

# Effect of Amino Acid Infusion on Central Thermoregulatory Control in Humans

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**Background:** Administration of protein or amino acids enhances thermogenesis, presumably by stimulating oxidative metabolism. However, hyperthermia results even when thermoregulatory responses are intact, suggesting that amino acids also alter central thermoregulatory control. Therefore, the authors tested the hypothesis that amino acid infusion increases the thermoregulatory set point.

**Methods:** Nine male volunteers each participated on 4 study days in randomized order: (1) intravenous amino acids infused at  $4 \text{ kJ} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  for 2.5 h combined with skin-surface warming, (2) amino acid infusion combined with cutaneous cooling, (3) saline infusion combined with skin-surface warming, and (4) saline infusion combined with cutaneous cooling.

**Results:** Amino acid infusion increased resting core temperature by  $0.3 \pm 0.1^\circ\text{C}$  (mean  $\pm$  SD) and oxygen consumption by  $18 \pm 12\%$ . Furthermore, amino acid infusion increased the calculated core temperature threshold (triggering core temperature at a designated mean skin temperature of  $34^\circ\text{C}$ ) for active cutaneous vasodilation by  $0.3 \pm 0.3^\circ\text{C}$ , for sweating by  $0.2 \pm 0.2^\circ\text{C}$ , for thermoregulatory vasoconstriction by  $0.3 \pm 0.3^\circ\text{C}$ , and for thermogenesis by  $0.4 \pm 0.5^\circ\text{C}$ . Amino acid infusion did not alter the incremental response intensity (*i.e.*, gain) of thermoregulatory defenses.

**Conclusions:** Amino acid infusion increased the metabolic rate and the resting core temperature. However, amino acids also produced a synchronous increase in all major autonomic thermoregulatory defense thresholds; the increase in core temperature was identical to the set point increase, even in a cold environment with ample potential to dissipate heat. In subjects with intact thermoregulatory defenses, amino acid-induced hyperthermia seems to result from an increased set point rather than increased metabolic rate *per se*.

INTRAOPERATIVE core temperature depends both on distribution of heat within the body and on systemic heat balance. During the first hour of anesthesia, core-to-peripheral redistribution of heat is the primary cause

of core hypothermia.<sup>1</sup> Subsequently, however, hypothermia results from heat loss exceeding heat production.<sup>2</sup> Core temperature during this second phase of the hypothermia curve therefore depends on systemic heat balance. Because anesthetics profoundly impair thermoregulatory control,<sup>3,4</sup> factors that increase thermogenesis or reduce loss of heat to the environment moderate the rate at which intraoperative hypothermia develops.<sup>5-7</sup>

Ingestion of glucose or fat only minimally increases the metabolic rate. However, enteral or parenteral administration of protein or an amino acid mixture stimulates oxidative metabolism, typically increasing the metabolic rate approximately 20%.<sup>8,9</sup> This postprandial hypermetabolism far exceeds the obligatory metabolic cost of digestion, absorption, processing, and storage of administered nutrients.<sup>10</sup> As might therefore be expected, thermogenesis associated with amino acid infusions have been shown in numerous studies to help preserve intraoperative core temperature<sup>5,11</sup> and to moderate complications associated with hypothermia.<sup>12-14</sup>

An interesting consequence of the hypermetabolism associated with protein ingestion or amino acid infusion is that each increases core temperature, even when thermoregulation remains intact (*i.e.*, in unanesthetized volunteers).<sup>8,9</sup> Although hyperthermia might seem to be a logical consequence of hypermetabolism, this is the case only in the absence of effective thermoregulatory control (*e.g.*, during anesthesia) because thermoregulatory defenses normally maintain core temperature despite alterations in heat production or heat loss. A single light cotton blanket, for example, reduces heat loss by approximately 30%,<sup>15</sup> which improves systemic heat balance more than the hypermetabolism associated with protein or amino acid administration. However, a blanket does not normally provoke hyperthermia because thermoregulatory defenses maintain core temperature.

