Review Article

Modification of core body temperature by amino acid administration

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The feeling of warmth after a meal is caused by the ingestion of nutrients and the sensation is known as nutrition-induced thermogenesis or specific dynamic action. Core body temperature (Tb) is constantly maintained within a narrow range, but thermoregulation can become impaired by the inhalation or intravenous administration of anesthetics that inhibit hypothalamic thermoregulation. Hypothermia during surgery is directly associated with postoperative complications. Devices are available to maintain heat during surgery and thus prevent hypothermia. On the other hand, intravenous amino acid (AA) administration can attenuate hypothermia during anaesthesia, prompting many clinical trials of AA mixtures to maintain Tb. However, although the thermal effect of AA during anaesthesia is obvious, the underlying mechanism of metabolic heat production and accumulation remains obscure. A nutritional physiological approach using a rat model will be introduced in this symposium. Data from our recent studies suggest that the administration of an AA mixture during anaesthesia stimulates muscle protein synthesis via insulin-mTOR-dependent activation of the translation initiation factors, 4E-BP 1 and S6K1, as a result of increased insulin concentrations. Thus, heat accumulation in the body is facilitated. Furthermore, the content of the AA mixture applied during anaesthesia alters the thermal effect and branched chain AAs are necessary, but not sufficient, for the prevention of hypothermia.

Key Words: thermoregulation, hypothermia, anaesthesia, heat production

INTRODUCTION

Daily energy expenditure is affected by physical or mental stress as well as basal metabolism. Energy expenditure also increases after nutrient ingestion due to the metabolic cost of transporting and converting absorbed nutrients into their respective storage forms. The proportion of energy expended relative to the energy content of the nutrients is 30-40% for protein or amino acids, 5-10% for carbohydrate or glucose and 0-3% for fat.[1] That is, proteins or amino acids are metabolized via many reactions that require ATP reduction, which is sensed as a feeling of warmth after a meal.

Core body temperature (Tb) in endotherms is maintained within a narrow range, which serves as the optimal temperature for metabolic activities. Fluctuations in Tb can be minimized by negative and positive physiological feedback systems via the thermo-centre. Abnormalities in Tb result when thermoregulation malfunctions. Representative conditions accompanying an increase in Tb include fever, heat injury and malignant hyperthermia. In contrast, conditions associated with a decrease in Tb are less frequent and include metabolic disturbances such as hypopituitarism or hypothyroidism. However, Tb in even endotherms can be disrupted by general anaesthesia, which causes hypothermia.

Between induction and the first hour of anaesthesia, body heat is redistributed from the core (warmer region) to the periphery (cooler region), resulting in a decrease in core temperature and an increase in peripheral temperature. Thereafter, the thermal curve of the core temperature progressively drops as heat loss exceeds metabolic heat production. Anaesthesia causes a 30 to 40% decrease in heat production compared with that during normal consciousness.

Hypothermia during anaesthesia does not interfere with the management of surgery because Tb subsides when patients awaken and thermoregulation becomes normal. However, even mild hypothermia multiplies the likelihood of postoperative infection of surgical incisions, prolongs hospitalization and increases the incidence of cardiovascular events.[2, 3]

Patients under anaesthesia can be intensively warmed or simply kept warm either by elevating the room temperature or by the use of extra-corporeal devices. However, elevating operating room temperature fatigues the surgical staff. Therefore, devices have been produced to maintain the temperature of surgical patients and to prevent hypothermia. On the other hand, intravenous amino acid administration is effective in attenuating hypothermia during anesthesia.[4] The possibility of warming patients from inside the body using AA mixtures have since prompted many clinical trials.[5-8]

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ATTENUATION OF HYPOTHERMIA DURING ANAESTHESIA USING A GENERAL AMINO ACID MIXTURE [9]

We have reported that AAs inhibit hypothermia in an anesthetized rat model. This effect did not arise in rats given an equivalent caloric amount of glucose. We monitored physiological indexes associated with the state of anaesthesia in rats chronically implanted (seven days before the experiment) with electrodes and a transmitter. One day before the experiment, a silicon catheter was inserted into the rat's jugular vein. These procedures stressed the rats and their weight gain during recovery showed multiple dispersion, which was interpreted as an index of their nutritional status. Interestingly, we clarified that the weight gain during recovery and the degree of decreased Tb during anaesthesia was negatively and closely correlated in anesthetized rats given saline (y [decreased Tb] = -0.0558 × x [body weight gain in grams] + 7.8823, r = -0.65, n=9) and a balanced mixture of AAs (y = -0.167 × x + 7.7269, r = -0.66, n=9). This suggested not only that nutritional status affects the decrease in Tb during anaesthesia, but also that the inhibitory effect of AA on hypothermia during anaesthesia is profoundly involved in nutritional status. In other words, the prospective effect of AA on the attenuation of hypothermia during anaesthesia can be estimated before the start of surgery.

STIMULATION OF MUSCLE PROTEIN SYNTHESIS BY AA ADMINISTRATION DURING ANAESTHESIA [11]

Many reports have indicated that AAs attenuate hypothermia during anaesthesia, but the location where energy expenditure increase and how it affects internal heat accumulation remains obscure. The ratio of extrasplanchnic oxygen consumption to total oxidative metabolism increases in patients given an AA mixture during surgery as compared with alert individuals.[8] Intravenous administration of an AA mixture not only increases oxygen uptake but also augments blood flow in extrasplanchnic tissues in alert individuals.[10] Since skeletal muscle accounts for the largest proportion of body mass, an increase in heat production in the muscle would significantly contribute to the attenuation of hypothermia. Amino acids are remarkably effective at increasing energy expenditure via either the degradable pathway (gluconeogenesis and ureagenesis) or the nonoxidative disposal pathway (protein synthesis).[1] Whether AA administration affects protein synthesis or AA catabolism in tissues remains unknown.

