Bolus Oral or Continuous Intestinal Amino Acids Reduce Hypothermia during Anesthesia in Rats

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Summary We hypothesized that, with oral or intestinal administration of amino acids (AA), we may reduce hypothermia during general anesthesia as effectively as with intravenous AA. We, therefore, examined the effect of bolus oral and continuous intestinal AA in preventing hypothermia in rats. Male Wistar rats were anesthetized with sevoflurane for induction and with propofol for maintenance. In the first experiment, 30 min before anesthesia, rats received one bolus 42 mL/kg of AA solution (100 g/L) or saline orally. Then for the next 3 h during anesthesia, they received 14 mL/kg/h of AA and/or saline intravenously. They were in 4 groups: I-A/A, both AA; I-A/S, oral AA and intravenous saline; I-S/A, oral saline and intravenous AA; I-S/S, both saline. In the second experiment, rats received 14 mL/kg/h duodenal AA and/or saline for 2 h. They were in 3 groups: II-A/S, duodenal AA and intravenous saline; II-S/A, duodenal saline and intravenous AA; II-S/S, both saline. Core body temperature was measured rectally. After the second experiment, serum electrolytes were examined. In both experiments, rectal temperature decreased in all groups during anesthesia. However, the decrease in rectal temperature was significantly less in groups receiving AA than in groups receiving only saline. In the second experiment, although there was no significant difference in the decrease in body temperature between II-A/S and II-S/A, Na⁺ concentration was significantly lower in II-S/A. In conclusion, AA, administered orally or intestinally, tended to keep the body temperature stable during anesthesia without disturbing electrolyte balance. These results suggest that oral or enteral AA may be useful for prevention of hypothermia in patients.

Key Words amino acid, oral ingestion, intestinal administration, perioperative hypothermia, general anesthesia

Hypothermia during anesthesia is caused by decreased heat production as well as increased heat loss and impaired hypothalamic thermoregulation (1). Body heat redistribution between core and peripheral tissues also may be contributory. Hypothermia induces shivering and prolongation of recovery from anesthesia, and increases bleeding during surgery and risk of ischemic heart disease and postoperative wound infection (2, 3). Therefore it is routine to protect temperature balance during anesthesia, mainly by using external heating devices. It was reported that intravenous amino acid infusion prevents hypothermia during surgery under both general and spinal anesthesia (4–8), and thereby shortens hospital stay (9, 10). These results may be interpreted as showing evidence of thermogenesis from proteins and amino acids (11). The thermogenesis during anesthesia is markedly increased by amino acids (4). However, amino acid solution is not typically prepared for the perioperative period and may not be suitable for intravenous infusion during surgery because of inappropriate concentrations of electrolytes. Hyponatremia is often caused during perioperative period by intraoperative secretion of antidiuretic hormone and dilution with infusion of hypotonic saline, especially in children (12, 13). Therefore, infusion of a low Na⁺ solution, such as 5% glucose solution, is usually avoided during the perioperative period. Amino acid infusion also may cause disorder in serum electrolyte levels. Doses of its administration during surgery may be limited to avoid such complications.

We hypothesized that oral or intestinal administration of amino acids is effective for reducing hypothermia during anesthesia, and that the effect of one bolus
administration of oral amino acids may be additive to that of intravenous administration of amino acids. We examined, therefore, the effect of one bolus administration of oral amino acids before anesthesia with or without intravenous infusion of amino acids for prevention of hypothermia during anesthesia in rats. In addition, we examined the effect of continuous duodenal administration of amino acids on reducing the degree of hypothermia and on serum electrolyte balance.

MATERIALS AND METHODS

Male Wistar rats from Japan SLC, Inc. (Hamamatsu, Japan), weighing 250–270 g, were maintained under conditions of constant humidity and temperature (22±2°C) on a 12:12 hour light-dark cycle in an acryl box. They were fed with a standard diet and water. The following surgical and experimental procedures were approved by the Ethical Committee of the Animal Care Center of Kochi Medical School.