The observation that hyperthermia results from protein ingestion or amino acid infusion in volunteers with intact thermoregulation suggests that these treatments produce a regulated increase in core temperature. Thermoregulatory defenses are best characterized by their thresholds (core temperature triggering defense activation) and gain (incremental increase in response intensity as core temperature deviates from the threshold). The major thermoregulatory defenses in humans are sweating, active precapillary vasodilation, arteriovenous shunt vasoconstriction, and thermogenesis.<sup>16</sup> A synchronous change in all autonomic thresholds can be considered a set point alteration. Therefore, we tested the

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**Table 1. Baseline Values (before Saline or Amino Acid Infusion)**

	Saline	Amino Acid
Mean arterial pressure, mmHg	86 ± 18	92 ± 21
Heart rate, beats/min	59 ± 19	64 ± 12
Oxygen consumption, ml/min	204 ± 48	210 ± 46
Esophageal temperature, °C	36.75 ± 0.37	36.68 ± 0.27
Mean skin temperature, °C	32.34 ± 0.46	32.22 ± 0.54
Epinephrine, ng/ml	0.04 ± 0.07	0.05 ± 0.03
Norepinephrine, ng/ml	0.20 ± 0.12	0.23 ± 0.09

Values are expressed as mean ± SD for nine subjects. There were no statistically significant differences between the infusion days.

hypothesis that an amino acid infusion increases the thermoregulatory set point.

## Materials and Methods

With approval by the Review Board on Human Experiments of Kyoto Prefectural University of Medicine (Kyoto, Japan), written informed consent was obtained from nine healthy men. Their average age was 26 ± 6 yr, their body weight was 69 ± 3 kg, and their height was 172 ± 6 cm (mean ± SD).

### Protocol

Each volunteer participated on 4 different study days, separated by at least 6 days. We tested autonomic thermoregulatory responses to external heating and cooling (designated as the heat test and the cold test) after amino acid infusion and saline infusion. The order of the experiments was randomized. To avoid circadian variations, the studies started at 09:00 each day. Volunteers refrained from salty food and beverages containing caffeine or alcohol beginning the night before the experiment. They were not allowed to eat breakfast but could drink water.

After voiding, subjects entered a chamber in which ambient temperature was maintained at 28°C and relative humidity was maintained at 30%. Each subject wore only thin cotton trunks. A 22-gauge intravenous catheter was inserted in an antecubital vein for the administration of amino acids. Another 22-gauge intravenous catheter was placed in a contralateral antecubital vein for blood sampling. Throughout each study day, the volunteers assumed an upright sitting position, leaning against a backrest.

After a 30-min rest period during which baseline data were collected (table 1), amino acid (Teruamino 12, a mixture of 18 amino acids, 18 gN<sub>2</sub>/l; Terumo, Tokyo, Japan) or saline infusion was given for 150 min/randomization. The solutions were given at a rate of 2 ml · kg<sup>-1</sup> · h<sup>-1</sup>, which corresponded, in the case of amino acid, to 4 kJ · kg<sup>-1</sup> · h<sup>-1</sup>. Subjects were monitored during the infusion and for 60 subsequent minutes. Depending on

the randomization, the participants were then either warmed or cooled.

Warming consisted of the volunteers immersing their lower legs into water at 42°C. Leg heating was maintained until active vasodilation and sweating were observed. Ambient temperature was maintained at 28°C, with a relative humidity of 30% during warming. Alternatively, the volunteers were warmed with a water-perfused suit that covered the entire body except the face, head, forearm, and fingers. Warm water (approximately 40°C) was circulated through the water-perfused suit for approximately 10 min until active cutaneous vasodilation was observed. Core temperature was then decreased at a rate of approximately 2°C/h by reducing mean skin temperature approximately 7.0°C/h by progressively reducing the circulating-water temperature. Cooling continued until vasoconstriction and vigorous shivering were observed, a process that typically took approximately 70 min. Ambient temperature was maintained at 18°C, with a relative humidity of 30% during cooling.

### Measurements

Core temperature was measured in the distal esophagus with a thermocouple probe in polyethylene tubing (PE-90; Clay Adams, Parsippany, NJ) that was positioned at a distance of one fourth of the subject's standing height from the external nares.<sup>17</sup> Skin temperature was measured on the forehead, chest, back, forearm, thigh, and calf. Forearm skin temperature was measured on the noninfused arm. Mean skin temperature was calculated from the body surface area distribution and thermal sensitivity of each skin area.<sup>18</sup>

Heart rate was continuously monitored using an electrocardiogram recorder, and blood pressure was measured every 5 min in the noninfused arm (model STBT-780; Colin, Nagoya, Japan). Mean arterial pressure was calculated as (SBP/3)+DBP, where SBP is systolic blood pressure and DBP is diastolic blood pressure.