We indicated that muscle protein synthesis results from AA administration in anesthetized and conscious rats, although the rate of protein synthesis (Ks) in skeletal muscle remained lower in the anesthetized, than in conscious rats. Co-infusion of an AA mixture and anesthetics synergistically elevated insulin levels. Anesthetics might augment insulin secretion affected by AA administration in the absence of neuronal-adrenal-feedback inhibition. Increasing insulin to supra-physiologic blood concentrations or correcting an insulin deficiency activates protein synthesis in skeletal muscle.[12-14] Therefore insulin increase in anesthetized rats given an AA mixture might play an important role in stimulating muscle protein synthesis. Indeed, we further demonstrated that the administration of both AA and an anaesthetic exerts a synergistic effect on the phosphorylation of translation initiation factors (S6K1 and 4E-BP1) and components in insulin-mTOR signalling. This suggests that elevated translation initiation might play a primary role in AA-induced stimulation of protein synthesis under anaesthesia. These responses are likely to be triggered by the elevated insulin levels that result from administering AA to anesthetized rats.

EFFECT OF DIFFERENT AA MIXTURES ON CORE BODY TEMPERATURE DURING ANAESTHESIA [9]

It was unknown whether different AA compositions caused different changes in Tb in anesthetized rats, although a report indicates that energy expenditure is altered in conscious rats. [15] We examined the effect of various AA mixtures on Tb in anesthetized rats to understand which AAs are involved in the attenuation of hypothermia during anesthesia. Firstly, we gave propofol-anesthetized rats A) a balanced AA mixture (% weight: 1.4% L-Leu, 0.8% L-Ile, 0.8% valine, 1.05 % L-Lys, 0.57% L-Thr, 0.2% L-Trp, 0.39% L-Met, 0.7% L-Phe, 0.1 % L-Cystine, 0.05% L-Tyr, 1.05% L-Arg, 0.5% L-His, 0.8% L-Ala, 0.5% L-Pro, 0.3% L-Ser, 0.59% Gly, 0.1% L-Asp and 0.1% L-Glu: 10% total AA conc.) , B) an essential AA mixture (the same composition to the balanced AA mixture without L- Cystine, L-Tyr, L-Ala, L-Pro, L-Ser, Gly, L-Asp and L-Glu) and C) another essential AA mixture (the same composition to the balanced AA mixture without L-Arg, L-His, L- Cystine, L-Tyr, L-Ala, L-Pro, L-Ser, Gly, L-Asp, L-Glu) at a rate of 14 mL/kg/hr for 3 hours during anaesthesia. All AA mixtures examined attenuated hypothermia during anaesthesia when compared with saline administration. Moreover, the inhibitory effect was not affected by the composition of the AA mixture.

We then examined the anti-hypothermic effect of AA mixtures without 1) branched chain AAs, 2) aromatic AAs, 3) basic AAs and 4) L-Met and L-Thr from the essential AA mixture (C). The results showed that Tb was significantly decreased only in rats given the AA mixture without branched chain AAs. We then examined the effect of a branched chain AAs mixture and a basic AAs mixture, where each AA composition is the same to the balanced AA mixture. The results showed that the Tb of rats given both test mixtures decreased, and that hypothermia was not inhibited. We postulated that branched chain AAs play an important role in the inhibitory effect of AAs because 1) leucine alone elicits whole body energy expenditure, 2) leucine alone stimulates muscle protein synthesis and 3) leucine and isoleucine produces relatively more ATP via reduction.[15, 16] However, Tb did not differ between rats given branched chain AAs or saline, implying that metabolic heat production and heat dissipation are simultaneously elicited by branched chain AAs via an unknown mechanism. However, since this study was designed solely to examine changes in Tb, further studies should investigate the relationship between Tb and respiratory gases. Moreover, each group of rats

received different amounts of total AAs, although the respective AA content was identical to that of the balanced AA mixture. The present study nevertheless demonstrated that the inhibitory effect of AAs on hypothermia during surgery was affected by the composition of the AA mixture and suggested that branched AAs are necessary, but do not solely prevent hypothermia.

RECENT TOPICS AND CONCLUSION

Thermogenesis after nutrient ingestion has been investigated in detail for many years, whereas studies of body temperature other than thermogenesis have a short history. The application of AAs in the prevention of hypothermia during anaesthesia has been translated into reality and the mechanism whereby the inhibitory effect of AAs is expressed has been examined using novel approaches. Recent results have shown that AAs are not only nutrients that elicit thermogenesis but that they also produce a synchronous increase in all major autonomic thermoregulatory defence thresholds (set point increase).[17] The relationship between the rate of muscle protein synthesis and body temperature has also been elucidated.[18]

Live cells proliferate and create organized tissues and thus increase order in the body, which, seems to contradict the second law of thermodynamics. This is possible because cells are not isolated systems in the thermodynamic sense. Cells absorb fuel from the environment and create intracellular order. The energy used in reactions to create order is dissipated as heat, which increases disorder in the surrounding milieu. Thus, total disorder is increased and consequently the second law of thermodynamics is satisfied. [19] The existence of AAs as proteins rather than as individual AA molecules can maintain intracellular order. Protein synthesis increases order whereas energy expended during reactions increases disorder in the intercellular milieu. The idea that AAs can prevent hypothermia during anaesthesia while also being the most efficient substrate for protein synthesis might agree with the notion that thermogenesis is closely associated with increases in the molecular order of AA.

AUTHOR DISCLOSURES

Ippei Yamaoka, no conflicts of interest, except that this paper is authored from Otsuka Pharmaceutical.

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