

1. Introduction

Elevated resting energy expenditure (REE) contributes to weight loss in patients with solid cancer [1,2]. This phenomenon may in part be directly related to tumour metabolism since elevated energy expenditure declined following curative tumour resection [3,4], although host metabolism is also involved [5,6]. Our previous work has indicated that elevated resting metabolism in cancer patients is in part explained by increased adrenergic activity and adrenergic sensitivity in tumour-bearing animals and cancer patients [7–9]. These alterations may be a composite of classical hormone stress adaptation during partial starvation due to anorexia as well as systemic inflammation [10,11]. Observations by us in both experimental and clinical studies thus point to the possibility that alterations in energy expenditure in cancer disease are related to the cardiovascular system [11], partly explained by anaemia and decreased stroke volume [9], which was compensated for by elevated chronotrophic effects [12]. Such alterations may reflect an inevitable adaptation to undernutrition and systemic inflammation to prolong the survival of a living organism. These adaptive changes may thus promote energy wasting and thereby create a vicious circle for energy homeostasis in cancer disease. If so, it would be possible in principle to improve long-term outcome in cancer patients by appropriate β-adrenoceptor blockade of activated metabolism related to increased cardiovascular workload and peripheral tissue lipolysis [13]. We have previously reported that non-specific β-blockade lowers resting metabolism in cancer patients, which was not

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evident from anti-inflammatory treatment [13]. Therefore, the aim of this study was to elucidate the relationship between β_1- and β_2-adrenoceptor specificity and attenuation of resting energy metabolism in cancer patients with progressive weight loss.

2. Patients and methods

All cancer patients were previously treated at the Department of Surgery Sahlgrenska Hospital. They were included in the study after informed consent. All patients had solid tumours in different stages with progressive tumour growth. They had experienced a mean weight loss during the last 3 months corresponding to $10 \pm 2\%$ (mean ± SEM). None of the patients were hospitalised or bedridden. Inclusion criteria were ongoing weight loss due to solid gastrointestinal tumour disease and cooperability. Exclusion criteria were cardiac insufficiency, atrio-ventricular block, low blood pressure with clinical symptoms, bradycardia (<60 beats/min), obstructive pulmonary disease, liver disease or pathological liver function tests, impaired kidney function with serum creatinine >150 μmol/l, body temperature >37.6°C, ongoing treatment with β-blockers, steroids or other anti-inflammatory agents.

10 cancer patients experiencing weight-loss, 5 women and 5 men, were recruited for the study. The diagnoses were: gastric carcinoma ($n=5$), rectal carcinoma ($n=3$), pancreatic carcinoma ($n=1$) and hepatocellular carcinoma ($n=1$). These patients were randomised to receive 5 days treatment with atenolol 50 mg×1 (selective, β_1 receptor blocker) and after a 3-day washout period propranolol treatment (80 mg×1, non-selective, β_{1+2} receptor blocker: both drugs from Zeneca, UK) or vice versa. The order of drug administration, either atenolol or propranolol as their first treatment, was selected randomly leading to 6 patients starting with atenolol and 4 with propranolol.

The randomisation for the treatment order was performed by a computer-based algorithm stratifying for age, gender, height, body weight, weight loss during the previous 3 months, pretreatment REE, heart rate, haemoglobin concentration, erythrocyte sedimentation rate, triceps skinfold (TSF), arm muscle circumference (AMC), previous surgery, previous other treatment, expected survival, origin of the tumour and tumour stage [14]. After randomisation to one of the two treatment regimens of β-receptor blockade, after 5 days of treatment new measurements of REE, heart rate, blood pressure and biochemical tests including glucose, glycerol and free fatty acids (FFA) were made. A 3-day washout period was used to minimise carryover of metabolic effects in response to the first drug. Repeated measurements and another 5-day treatment period with the second of the two drugs were then performed. All measurements were repeated after the second 5-day treatment period. Resting heart rate was also checked before starting the second treatment in order to ensure sufficient washout time, i.e. resting heart rate should be back to pretreatment values.