The sweating rate on the chest was estimated using a ventilated capsule. Anhydrous air was flushed across a 6-cm-diameter circle of skin surrounded by an airtight adhesive ostomy appliance at a rate of 2.0 l/min. Cutaneous water loss was calculated from the gas flow rate, gas temperature, and relative humidity (HMP233 L; Visala, Helsinki, Finland). The sweating rate on the chest was expressed as mg · cm<sup>-2</sup> · min<sup>-1</sup>. This is a well-established method.<sup>19</sup>

Skin blood flow was assessed with a laser-Doppler flowmeter (ALF21; Advance, Tokyo, Japan) on the noninfused forearm during heating and on the noninfused middle finger during cooling.<sup>17</sup> Cutaneous vascular conductance was calculated from the output voltage indicated by the laser-Doppler flowmeter and mean arterial pressure, which was presented as the percent change from the mean value obtained before heating or cooling.

Oxygen consumption is the most reliable method of quantifying thermogenesis.<sup>20</sup> Oxygen consumption was therefore determined at 1-min intervals using a flow/gas analyzer (Aeromonitor AE260; Minato, Tokyo, Japan).

Blood samples were collected before the amino acid (or saline) infusion started, immediately after completion of the infusion, and 1 h after completion of the infusion (before heating or cooling). Plasma aliquots for the measurement of hormone concentrations were centrifuged at 4°C and stored at -80°C until the hormone and amino acid assays were performed. To determine free plasma amino acid concentrations, high-performance liquid chromatography (JLC-300V; JEOL, Tokyo, Japan) was performed using the ninhydrin method. The detection limit of the assay was 1 nM, and the intraassay and interassay coefficients of variation were less than 3%. Catecholamine concentrations were also determined by high-performance liquid chromatography (HLC-725CA; Tosoh, Tokyo, Japan) using an electrochemical detector after alumina extraction. The detection limit of the assay was 8 pg/ml, and the intraassay and interassay coefficients of variation were less than 5%.

#### Data and Statistical Analysis

The core temperature thresholds for sweating, vasodilation, and thermogenesis were defined by the core temperatures triggering sustained sweating, forearm cutaneous vascular conductance, and total body oxygen consumption increases of 25% above baseline values.<sup>4,21</sup> The core temperature threshold for vasoconstriction was defined by the core temperature triggering a reduction in fingertip-skin vascular conductance to at least 50% of the baseline value.<sup>22</sup> The threshold was individually determined for each condition in each subject by the same inspector who was blinded to the experimental conditions. Thermal responsiveness (gain) was defined by the slope of the linear portion of each thermoregulatory response above or below the threshold core temperature and was calculated by least-squares linear regression on an individual basis.

To compare thresholds between conditions in which both core temperature and mean skin temperature were changing, the following equation was used to correct the core temperature ( $T_c$ ) for a designated mean skin temperature ( $\bar{T}_{SK}$ ):

$$\text{Calculated } T_c = T_c + [\beta/(1 - \beta)] [\bar{T}_{SK} - \text{Designated } \bar{T}_{SK}],$$

where designated  $\bar{T}_{SK}$  was set as 34°C, and  $\beta$  was the fractional contribution of the skin to the vasoconstriction and shivering response (0.2) and to the vasodilation and sweating response (0.1). This methodology is well established.<sup>4</sup>

Morphometric data, thresholds, and thermal responsiveness were analyzed by two-tailed paired *t* tests. The effects of amino acid infusion on the cardiovascular, temperature, and metabolic responses were analyzed by

