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**Modulation of core body temperature and energy metabolism by amino acids**

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**Abstract** Core body temperature fluctuates within a narrow range due to inherent thermoregulatory control. Anesthetics impair thermostatic mechanisms, which leads to hypothermia during surgical procedures. Hypothermia that arises during surgery is associated with postoperative complications, and it can be prevented by delivering intravenous solutions, containing amino acids, that have a higher thermic effect than other macronutrients. Recent studies using anesthetized rats have determined that infusion of intravenous amino acids increases plasma insulin concentrations under anesthesia much more than while conscious, and stimulates skeletal muscle protein synthesis via the insulin-mTOR pathway. The increases in insulin levels, under anesthesia, contribute to amino acid-induced elevations in skeletal muscle protein synthesis, energy metabolism and core body temperature. Amino acid infusions also elevate protein breakdown in skeletal muscle; and the resultant increase in muscular protein turnover is positively involved in the modification of core body temperature. These collateral results indicate that amino acids play a unique role in the control of core body temperature, which is a vital sign that is closely indicative of changes in physical status.

**Keywords**: thermogenesis, protein synthesis, anesthesia, hypothermia

**Introduction**

Energy is required to metabolize, oxidize or convert nutrients for storage, and consequently energy expenditure is affected after eating meals (nutrient-induced thermogenesis). Both the catabolism and anabolism of proteins or amino acids comprise many more energy-dependent reactions than lipid or glucose metabolism. The proportion of consumed energy against the amount of energy produced by each macronutrient is 30 - 40%, 5 - 10% and 0 - 3% for protein or amino acids, carbohydrate or glucose, and fat, respectively. Humans, therefore, experience such energy expenditure after meals as warmth.

Core body temperature (Tc) is defined as both internal thermogenesis and heat dissipation from blood vessels. The Tc of endotherms, such as humans, is not significantly changed by the external environment. However, Tc is affected by diurnal rhythms. When exposed to an environment that could cause Tc to decline, humans seek warmer environments and/or wear more clothes to maintain Tc in a specific range. These are examples of behavioral thermoregulation. Furthermore, the constriction and dilation of blood vessels in the skin surface with the environmental change, is referred to as autonomic thermoregulation. Recent advances in neuroscience research have clarified that the central nervous system can mimic Tc changes in response to cold and hot environments.

Not only general, but also epidural and spinal types of anesthesia can easily impair central Tc controls, resulting in a significant decline in Tc during surgical procedures. Heat redistribution, due to vasodilation after inducing anesthesia, initially contributes to Tc declines. In addition, the thermoregulatory Tc set-point falls in response to lowered Tc caused by anesthesia. Anesthesia causes a 30 - 40% decrease in metabolic rates compared with conscious states, and the Tc decline itself weakens thermogenesis, leading to a further decline in Tc during anesthesia. Adverse consequences abound in the clinical setting when Tc declines during surgery except for therapeutic hypothermia protocols such as cerebral hypothermia. A deterioration in Tc, of even only a few degrees Celsius around surgical periods, significantly prolongs the duration of anesthetic or muscular relaxant action, induces intensive shivering, and increases hemorrhage volume due to disordered blood coagulation. From the long-term viewpoint, such a decline in Tc also relates to increased wound infection and prolonged hospital stay. Therefore, hypothermia during surgical procedures is a problem in terms of medical care costs. The usage of heat devices such as hot-water mats or warmed air or elevating the operating room temperature helps to maintain Tc of surgical patients within a constant range. Swedish anesthesiologists origi-
nally applied the concept of thermogenesis induced by amino acid ingestion during 1990 to prevent hypothermia during surgery\textsuperscript{5}. Rectal temperature was significantly higher among patients undergoing elective hysterectomy, who were infused with a mixture of amino acids for one or two hours before anesthesia induction than those who received saline. Many articles have since been published, and a novel methodology in which intravenous solutions warm patients from inside the body is under development. By contrast, the mechanisms, underlying how amino acid infusion prevents Tc falling during surgical procedure, remain obscure.