REE was measured for 60 min in the morning after an overnight fast during resting conditions by indirect calorimetry (Deltatrac©, Datex, Finland) as previously described [13]. Substrate oxidation was automatically calculated by a computer according to principles described by Lusk [15]. Anthropometric variables, TSF and AMC, were measured by a specially trained nurse [16]. Blood samples were taken after REE measurements. Biochemical tests were performed according to routine hospital measurements. Plasma glucose and glycerol levels were measured using kits from Boehringer Mannheim, Germany and plasma FFA, by the Nefa C kit from Waco, Germany.

2.1. Statistics

Comparisons of differences between the effects of the two drugs were made by Mann–Whitney U-test for unpaired observations, and measurements before and after treatment were performed by the Wilcoxon signed rank test for paired observations. Two-tailed tests were used and *P*-values less than 0.05 were considered statistically significant. No patient was excluded during the study and significant side-effects due to treatment were not observed.

3. Results

3.1. Randomisation

All patients displayed malnutrition due to progressive tumour growth. The outcome of the randomisation led to a balanced distribution of patient variables in those individuals who experienced the administration order of atenolol–propranolol compared with those with propranolol–atenolol (Table 1).

3.2. Measurements before drug treatment

Routine blood chemical tests, plasma substrate profiles (glucose, glycerol and FFA), REE, resting heart rate and blood pressure were well distributed across treatment orders (Tables 2 and 3). Mean carbohydrate oxidation was significantly lower and mean fat oxidation was significantly higher in those patients who started with atenolol treatment compared with those who started with propranolol (Table 4). This was due to findings in 1 patient who revealed low values for carbohydrate oxidation (16 g/day, mean value 43 g/day ± 8), before atenolol treatment.

Table 1
Distribution of variables for nutritional state and biochemical tests in 10 cancer patients who started with atenolol (patients 1–6) compared with those who started with propranolol (patients 7–10)

	Treatment order in 10 patients		
	Atenolol–propranolol ± SEM	Propranolol–atenolol ± SEM	$P < 0.05$
Nutritional state			
Height (cm)	167 ± 5	173 ± 4	n.s.
Body weight (kg)	59 ± 10	74 ± 15	n.s.
Weight loss (%)	12 ± 3	8 ± 2	n.s.
TSF (mm)	11 ± 2	18 ± 4	n.s.
AMC (cm)	23 ± 1	25 ± 3	n.s.
Biochemical tests			
Haemoglobin (g/l)	123 ± 6	117 ± 11	n.s.
ESR (mm/h)	44 ± 16	10 ± 7	n.s.
Albumin (g/l)	35 ± 2	31 ± 4	n.s.
Plasma proteins (g/l)	74 ± 5	69 ± 2	n.s.
Creatinine (μmol/l)	72 ± 16	90 ± 8	n.s.
Bil (μmol/l)	13 ± 2	8 ± 1	n.s.
ASAT (μkat/l)	0.8 ± 0.9	0.4 ± 0.1	n.s.
ALAT (μkat/l)	1.6 ± 1.0	0.5 ± 0.2	n.s.
ALP (μkat/l)	6 ± 2	4 ± 1	n.s.

SEM, standard error of the mean; TSF, triceps skinfold; AMC, arm muscle circumference; ESR, erythrocyte sedimentation rate; Bil, bilirubin concentration; ASAT, aspartate-aminotransferase; ALAT, alanine-aminotransferase; ALP, alkaline phosphatase activity; n.s., non significant.

3.3. Measurements after drug treatment

Atenolol treatment decreased REE by 6 ± 1% (−77 ± 14 kcal/day) and propranolol by 4 ± 1% (−48 ± 13 kcal/day) which both represented a significant decrease compared with pretreatment values ($P < 0.05$) (Table 3). Whole body oxygen uptake and carbon dioxide production decreased following administration of atenolol or propranolol ($P < 0.05$). Resting heart rate decreased by 21 ± 2% (−16 ± 2 beats/min, atenolol), versus 12 ± 2% (−8 ± 1 beats/min, propranolol) ($P < 0.05$), compared with pretreatment values ($P < 0.05$) (Table 3).