**Table 2. Plasma Amino Acid Concentrations (nM/ml)**

	Baseline	Immediately after Infusion Completion	1 h after Infusion Completion
Aspartate	3 ± 3	18 ± 25*	3 ± 3
Glutamate	52 ± 9	67 ± 25*	52 ± 19
Asparagine	49 ± 10	30 ± 9*	30 ± 7*
Serine	132 ± 15	230 ± 90*	151 ± 21
Glutamine	590 ± 57	604 ± 34	572 ± 60
Histidine	83 ± 6	142 ± 63*	92 ± 13
Glycine	250 ± 48	675 ± 423*	325 ± 58*
Threonine	150 ± 36	255 ± 105*	160 ± 33
Citrulline	34 ± 7	50 ± 13*	41 ± 10
Taurine	38 ± 7	37 ± 7	32 ± 2*
Arginine	92 ± 9	277 ± 129*	129 ± 22*
Alanine	358 ± 70	471 ± 157*	283 ± 46
Tyrosine	53 ± 9	65 ± 18	47 ± 9
α-Amino Butyrate	21 ± 7	25 ± 7	25 ± 6
Methionine	26 ± 3	108 ± 42*	51 ± 12*
Valine	239 ± 27	526 ± 126*	361 ± 54*
Phenylalanine	53 ± 6	227 ± 88*	119 ± 25*
Isoleucine	69 ± 12	177 ± 73*	80 ± 21
Leucine	135 ± 18	398 ± 145*	212 ± 39*
Ornithine	59 ± 9	126 ± 27*	82 ± 16*

Values, which are the average of the two trials, are expressed as mean ± SD for nine subjects.

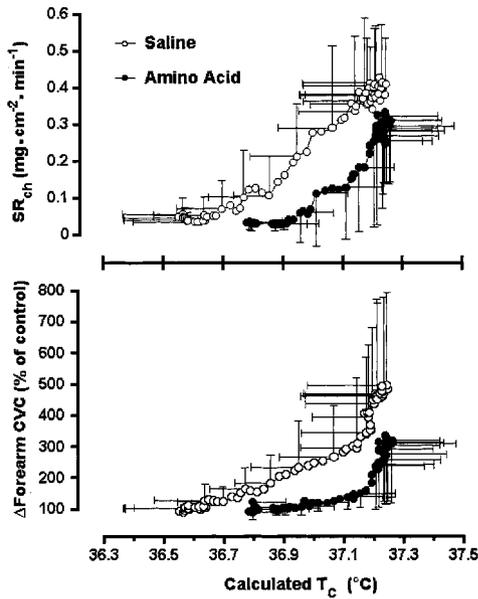
\*  $P < 0.05$  compared with baseline level.

a general linear regression model for analysis of variance with repeated measures (two within, zero between factors), followed by Student-Newman-Keuls multiple comparison tests. All data are reported as mean ± SD;  $P < 0.05$  was considered statistically significant.

#### Results

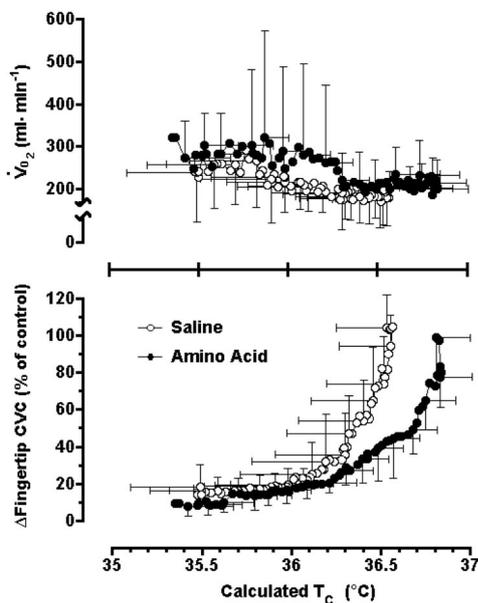
Cardiovascular, thermal, metabolic, and plasma catecholamine variables were similar before saline or amino acid infusion (table 1). Amino acid infusion increased core temperature by  $0.3 \pm 0.1^\circ\text{C}$  and oxygen consumption by  $18 \pm 12\%$ . Mean arterial pressure, heart rate, mean skin temperature, and plasma epinephrine and norepinephrine concentrations did not differ significantly during infusion of amino acid or saline (data not shown). Core temperature stabilized within 1 h after the infusion was completed. Table 2 shows plasma amino acid concentrations before infusion, immediately after completion of the amino acid infusion, and 1 h later. Plasma amino acid concentrations 1 h after completion of the amino acid infusion decreased toward baseline values, indicating that the amino acids were metabolized.

