Augmented thermic effect of amino acids under general anaesthesia: a mechanism useful for prevention of anaesthesia-induced hypothermia

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INTRODUCTION

It is well established that patients undergoing anaesthesia and surgery frequently develop hypothermia [1]. Thus during minor abdominal surgery the patient's body core temperature may fall by 1°C [2] and during major abdominal procedures by as much as 3–4°C [3]. Postoperative hypothermia may constitute a clinical problem [4] and artificial external heating is often needed to rewarm patients, especially after surgery of long duration and in elderly patients [5, 6]. General anaesthesia may cause hypothermia by redistribution of heat within the body, by increased dissipation of heat from skin surface and/or by diminished heat production due to reduction of the energy expenditure. The possible interference of anaesthetic agents with normal hypothalamic thermoregulation has focused interest on the heat dissipation mechanisms [7, 8, 9], not least in view of the low operating theatre temperatures used in recent years [8]. However, even with heat dissipation maintained at the pre-anaesthesia level, the marked fall in energy expenditure and heat generation during anaesthesia [9] may, per se, be expected to cause substantial hypothermia.

From studies in awake subjects it is well known that the administration of nutrients, especially proteins [10] and amino acids [11], stimulates resting energy expenditure and hence thermogenesis. Recent studies have shown that oral protein ingestion is also accompanied by a significant rise in mixed blood temperature [12]. Similarly, 2–3 h of intravenous infusion of amino acid mixtures may increase the energy expenditure and thermogenesis by more than 20% and, in addition, raise the blood temperature above its basal level [13]. The mechanisms whereby proteins or amino acids stimulate thermogenesis and heat accumulation are not completely understood. The present study was undertaken in order to determine whether amino acids are also able to exert thermogenic stimulation under...
general anaesthesia. If so, amino acid administration may counteract the reduction in thermogenesis and possibly prevent anaesthesia-induced hypothermia. Pulmonary oxygen uptake and mixed venous blood temperature were therefore measured in a group of patients undergoing anaesthesia and elective abdominal surgery during continuous intravenous infusion of an amino acid mixture. The results were compared with those from a control group receiving nutrient-free standard saline solutions.

METHODS

Patients

Twenty-one male patients, scheduled for abdominal surgery, were studied (Table I). Except for partial gastric resection in one patient in the amino acid-treated group, the surgical procedures were of minor character. The patients were otherwise healthy and had no medication. In ten of the patients an intravenous amino acid infusion was started immediately before and continued throughout the anaesthesia. The operations performed in these ten patients were four cholecystectomies, two umbilical hernias, two colonic resections, one vagotomy and one partial gastric resection as mentioned above. Eleven patients, serving as controls, received corresponding volumes of intravenous nutrient-free saline solutions. The operations performed in these 11 patients were five cholecystectomies, two colostomy revisions, one umbilical hernia, one gastroenteral anastomosis, one vagotomy and one ileum resection. The patients were informed of the nature, purpose and possible risks of the study before giving their voluntary consent to participate. The study protocol was reviewed and approved by the institutional ethics committee.

Procedure

Every second patient who agreed to participate in the study was assigned to the amino acid treatment. The others were controls. The patients, the nurses giving the anaesthesia and the operating surgeons were unaware of whether amino acids or saline were given. Otherwise the study was not blinded. All patients were prepared according to standard preoperative routine after an overnight fast. At 2h before anaesthesia, they were given oral premedication (lorazepam, 2–3 mg). The room temperature in the operating theatre was 21–23°C. Except for four units of warmed blood given to the patient subjected to partial gastrectomy in the amino acid-treated group, no kinds of warming devices were used. The nutrient-free saline infusion fluids given, 500 ml/h to all the patients, were at room temperature. Before anaesthesia, a thermistor-equipped catheter (Arrow AH-05050-H-7.5F; Arrow International Inc., Reading, PA, U.S.A.) was inserted percutaneously from an antecubital vein into the pulmonary artery under local anaesthesia and fluoroscopic control. One radial artery was also catheterized percutaneously. The mixed venous blood temperature was continuously recorded [14] from 20–30 min before the onset of anaesthesia until the patient woke up. Cardiac output was determined with the thermodilution technique, and blood samples were drawn from the pulmonary and radial arteries for analyses of oxygen and haemoglobin concentrations. After the basal measurements, a mixture of 19 amino acids (Vamin; 18 g of N/l; Kabi Pharmacia, Stockholm, Sweden) was infused intravenously to ten of the patients, at a rate of 126 ml/h corresponding to 240 kJ of energy/h. The control patients received equal additional volumes of nutrient-free saline solution. The measurements were repeated three times during the study: (1) ‘anaesthesia’, before surgery, after 32±6 and 36±6 min of anaesthesia in the amino acid-treated and control groups, respectively; (2) ‘operation’, in the middle of the operation, after 88±10 and 91±11 min of anaesthesia in the amino acid-treated and control groups, respectively; and (3) ‘awake’, within 5 min after the patient had woken up, after 155±22 and 130±15 min of anaesthesia in the amino acid-treated and control groups, respectively.