Table 2
Plasma energy substrate concentrations before (B) and after (A) drug treatment

		Treatment in 10 patients		
		Atenolol ± SEM	Propranolol ± SEM	$P < 0.05$
Glucose (mmol/l)	B	5.2 ± 0.4	5.7 ± 0.5	n.s.
	A	5.4 ± 0.3	5.8 ± 0.5	n.s.
FFA (mmol/l)	B	0.72 ± 0.11	0.52 ± 0.10	n.s.
	A	0.58 ± 0.12	0.49 ± 0.09	n.s.
Glycerol (μmol/l)	B	278 ± 46	283 ± 13	n.s.
	A	243 ± 46	250 ± 50	n.s.

SEM, standard error of the mean; FFA, free fatty acids; n.s., non significant.

The ratio between the decrease in REE versus the decrease in resting heart rate was 5.2 ± 1.0 (kcal/beat) following atenolol and 8.2 ± 2.7 following propranolol treatment ($P < 0.05$) (Fig. 1). Carbohydrate oxidation was increased by atenolol and decreased by propranolol, whilst the fat oxidation was decreased by atenolol treatment and unchanged by propranolol (Table 4).

Plasma substrate concentrations of glucose, FFA and glycerol were not significantly changed during treatment with either of the two drugs (Table 2).

4. Discussion

Elevated resting energy expenditure is an important factor contributing to progressive weight loss in both treated and untreated cancer patients [1,13,17,18]. Cytokines are central mediators behind both inflammation and anaemia and previous experimental work has confirmed that cytokines are mediators behind cancer cachexia [5,19,20]. It is thus likely that a combination of factors such as stress hormones, cytokines and prostanoids explain the cachectic process [21,22]. Moreover, it has been demonstrated that cytokines interact with the classical hormonal system at both hypothalamic and glandular levels and that prostanoids may act as secondary mediators of the neuroendocrine effects exerted by cytokines [23,24]. However, less defined effects may also be involved such as non-inflammatory stimuli; pain and tumour hypoxia [25]. Our previous studies have also suggested that adrenergic factors are significant mediators behind elevated resting energy expenditure in cancer indicating both increased sensitivity and reactivity to adrenergic agonists in cancer patients suffering weight loss [8,26]. In contrast, evaluation of patients on

Table 3
Resting energy expenditure, respiratory gas exchange and heart rate before (B) and after (A) drug treatment

		Treatment in 10 patients		
		Atenolol ± SEM	Propranolol ± SEM	$P < 0.05$
REE (kcal/day)	B	1439 ± 74	1402 ± 74	n.s.
	A	1362 ± 75[a]	1354 ± 72[a]	n.s.
RQ	B	0.75 ± 0.01	0.78 ± 0.01	0.05
	A	0.78 ± 0.01[a]	0.78 ± 0.01	n.s.
O_2 (ml/min)	B	214 ± 10	208 ± 11	n.s.
	A	202 ± 11[a]	201 ± 11[a]	n.s.
CO_2 (ml/min)	B	161 ± 8	163 ± 8	n.s
	A	151 ± 7[a]	156 ± 7[a]	n.s.
Heart rate (beats/min)	B	75 ± 4	70 ± 4	n.s.
	A	58 ± 3[a]	62 ± 4[a]	0.05

SEM, standard error of the mean; REE, resting energy expenditure; RQ, respiratory quotient; n.s., non significant.

[a] Significantly different compared with pretreatment values (Wilcoxon signed rank test).

Table 4
Substrate oxidation before (B) and after (A) drug treatment ±SEM

		Treatment in 10 patients		
		Atenolol ±SEM	Propranolol ±SEM	$P < 0.05$
CHO oxidation (g/day)	B	43 ± 8	67 ± 10	0.05
	A	59 ± 9[a]	52 ± 12[a]	n.s.
Fat oxidation (g/day)	B	89 ± 5	76 ± 6	0.05
	A	77 ± 6[a]	75 ± 8	n.s.

CHO, carbohydrate.
[a] Significantly different versus pretreatment values (Wilcoxon signed rank test).

β-receptor blockade due to hyperthyroidism revealed a different drug effect compared with findings in cancer patients (data not shown). Selective β-blockade did not decrease whole body resting energy expenditure in thyrotoxic patients, whilst non-selective β-blockade had a pronounced effect (> 50%).