During warming, core temperature increased at a rate of  $0.6 \pm 0.3^\circ\text{C/h}$  with the saline infusion and  $0.4 \pm 0.3^\circ\text{C/h}$  with the amino acid infusion. During cooling, calculated core temperature decreased at a rate of  $1.7 \pm 0.6^\circ\text{C/h}$  with the saline infusion and  $2.3 \pm 0.6^\circ\text{C/h}$  with the amino acid infusion. Sweating rate, active cutaneous vasodilation, oxygen consumption, and cutaneous vasoconstriction as a function of calculated core temperature are shown in figures 1 and 2.



**Fig. 1.** Sweating rate on chest ( $SR_{ch}$ ; *top*) or forearm cutaneous vascular conductance (CVC; *bottom*) as a function of calculated core temperature ( $T_c$ ) during heating. Amino acid infusion significantly increased the threshold for sweating and cutaneous vasodilation. Values are plotted at 1-min intervals and shown as mean  $\pm$  SD for nine men.

Mean skin, core temperatures at the onset of each thermoregulatory response, the thresholds calculated from these values, gains, and hemodynamic responses are summarized in table 3. Amino acid infusion increased the calculated core temperature threshold for active cutaneous vasodilation by  $0.3 \pm 0.3^\circ\text{C}$ , for sweating by



**Fig. 2.** Oxygen consumption ( $\dot{V}O_2$ ; *top*) or fingertip cutaneous vascular conductance (CVC; *bottom*) as a function of calculated core temperature ( $T_c$ ) during cooling. Amino acid infusion significantly increased the threshold for thermogenesis and cutaneous vasoconstriction. Values are plotted at 1-min intervals and shown as mean  $\pm$  SD for nine men.

**Table 3.** Mean Skin Temperatures, Core Temperatures, Calculated Thresholds, and Gains

	Saline	Amino Acid
<b>Sweating</b>		
Mean skin, $^\circ\text{C}$	$32.5 \pm 0.3$	$32.2 \pm 0.7$
Measured core, $^\circ\text{C}$	$36.9 \pm 0.3$	$37.2 \pm 0.4^*$
Calculated threshold, $^\circ\text{C}$	$36.7 \pm 0.3$	$37.0 \pm 0.3^*$
Gain, $\text{mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1} \cdot ^\circ\text{C}^{-1}$	$0.8 \pm 0.4$	$1.0 \pm 0.7$
<b>Vasodilation</b>		
Mean skin, $^\circ\text{C}$	$32.5 \pm 0.4$	$32.1 \pm 0.7$
Measured core, $^\circ\text{C}$	$37.0 \pm 0.3$	$37.3 \pm 0.3^*$
Calculated threshold, $^\circ\text{C}$	$36.8 \pm 0.3$	$37.0 \pm 0.3^*$
Gain, $\% / ^\circ\text{C}$	$444 \pm 421$	$810 \pm 1404$
MAP, mmHg	$90 \pm 15$	$87 \pm 21$
Heart rate, beats/min	$78 \pm 18$	$80 \pm 18$
<b>Thermogenesis</b>		
Mean skin, $^\circ\text{C}$	$29.3 \pm 1.9$	$31.1 \pm 1.5^*$
Measured core, $^\circ\text{C}$	$37.0 \pm 0.3$	$37.0 \pm 0.4$
Calculated threshold, $^\circ\text{C}$	$35.8 \pm 0.3$	$36.2 \pm 0.3^*$
Gain, $\text{ml} \cdot \text{min}^{-1} \cdot ^\circ\text{C}^{-1}$	$-149 \pm 180$	$-100 \pm 166$
<b>Vasoconstriction</b>		
Mean skin, $^\circ\text{C}$	$31.4 \pm 1.2$	$32.2 \pm 0.9$
Measured core, $^\circ\text{C}$	$37.0 \pm 0.4$	$37.1 \pm 0.3$
Calculated threshold, $^\circ\text{C}$	$36.3 \pm 0.4$	$36.6 \pm 0.3^*$
Gain, $\% / ^\circ\text{C}$	$24 \pm 15$	$36 \pm 30$
MAP, mmHg	$92 \pm 24$	$95 \pm 21$
Heart rate, beats/min	$75 \pm 18$	$77 \pm 24$

Thresholds were calculated based on a designated mean skin temperature of  $34^\circ\text{C}$ . Mean arterial pressure (MAP) and heart rate values were recorded at the threshold. Results are presented as mean  $\pm$  SD for nine subjects.

\* $P < 0.05$  compared with saline infusion condition.