The catheters were then withdrawn and the thermistors were calibrated against a precision thermometer [14]. During recovery all patients were monitored by the same observer for the presence or absence of clinically apparent generalized shivering.

Anaesthesia

Anaesthesia was given in the same way to all patients. It was induced with thiopentone (5 mg/kg) and maintained with 1–2% isoflurane in 40% oxygen/60% nitrous oxide, using an Engström ventilator 2000 (Gambro Engström AB, Bromma, Sweden). All patients were monitored with pulse oximetry (Datex, Sweden). Muscle relaxation, controlled by the train of four technique [15], was achieved with atracurium as a continuous infusion of 0.5 mg/h·kg⁻¹ after an initial bolus dose of 0.5 mg/kg. Before surgery was started, fentanyl (3 μg/kg) was given. The atracurium infusion was terminated half an hour before the end of the operation, and the remaining effect of muscle relaxant was antagonized with 2.5 mg of neostigmine together with 0.5 mg of atropine immediately after the end of the surgery. Heart rate was recorded from the ECG,
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Analyses and calculations

Blood temperature was recorded continuously at a sampling frequency of 1 Hz as described previously [14]. Technically, the high-precision blood thermometer allows the detection of small temperature variations. Its absolute measuring accuracy is ±0.001 °C and its sensitivity is 0.0003 °C. Blood oxygen and haemoglobin concentrations were analysed spectrophotometrically (OSM 3 Hemoximeter; Radiometer, Copenhagen, Denmark). Pulmonary oxygen uptake was calculated as the product of the measured arteriovenous oxygen difference and cardiac output, according to the Fick principle. Standard statistical methods were employed. For comparison of absolute values, data were first analysed by repeated measures analysis of variance and differences between groups at each of the three measurement periods were calculated by post hoc testing [16]. Data in the text and tables are given as means±SEM, and in the Figures as mean changes±SEM. The Figures also demonstrate the differences in time course between the groups.

RESULTS

Blood temperature

In the basal state, before anaesthesia, the average mixed venous blood temperature for all patients was 36.6 ± 0.1 °C, not differing significantly between the groups (see Table 2). At anaesthesia, it started to fall immediately in both groups. From 20 min after the onset of anaesthesia, the temperature decrease from basal was significantly greater (P < 0.05) in the control patients than in the amino acid-treated patients (Fig. 1) and remained so during the entire study period (Fig. 2). During 34 ± 4 min of anaesthesia, before surgery, cardiac output decreased in the control group to 4.1 ± 0.03 litres/min (P < 0.02), whereas in the amino acid-treated group, it only tended to

Cardiac output

In the basal, pre-anaesthesia state, cardiac output was 6.0 ± 0.4 and 5.4 ± 0.3 litres/min (not significant) in the control and amino acid-treated groups, respectively. During 34 ± 4 min of anaesthesia before surgery, cardiac output decreased in the control group to 4.1 ± 0.03 litres/min (P < 0.02), whereas in the amino acid-treated group, it only tended to
Anaesthesia Operation Awake

Fig. 3. Changes in cardiac output during anaesthesia, operation and awakening in 11 control patients (○) and 10 patients (●) receiving intravenous infusion of amino acids (4 kJ/min) started at the onset of anaesthesia. Vertical bars indicate ±SEM of mean changes. Horizontal bars indicate ±SEM of time after the onset of anaesthesia.

Decline to 4.5 ± 0.4 litres/min (not significant). At awakening, cardiac output did not significantly exceed the basal level in the control patients, whereas in the amino acid-treated group it was significantly (P < 0.01) higher than the basal level, 7.2 ± 0.5 litres/min (Fig. 3, Table 2).