The results in the present study demonstrate a reduction in whole body REE following a moderate daily dose of either specific or non-specific β-blockers. However, accounting for the effect on resting heart rate, treatment with non-selective β-blockade (propranolol), resulted in a significantly more pronounced reduction in resting metabolism in proportion to the decrease in heart rate (Table 3, Fig. 1), whilst atenolol treatment displayed a significantly lower decrease in metabolism accounting for the decline in heart rate. This difference reflects differentiated drug effect(s) on cardiovascular activity and whole body substrate metabolism (amino acid, glucose, lipid), although it is always difficult to be sure to what extent treatment effects observed in small numbers of patients are representative of larger groups of unselected patients. Therefore, we have used a study design where all patients were evaluated in a random order to test both drugs. This approach should decrease the risk of misinterpretations due to skewness, although extreme metabolic outliers may still represent an uncertain factor; for example one of our patients had a particularly low carbohydrate oxidation. However, the metabolic values seen in the present group of 10 cancer patients were not obviously different from observations in our previous studies on larger groups of cancer patients suffering weight loss [2]. Therefore, we regard the low carbohydrate oxidation in 1 patient as an indication of a more pronounced state of cachexia [27–29]. Thus, our present study of 10 patients is probably representative of patient cohorts with large variations in metabolic adaptation due to solid cancer. Our results support the theory that energy drainage in weight-losing cancer patients involves both β_1 and β_2-adrenoceptors and to some extent is related to cardiovascular workload following metabolic alterations in peripheral and liver tissues [30]. This conclusion was based on the fact that when the decline in heart rate is also considered, propranolol ($\beta_1 + \beta_2$) decreased overall metabolism significantly more than a comparable dose of β_1 (atenolol) alone.

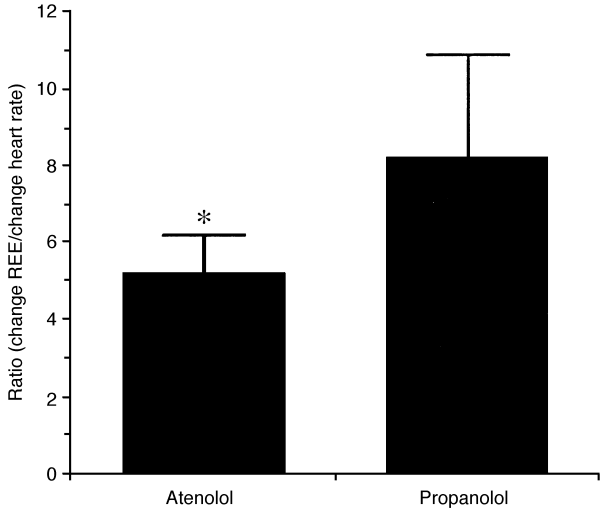

Fig. 1. The ratio between reduction in whole body resting energy expenditure and reduction in heart rate following treatment with atenolol and propranolol in 10 cancer patients with progressive cachexia. *$P = < 0.05$, ±SEM (standard error of the mean).

Based on previous mathematical computations and experimental observations we have regarded anaemia as a promoter of adrenergic activity and increased cardiac workload in both cachectic animals and patients [13]. Our recent studies on the treatment of anaemia in cancer patients, where recombinant erythropoietin was provided, have confirmed this hypothesis demonstrating that both exercise power and working efficiency were improved following normalisation of anaemia [31]. Therefore, it is likely that cytokines cause anaemia, which induces both increased sensitivity and reactivity in the cardiovascular system for maintenance of oxygen delivery despite a decline in cardiac reserves due to undernutrition in cancer patients [10]. These adaptations and mechanisms are not specific for cancer disease and involve classical systems such as thyroid hormones, catecholamines and glucocorticoids [26,32]. However, it is likely that wasting in cancer and thyrotoxic patients are in part different, as suggested by varying reactions observed towards β_1 antagonists (data not shown).

The net reduction in resting energy expenditure by β-adrenoceptor blockade may seem modest. However, the reduction in REE corresponds to 0.5–1 kg fat tissue or 2–3 kg muscle tissue over a period of 4–6 months. It represents the metabolic cost for increased cardiovascular workload in cancer patients suffering weight loss. This is not to say that β-adrenoceptor blockade should be used regularly to attenuate progressive weight loss in palliation of cancer patients, at least not until more knowledge has been gained in this field of research.

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