$0.2 \pm 0.2^\circ\text{C}$ , for thermoregulatory vasoconstriction by  $0.3 \pm 0.3^\circ\text{C}$ , and for thermogenesis by  $0.4 \pm 0.5^\circ\text{C}$  compared with saline infusion. In contrast, amino acid administration did not alter the gain of any thermoregulatory defense.

**Discussion**

It is well established that amino acid infusion provokes thermogenesis<sup>5,11</sup> and hyperthermia,<sup>9</sup> and our results confirm previous observations. However, our results also indicate that amino acid infusion synchronously increases the triggering threshold for all major autonomic thermoregulatory defenses in humans, which is equivalent to a set point increase. Therefore, amino acids influence both peripheral heat production and central thermoregulatory control.

Synchronous increases in each of the major autonomic thermoregulatory thresholds suggest an alteration in central thermoregulatory function rather than the summation of individual peripheral actions related to each thermoregulatory defense. The mechanisms by which amino acid infusion increases the set point were not addressed in this study and remain unknown. However, peripherally infused amino acids are unlikely to cross the blood-brain barrier. It is therefore unlikely that amino acids directly alter central thermoregulatory control.

One potential mediator is the sympathetic nervous

system. This is relevant because the thermic effects of nutrition are divided into an obligatory component, which represents the theoretical metabolic costs for processing and storing ingested nutrients, and a facultative component, which augments systemic energy expenditure and is reportedly attributable to central activation of the sympathoadrenal system.<sup>23-25</sup> However, intravenous administration of amino acid solutions to tetraplegic patients causes a normal or even supranormal increase in metabolic rate, even though pathways connecting the brain with the peripheral sympathetic nerve pathways to the brain are severed in these patients and they typically exhibit low peripheral sympathetic nervous system activity.<sup>26</sup> Plasma epinephrine and norepinephrine concentrations did not increase after amino acid infusion in our volunteers. Furthermore, increased hypothalamic catecholamine concentrations are associated with hypothermia rather than hyperthermia.<sup>27,28</sup> Taken together, these data suggest that amino acids do not increase the thermoregulatory set point by activating the sympathoadrenal system.

An additional mechanism by which amino acid infusion might increase the thermoregulatory set point is *via* metabolites that alter central thermoregulatory control. Alternatively, amino acid infusion might activate peripheral receptors and thus afferent pathways. This possibility is by no means unprecedented: for example, the pyrogenic effect of many cytokines is mediated *via* the vagus nerve.<sup>29,30</sup> Although the hyperthermia associated with amino acid infusion resembles fever in being a set point increase, it is presumably not mediated by endogenous pyrogens and cannot be blocked by prostaglandin inhibitors such as acetaminophen.<sup>31</sup> Hyperthermia associated with amino acid infusion also differs from the temperature elevation associated with exercise that simultaneously reduces the sweating threshold.<sup>32</sup> In contrast, the synchronous elevation of all major autonomic thermoregulatory thresholds is reminiscent of the menstrual cycle and circadian rhythm, both of which produce similar increases in the set point.<sup>33,34</sup> Our current results are consistent with the observation that an amino acid infusion increases the threshold for vasoconstriction during spinal anesthesia.<sup>11</sup>

Hyperthermia in response to amino acid infusion has been considered a passive response to hypermetabolism and the resulting thermogenesis. This interpretation is likely correct during anesthesia when thermoregulatory defenses are profoundly impaired.<sup>16</sup> However, it is interesting to note that the increase in core temperature was identical to the increase in set point. Furthermore, with either saline or amino acid infusion, measured core temperatures were virtually identical during warming and cooling. That core temperature did not decrease during intense cooling (and therefore considerable heat loss) indicates that core temperature was actively maintained with vasoconstriction and thermogenesis according to

the central thermoregulatory control. This conclusion is consistent with the general theory that, over a wide range of metabolic rates and ambient environments, central thermoregulatory processing dominates control of core temperature.

In summary, amino acid infusion increased both metabolic rate and resting core temperature. However, amino acids also produced a synchronous increase in all major autonomic thermoregulatory defense thresholds (*i.e.*, a set point increase), and the increase in core temperature was identical to the set point increase. In subjects with intact thermoregulatory defenses, it is likely that amino acid-induced hyperthermia results from a set point increase rather than an augmented metabolic rate *per se*.

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