Arteriovenous oxygen difference

The arteriovenous oxygen difference tended to decrease in both groups during anaesthesia and surgery, but did not change significantly from the basal level of 44 ± 2 ml/l. At awakening, however, the arteriovenous oxygen difference rose sharply in the amino acid-treated group to 58 ± 7 ml/l, significantly higher (P < 0.05) than the corresponding value in the control group, 38 ± 4 ml/l (Table 2, Fig. 4).

Pulmonary oxygen uptake

In the basal, pre-anaesthesia state the pulmonary oxygen uptake did not differ significantly between the groups. In the control group it was 275 ± 10 ml/min, corresponding to 114 ± 7% of basal oxygen consumption calculated from body dimensions and age [17]. In the amino acid-treated group, the corresponding values were 238 ± 15 ml/min and 102 ± 6% (Table 2). During 34 ± 4 min of anaesthesia before surgery, the oxygen consumption decreased by 145 ± 9 ml/min or 54 ± 4% of basal in the control patients and by no more than 81 ± 110 ml/min or 34 ± 4% of basal in the amino acid-treated patients (P < 0.001) (Fig. 4). During the entire period of anaesthesia and surgery, the average fall in oxygen consumption was approximately 136 ml/min, or 49% of the pre-anaesthesia level, in the control group, and approximately 67 ml/min or 28% in the amino acid-treated group. At awakening, the oxygen uptake was 257 ± 25 ml/min or 7 ± 9% below the pre-anaesthesia level in the control group, whereas in the amino acid-treated group it was 408 ± 60 ml/min or 71 ± 21% above the pre-anaesthesia level (P < 0.05) (Fig. 5).

Heart rate

The changes in heart rate during the observation period were small and not significantly different between the groups (Table 2).

Stroke volume

The changes in stroke volume closely followed those of cardiac output, with a steep fall in the control patients during anaesthesia and surgery (P < 0.002), followed by a return to almost pre-anaesthesia values at awakening (Table 2). In the
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Table 2. Blood temperature, pulmonary oxygen uptake, cardiac output, arteriovenous oxygen difference, heart rate and stroke volume before, during and at termination of anaesthesia in 10 patients receiving intravenous amino acids (240kJ/h) and in 11 control patients. Values are means±SEM.

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Anaesthesia</th>
<th>Surgery</th>
<th>Awake</th>
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<tr>
<td>Mixed venous blood temperature (°C)</td>
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<tr>
<td>Amino acid-treated</td>
<td>36.54±0.112</td>
<td>36.14±0.244</td>
<td>35.99±0.168</td>
<td>36.26±0.150</td>
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<td>Control</td>
<td>36.58±0.035</td>
<td>35.94±0.116</td>
<td>35.57±0.122</td>
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<tr>
<td>Pulmonary oxygen uptake (ml/min)</td>
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<tr>
<td>Amino acid-treated</td>
<td>238±15</td>
<td>157±11</td>
<td>186±15</td>
<td>408±50</td>
</tr>
<tr>
<td>Control</td>
<td>275±10</td>
<td>128±14</td>
<td>144±17</td>
<td>257±25</td>
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<td>Cardiac output (litres/min)</td>
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<tr>
<td>Amino acid-treated</td>
<td>5.4±0.3</td>
<td>4.5±0.3</td>
<td>4.9±0.4</td>
<td>7.2±0.5</td>
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<tr>
<td>Control</td>
<td>6.0±0.4</td>
<td>4.1±0.3</td>
<td>4.3±0.3</td>
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<td>Arteriovenous oxygen difference (ml/l)</td>
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<td>38±4</td>
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<td>Heart rate (beats/min)</td>
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<td>Stroke volume (ml)</td>
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<tr>
<td>Amino acid-treated</td>
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<td>68±5</td>
<td>70±6</td>
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<tr>
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<td>78±4</td>
<td>57±5</td>
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<td>74±8</td>
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Amino acid-treated group, however, the stroke volume did not decrease significantly during anaesthesia. At awakening it rose from basal 75±3 to 89±4 ml in the amino acid-treated group, whereas in the control group it did not exceed the pre-anaesthesia level (P<0.02), (Table 2).

Arterial oxygen saturation

This was unchanged during the study period in all the patients, consistently showing 97–99%.

Shivering

This occurred at awakening in all the control patients, but in none of the patients receiving amino acids.