In the first experiment, rats were divided into two groups, receiving either amino acids or saline. Thirty minutes before anesthesia induction, they were sedated in an acryl box with inhalation of 5% sevoflurane for 1 min, and received one bolus 42 mL/kg of saline or amino acid solution (100 g/L, BCAA 30%). Ampirex® (Otsuka Pharmaceutical Co., Ltd., Japan) orally. This amino acid dose corresponds to 70.6 kJ/kg. They were then kept in the cage for 30 min until anesthesia induction. Anesthesia was induced in the acryl box with 5% sevoflurane for 1.5 min. Rats were put on a paper pad on the table. Room temperature was kept constant at 24°C. The right neck skin was incised and a catheter (24G) was inserted into the right internal jugular vein and anesthesia was maintained with propofol as in the first experiment. Subsequently upper abdominal skin was incised for 1 cm for cannulation into the duodenum with 16G polyamide catheter (PERFIX, B-BRAUN, Melsungen). Rats were divided into groups, receiving 14 mL/kg/h of amino acid solution for 2 h, either intravenously or duodenally. They were divided, therefore, into a total of three groups and named II-A/S, rats receiving enteral amino acids and intravenous saline; S/A, enteral saline and intravenous amino acids; S/S, enteral and intravenous saline. In addition, a control group was prepared for blood sampling. No warm pad was used for the experiment. Rectal temperature was measured every 30 min for 3 h after anesthetic induction using a digital thermometer (BDT-100, Bioresearch Inc. Tokyo). The intravenous amino acids or saline was given for 3 h in total.

In the second experiment, room temperature was also kept constant at 24°C. Anesthesia was induced with sevoflurane with no oral administration. A catheter (24G) was inserted into the right internal jugular vein and anesthesia was maintained with propofol as in the first experiment. Subsequently upper abdominal skin was incised for 1 cm for cannulation into the duodenum with 16G polyamide catheter (PERFIX, B-BRAUN, Melsungen). Rats were divided into groups, receiving 14 mL/kg/h of amino acid solution for 2 h, either intravenously or duodenally. They were divided, therefore, into a total of three groups and named II-A/S, rats receiving enteral amino acids and intravenous saline; S/A, enteral saline and intravenous amino acids; S/S, enteral and intravenous saline. In addition, a control group was prepared for blood sampling. No warm pad was used for the experiment. Rectal temperature was measured every 20 min for 2 h after anesthetic induction. In addition, arterial blood samples were taken from the aorta at the end of the experiment for measurement of serum electrolyte concentration (Na⁺, K⁺, Ca²⁺, Cl⁻). These values were compared to samples taken from the pre-treated control group just after induction of anesthesia with sevoflurane.

In both experiments, alterations of rectal temperature of each group were analyzed with an ANOVA repeated measures for the difference among groups and the difference over time. Post hoc testing was performed with a Scheffe’s procedure for the difference among groups and for the difference over time in each group. Differences were considered significant at p<0.05 and the difference of decrease in temperature among groups at each time was presented by the absence of shared superscript letters. Differences of serum electrolytes were also analyzed with an ANOVA with the post-hoc Scheffe’s procedure for the difference among groups. Differences were considered significant at p<0.05.

RESULTS

In the first experiment, rectal temperature gradually decreased from baseline (I-A/A (n=6). 37.6±0.3°C; I-A/S (n=6). 37.6±0.4°C; I-S/A (n=6). 37.6±0.4°C; I-
rectal temperature of the study groups were 32.5˚C (I-A/A), 31.8±0.7˚C (I-A/S), 31.9˚C (I-S/A) and 30.2±0.7˚C (I-S/S). In the first experiment, 2 rats in the A/S group and 1 rat in the A/S group were excluded from the study, because they died of airway occlusion because of vomiting. However, rats receiving oral saline did not vomit during the experiment.

In the second experiment, rectal temperature gradually decreased from baseline (II-A/S (n=7): 37.0±0.2˚C, II-S/A (n=7): 36.9±0.4˚C, II-S/S (n=7): 36.8±0.4˚C) in all groups during 2 h of anesthesia (Table 2). The decrease in rectal temperature in the II-S/A group was significantly less from 20 min after the start of infusion to the end of the study than in the II-S/S group receiving only saline. The decrease in rectal temperature was significantly less from 20 min after the start of infusion to the end of the study than in the II-S/S group receiving only saline. The decrease in rectal temperature was significantly less from 20 min after the start of infusion to the end of the study than in the II-S/S group receiving only saline. The decrease in rectal temperature was significantly less from 20 min after the start of infusion to the end of the study than in the II-S/S group receiving only saline.

**DISCUSSION**

In the present study, we intended to elucidate the contribution of oral or intestinal administration of amino acid solution to the prevention of hypothermia during anesthesia. In the first experiment, we confirmed that one bolus administration of oral amino acids before anesthesia attenuated the marked decrease of core temperature during anesthesia using propofol-treated rats. In addition, prevention of hypothermia with amino acids was more effective when they were given both orally and intravenously combined than when they were given only intravenously. These results indicate that oral amino acids have an additive effect to intravenous amino acids for reducing hypothermia.
However, 3 rats with one bolus administration of oral amino acids died of airway occlusion caused by vomiting in the first experiment. The dose of oral amino acids before anesthesia may be limited. In the second experiment, we confirmed that continuous duodenal administration of amino acids also attenuated markedly a decrease of rectal temperature during anesthesia. In addition, serum electrolytes were maintained in rats receiving duodenal amino acids better than in rats receiving intravenous amino acids.