**Contribution of insulin to core body temperature, thermogenesis and skeletal muscle protein synthesis during anesthesia**

Intravenously infused amino acid mixtures prevent hypothermia under anesthesia in rats, whereas glucose and lipids do not. These findings suggest that the thermal response positively reflects the amount of energy consumed when each nutrient is metabolized. The metabolic fate of infused amino acids largely comprises direct oxidation including ureogenesis and substrates for de novo protein synthesis. Because both reactions require energy, thermogenesis would occur regardless of which pathway was utilized. We focused on protein synthesis in skeletal muscle, because the proportion of this type of muscle in the human body is extremely large, and thus a considerable amount of heat should be generated. Rates of protein synthesis are actually higher in the skeletal muscle of anesthetized rats that are intravenously administered with a mixture of amino acids than in those given saline; and they are similar to those in conscious rats given amino acids\textsuperscript{9}. The obvious elevation of plasma insulin concentrations in anesthetized rats given amino acids, compared to their conscious counterparts, is of particular interest. Insulin stimulates muscle protein synthesis by activating translation initiation factors via the mammalian target of rapamycin (mTOR) signaling pathway. Infused amino acid phosphorylates protein kinase B (PKB), mTOR and translation initiation factors (S6-K1 and 4E-BP1) in the skeletal muscles of anesthetized rats more than the amino acid-infused conscious rats. These results suggest that the administration of amino acids during anesthesia enhances muscle protein synthesis via the insulin-mTOR-dependent activation of translation initiation factors that are mainly induced by elevated plasma insulin concentrations. Thus, thermal accumulation in the body is facilitated. Clinical studies of surgical patients, thereafter, have also found that amino acid-induced elevation in plasma insulin concentrations increases protein synthesis\textsuperscript{7,8}. However, precisely how elevated plasma insulin concentrations and/or muscle protein synthesis directly help to alleviate hypothermia during anesthesia remains unknown. We therefore investigated the physiological role of elevated plasma insulin concentrations. Administration of the pancreatic hormone somatostatin with amino acids lowered plasma insulin concentrations during anesthesia irrespective of amino acid administration\textsuperscript{9}. The attenuated hypothermia induced by amino acids was abrogated and accompanied by significantly reduced metabolism. Furthermore, the elevated rates of muscle protein synthesis were reduced to control levels. Western blotting revealed that somatostatin had significantly weakened the phosphorylation of insulin-mTOR signaling components and translation initiation factors. These results support the notion that markedly elevated insulin triggers the linked acceleration of heat accumulation, energy metabolism, and muscle protein synthesis.

**Protein turnover and heat accumulation during anesthesia**

The building blocks of protein synthesized de novo are provided by the free amino acid pool, which includes not only exogenous amino acids given but also amino acids derived from extant protein. If muscle protein synthesis is stimulated for a short period after amino acid administration, a sufficient amount of amino acids will be recruited from extant muscle protein for protein synthesis reactions. We tested the hypothesis that infused amino acids enhance not only protein synthesis but also protein breakdown in skeletal muscle in anesthetized rats. We measured plasma concentrations of 3-methylhistidine, an index of myofibrillar protein breakdown, in anesthetized and conscious rats given amino acids or saline\textsuperscript{10}. Plasma 3-methylhistidine concentrations were higher in both anesthetized and conscious rats given amino acids compared with those that were not. Plots of plasma 3-methylhistidine concentrations vs. rectal temperature confirmed a positive correlation between these two parameters. Considering that administering amino acids results in subsequent muscle protein synthesis, an infusion of amino acids enhances muscular protein turnover, which contributes to the alleviation of hypothermia during anesthesia. We found that glucose infused into anesthetized rats inhibits muscular protein breakdown that is enhanced by surgical insult via the ubiquitin proteasome system\textsuperscript{11}. Whether infused amino acids modulate a similar pathway to that through which glucose infusion enhances myofibrillar breakdown remains to be determined.

Amino acids elevate systemic energy expenditure. The present report reviewed the growing popularity of amino acid usage among anesthesiologists to attenuate hypothermia during anesthesia. We also outlined a possible mechanism wherein muscular protein turnover plays a key role in the modification of energy metabolism and Tc. Although the notion of avoiding food and fluids on the night before surgery prevails, preoperatively providing patients with an oral rehydration solution relieves the need for intravenous delivery and reduces preoperative
stress. It was reported that providing preoperative oral amino acids to an experimental rat model also helped to prevent hypothermia during anesthesia, thus indicating a new clinical strategy\(^{12}\). Another plausible mechanism is that amino acids elevate thermoregulatory set-points such as vasoconstriction and shivering that helps to defend against a decrease in Tc\(^{13}\). Furthermore, the attenuation of hypothermia requires branched chain amino acids \(^{14}\). The anti-hypothermic effect of amino acids was not confirmed in a rat model of muscular atrophy, supporting the notion that involvement of increased amino acid metabolism in skeletal muscle is involved in this process\(^{15}\). The presence of amino acids as protein rather than as amino acids can maintain order in cell units. Increasing the order inside of the cell causes both extracellular disorder and heat production. The notion that amino acids can simultaneously prevent hypothermia during anesthesia and stimulate protein synthesis might agree with the notion that thermogenesis caused by incremental disorder is closely associated with increases in the ordered state of biological molecules.

References