DISCUSSION

The present results show that the administration of a balanced mixture of amino acids significantly counteracts hypothermia and hypometabolism during anaesthesia. Thus, during anaesthesia and surgery, the blood temperature decreased by 0.67±0.09 °C/h in a control group of patients, and by only 0.38±0.06 °C/h in a group of patients receiving intravenous infusions of 4kJ of amino acids/min. The whole body oxygen consumption decreased during 34±4 min of anaesthesia by 145±9 ml/min in the control group and by only 81±10 ml/min in the amino acid-treated group. Assuming an essentially unchanged respiratory exchange ratio, the energy expenditure could be calculated from the values of pulmonary oxygen uptake. The assumption of an unchanged respiratory exchange ratio is based on findings in unanaesthetized subjects whose respiratory exchange ratio never changes in response to protein or amino acid administration [11–13]. Calculated this way, the approximate anaesthesia-induced reduction in energy expenditure was 47 W in the control patients and 26 W in the amino acid-treated patients. The difference between these two values, approximately 21 W, illustrates the average thermogenic action of amino acids given. This value may be compared with that of 4 W, observed in healthy, unanaesthetized subjects in response to 30 min of identical amino acid infusions [13]. Thus during general anaesthesia with muscle relaxation, the thermic effect of intravenous amino acids was five times greater than in the normal, unanaesthetized state. The most marked change in metabolic rate occurred at awakening after the operation when, without obvious simultaneous shivering, the oxygen consumption rose steeply in the amino acid-treated patients to 71±21% above the pre-anaesthesia level. The resulting increase in heat generation almost restored the blood temperature to its pre-anaesthesia level within a few minutes. In the control patients, not receiving amino acids, the pulmonary oxygen uptake at awakening remained below the pre-anaesthesia level, despite sustained hypothermia and vigorous shivering.

It is not immediately apparent why the thermic effect of amino acids should be augmented during general anaesthesia. However, it might be explained by considering the possible influence of central thermoregulatory mechanisms [18–21]. In the
unanaesthetized state, the central thermosensors exert a blood-temperature related inhibition of the whole body oxidative metabolism and heat production [20–22]. Although the precise mechanisms underlying this inhibition are still obscure, a number of reports [12, 13, 19–25] support the existence of such an inhibitory action from the central thermosensors which, in the unanaesthetized state, suppresses oxidative metabolism when the arterial blood temperature exceeds the actual set point. Better known are the opposite thermoregulatory mechanisms, those whereby the central thermosensors, in response to low blood temperatures, stimulate metabolic rate by increasing the sympathetic nervous activity and, at lower temperatures, facilitate shivering [9, 26–28]. Recent studies have shown, that in tetraplegic patients with severed nervous connections between the central thermosensors and the rest of the body, the thermic effect of nutrients is augmented rather than reduced, leading to uncontrolled rises in arterial blood temperatures [24, 25]. These findings further support the view that protein and amino acids, per se or via a second messenger, stimulate energy expenditure primarily in the peripheral tissues and that intact centrifugal nervous tracts seem to be required for the inhibitory mechanisms, whereby the central thermosensors suppress the thermic effect of nutrients in healthy subjects. Earlier studies have shown that the thermic effect of proteins or amino acids probably does not involve central mechanisms, such as sympatho-adrenal activation [29].

General anaesthesia, known to silence the thermoregulatory nuclei [30], would probably abolish the origin for signals along both the inhibitory and stimulatory lines of the thermoregulatory influence on the whole body metabolism. The anaesthesia-induced drop in net metabolic rate, most likely due to the well-known negative direct metabolic effects of anaesthetics [9], constitute the dominating net influence on the metabolic rate during anaesthesia. Therefore the simultaneous loss of central metabolic inhibition can be demonstrated only if the administration of a certain amount of nutrient energy reduces the expected drop in metabolic rate to an extent greater than that calculated from the known thermic effect of the nutrient.

When the anaesthesia ends, the thermosensors wake up and record a blood temperature below the set point. This stimulus would induce the thermosensors to both continue the blockade of the inhibitory metabolic signals and elicit efferent signals along the stimulatory line that increase the sympathetic nervous activity and thereby stimulate the metabolic rate. The synergistic action of the still unrestricted amino acid-induced thermogenesis and the direct sympathetic stimulation would further increase oxidative metabolism and thus explain the overshoot that occurred at awakening in the amino acid-treated patients. In the control patients only the direct stimulation, including shivering, caused a relatively weak thermogenesis that barely restored the oxygen uptake to the pre-anaesthesia level.