Body core temperature increases after food ingestion. This nutrient-induced thermogenesis (NIT) relates to the “thermic effect” of the nutrient, and proteins contribute more than carbohydrates or fat (11). The heat production from infusion of amino acids is markedly increased during anesthesia and reduces the degree of hypothermia at emergence from anesthesia (4–6, 9, 10). The underlying mechanisms may be explained incompletely, and hence discussed by several authors (4, 7, 10, 14, 15). Most probably there is a combination of thermoregulatory and molecular factors. Proteins and amino acids may have a pyrogen-like influence and reset the set point in the awake state (16, 17), possibly via a second messenger. Body oxidative metabolism keeps the body core temperature constant and prevents hypothermia in the awake state (18). However, anesthesia may suppress this thermic control. Administration of amino acids augments the thermogenic effect mainly via increased extra-splanchnic oxygen consumption (5), presumably in skeletal muscle. Hence, this suggests an increased protein turnover (14, 19). Ribosomal S6 kinase plays a central role through the mammalian target of rapamycin pathway for translation initiation of protein synthesis (20–22). It has been reported that one bolus oral administration of leucine induces phosphorylation of the eukaryotic initiation factor 4E-binding protein and ribosomal S6 kinase (23). This phosphorylation was acute in the skeletal muscle and peaked at 1 h after oral administration, which paralleled the changes in plasma leucine concentration. In our first experiment, the rectal temperature of the I-A/S group decreased significantly more than that of the I-A/A group after 2 h of anesthesia, but the difference did not reach a significant level in the first half of the experiment. On the other hand, the temperature of the I-S/A group decreased significantly more than that of the I-A/A group after 1 h of anesthesia, but the difference was not significant at 3 h from the start of infusion. These results suggest that one bolus administration of oral amino acids before anesthesia may contribute to reduction of initial decrease of body temperature, but this effect may continue only for around a couple of hours, while intravenous amino acid infusion should be continued to maintain the effect of amino acids.

It has been reported that, in the awake state, enteral administration of amino acids increases the period of emergence, whereas parenteral administration reaches the plateau value in 30 min (24). However, the thermic effect of enteral administration of amino acids is twice higher than the thermic effect of parenteral administration. The high NIT effect of enteral administration of amino acids may include the metabolic cost for absorption from the digestive tract, processing and transportation through vessels. Therefore, oral or intestinal administration of amino acids may also have an additive effect together with intravenous amino acid infusion to reduce hypothermia. In the first experiment, rats in the I-A/A group and the I-A/S group received 4.2 mg/kg of amino acids corresponding to 70.6 kJ/kg through the oral route, and rats in the I-A/A group and the I-S/A group received the same dose of amino acids intravenously for 3 h. Rat metabolism is 5–7 times higher than in humans, and rats take in around 7 times as much protein by weight as humans (25). The infusion rate of amino acid solution was according to that reported by Yamaoka (14). This infusion rate, 14 mL/kg/h, corresponds to 7 times faster than the upper limit of clinical use for human patients.

The composition of amino acid solutions prepared for intravenous infusion is inappropriate for perioperative use because of their electrolyte concentrations. We used a standard amino acid solution in the current study, which contains 10% amino acids, 2 mEq/L of Na+, no Cl− and no K+. This solution has low electrolyte concentrations; the sodium concentration, in particular, is too low. Infusion of hypotonic saline during the perioperative period is a risk factor for hyponatremia, especially in children (12, 13). The infusion rate of the amino acid solution is limited to less than 2 mL/kg/h. Thus, we hypothesized that intravenous administration might cause an imbalance of serum electrolyte concentration, and the total amount to be given during surgery should be limited. In the second experiment, we measured serum electrolyte concentrations 2 h after the anesthetic induction in those 3 groups. In addition, we prepared another group for blood sampling just after anesthetic induction (baseline), since we were afraid that blood sampling might influence the anesthetic condition. In our results, serum sodium concentration was significantly low in both groups compared to that just after anesthetic induction. However, the sodium concentration in the II-S/A group decreased severely to 128.9 ± 3.2 mEq/L, significantly less than the sodium concentration in the II-A/S group (p<0.001). Effects of intestinal administration of amino acids on serum electrolyte concentration were less than those of intravenous administration.

In conclusion, our results show that both one bolus administration of oral amino acids and continuous administration of duodenal amino acids reduced the degree of hypothermia during general anesthesia in rats. The thermic effect of one bolus administration of oral amino acids was additive to intravenous administration of amino acids. These alternative routes might extend the limit of amino acid administration. In addition, continuous intestinal administration of amino acid maintained the balance of serum electrolytes better than intravenous administration. In further study, these results should be confirmed in human subjects.
REFERENCES