In previous studies of unanaesthetized healthy subjects, the administration of oral protein [12] or intravenous amino acids [13] caused an overflow of heat to be transported by the blood, thereby increasing the blood temperature. In order to keep the rise in blood temperature within the limits accepted by the actual set point [18, 21], the central thermosensors would need to inhibit the metabolic rate [20, 22, 23, 27] and/or stimulate the heat dissipation by increasing cutaneous blood flow. In the anaesthetized patients the blood temperatures were subnormal. In addition, the central thermosensors were anaesthetized and unable to operate. Therefore no inhibition of the metabolic rate or stimulation of extra heat dissipation would be expected to occur in the anaesthetized state. In accordance with these considerations, enhanced amino acid-induced rises in both oxidative metabolism and heat accumulation would be expected during anaesthesia. The differences observed between the anaesthetized and unanaesthetized subjects may thus be explained as consequences of normal thermoregulation.

When the amino acid-treated patients woke up after the anaesthesia, the oxygen consumption rose to $408 \pm 50 \text{ml/min}$, $71 \pm 21\%$ above the basal, pre-anaesthesia level. The total amount of energy produced by the increased oxidative metabolism, without assistance from shivering, almost restored the blood temperature to the pre-anaesthesia level in a few minutes. When the control patients not receiving amino acids woke up, and their very low blood temperature was recorded by the central thermosensors, vigorous shivering immediately started. However, the shivering was obviously unable to restore the oxygen uptake to the pre-anaesthesia level. Consequently, the hypothermia continued in the control patients, as usually seen in the postoperative state. The findings illustrate the magnitude of the amino acid-induced thermogenesis under anaesthesia and its facilitation of thermoregulation in the early postoperative state.

There may be other mechanisms contributing to the potentiation of the thermic effect of amino acids during anaesthesia. Possibly the hypothermia, per se, may stimulate peripheral heat production in tissues exposed to high extracellular amino acid concentrations.

Beside a possible extension of our knowledge about the mechanisms for amino acid-induced thermogenesis, the findings may have clinical applications. Since hypothermia may constitute a sometimes serious complication during and after general anaesthesia, efforts have been made to prevent its occurrence [3, 31]. Thus several techniques for external body heating have been presented, attempting to overcome the problem by minimizing the dissipation of heat from the body surface [6, 32, 33]. Such procedures are associated with technical difficulties, hardly eased by keeping operating theatre temperature at $21–23\degree C$, or lower, as is common.
nowadays [8]. It should be remembered, however, that general anaesthetics do not cause hypothermia only by influencing the hypothalamic control of heat dissipation. Most anaesthetic agents also considerably reduce the whole body oxidative metabolism and hence the production of heat [34]. This was illustrated by the findings in the control patients in the present study, in whom 30–40 min of general anaesthesia reduced the blood temperature by approximately 0.65°C and the pulmonary oxygen uptake by more than 50%. In consequence, the clinical problem of anaesthesia-induced hypothermia may be related to decreased heat production rather than increased heat dissipation.

Several studies have shown that the prevention of hypothermia during anaesthesia significantly improves the postoperative nitrogen balance [4, 32, 34]. Special studies will be required to determine whether a similar beneficial metabolic effect also ensues when the anaesthesia-induced hypothermia is prevented by the administration of amino acids. At awakening after amino acid treatment, the need for increased pulmonary ventilation to fulfill the sudden increase in oxygen demand may constitute a possible risk for patients with reduced ventilatory capacity. Likewise, in patients with hepatic or renal insufficiency, the infusion of amino acids might constitute a metabolic risk and should therefore be avoided or performed with low dosage. Otherwise, it seems difficult to pinpoint risks for harmful complications accompanying the clinical use of amino acids for the purpose of preventing anaesthesia-induced hypothermia.

It might be argued that starting the administration of the amino acids at the onset of anaesthesia may be too late for the effective prevention of hypothermia. The initial temperature fall (Fig. 1) might have been prevented to a greater extent, with the amino acid infusion starting earlier, before the onset of anaesthesia. Preliminary results (E. Selldén et al., unpublished work) from pre-operative amino acid infusions indicate that this is so. Further studies will be required to determine the optimal duration of the pre-anaesthesia infusion periods that most effectively prevent the development of hypothermia and hypometabolism during general anaesthesia.

It is concluded that the thermic effect of amino acids is greatly augmented under general anaesthesia with muscle relaxation and that intravenous administration of a balanced mixture of amino acids largely prevents anaesthesia-induced hypothermia and hypometabolism.

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