

# Oral L-Tyrosine Supplementation Improves Core Temperature Maintenance in Older Adults

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## ABSTRACT

LANG, J. A., A. C. KRAJEK, K. S. SCHWARTZ, and J. E. RAND. Oral L-Tyrosine Supplementation Improves Core Temperature Maintenance in Older Adults. *Med. Sci. Sports Exerc.*, Vol. 52, No. 4, pp. 928–934, 2020. **Introduction:** During cold exposure, an increase in sympathetic nerve activity evokes vasoconstriction (VC) of cutaneous vessels to minimize heat loss. In older adults, this reflex VC response is impaired thereby increasing their susceptibility to excess heat loss and hypothermia. Because L-tyrosine, the amino acid substrate necessary for catecholamine production, has been shown to augment reflex VC in age skin, we hypothesize that oral ingestion of L-tyrosine will attenuate the decline in core temperature ( $T_c$ ) during whole-body cooling in older adults. **Methods:** In a randomized, double-blind design, nine young ( $25 \pm 3$  yr) and nine older ( $72 \pm 8$  yr) participants ingested either 150 mg·kg<sup>-1</sup> of L-tyrosine or placebo before commencing 90 min of whole-body cooling to decrease skin temperature to approximately 29.5°C. Esophageal temperature and forearm laser Doppler flux (LDF) were measured continuously throughout the protocol to provide an index of  $T_c$  and skin blood flow, respectively. The change in esophageal temperature ( $\Delta T_{ES}$ ) was the difference in temperature at the end of cooling subtracted from baseline. Cutaneous vascular conductance (CVC) was calculated as  $CVC = LDF/\text{mean arterial pressure}$  and expressed as a percent change from baseline ( $\% \Delta CVC_{\text{BASELINE}}$ ). **Results:** Oral tyrosine ingestion augmented the cutaneous VC response to cooling in older adults (placebo,  $14.4 \pm 2.0$ ; tyrosine,  $32.7\% \pm 1.7\% \Delta CVC_{\text{BASELINE}}$ ;  $P < 0.05$ ). Additionally, tyrosine improved  $T_c$  maintenance throughout cooling in older adults (placebo,  $-0.29 \pm 0.07$ ; tyrosine,  $-0.07 \pm 0.07 \Delta T_{ES}$ ;  $P < 0.05$ ). Both the cutaneous VC and  $T_c$  during cooling were similar between young and older adults supplemented with tyrosine ( $P > 0.05$ ). **Conclusions:** These results indicate that L-tyrosine supplementation improves  $T_c$  maintenance in response to acute cold exposure in an older population. **Key Words:** SKIN BLOOD FLOW, TEMPERATURE REGULATION, AGING, WHOLE-BODY COOLING, REFLEX VASOCONSTRICTION, COLD PERCEPTION

Advancing age is accompanied by a decline in thermoregulatory responses to cold exposure. This is evidenced by an inability for older adults to maintain core temperature ( $T_c$ ) at cold air exposures ranging from 5°C to 10°C ambient temperature ( $T_a$ ) (1–3). However, even during mild cold exposure ( $T_a = \sim 22^\circ\text{C}$ ) while dressed in only undergarments, older adults exhibited a steady decline in esophageal temperature ( $T_{ES}$ ) ( $\sim 0.2^\circ\text{C}$ ) that became significantly lower than young after only approximately 30 min of cooling (4). These findings are consistent with the fact that over half of all hypothermia-related deaths occur in adults older than 65 yr (5,6). The mechanisms to maintain  $T_c$ , namely, metabolic heat production and cutaneous vasoconstriction (VC), are impaired in older adults (1,7–9). The majority of studies report that cold-induced heat production is lower in older adults (7).

Moreover, the reflex cutaneous VC response, which immediately functions to minimize heat loss to the environment, is approximately half of what is observed in young for a given cooling stimulus (10–13). Cumulatively, reduced heat production and greater heat loss during cold exposure increases the susceptibility to hypothermia in older adults (4,7). This increased risk may be exacerbated by reduced perception of cooling stimuli (14). Thus, it is of clinical importance to investigate interventions that mitigate the decline in  $T_c$  that occurs during cold exposure in older adults.

Administration of L-tyrosine, the amino acid substrate for the rate-limiting enzyme tyrosine hydroxylase in catecholamine biosynthesis, increases the cutaneous VC response during cold exposure in older adults (15,16). To sustain norepinephrine (NE) release and VC during cold stress, sufficient sympathetic nerve firing and an adequate axonal pool of L-tyrosine are required (17,18). In activated neurons, there is evidence indicating that tyrosine in the vicinity of tyrosine hydroxylase may become depleted (18). Furthermore, increased oxidative and nitrosative stress with aging may reduce axonal tyrosine during times of increased sympathetic activity and catecholamine production (19–21). With localized skin perfusion or oral ingestion of L-tyrosine, the compromised reflex cutaneous VC response in older adults is ameliorated, such that the VC is similar in magnitude to that of young (15,16). However, the extent to which increased VC improves  $T_c$  maintenance and

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protects against hypothermia during mild cold stress in older adults is unknown.

Studies that have incorporated L-tyrosine supplementation have found that tyrosine enhances cognitive and psychomotor performance in young adults during cold stress (22–24); however, the impact of L-tyrosine on thermoregulatory function during cooling is unclear. As an extension of our previous work demonstrating that oral ingestion of L-tyrosine augmented reflex VC in age skin (16), the primary purpose of this study was to determine the extent to which the augmented VC response improved  $T_{ES}$  maintenance during mild cold stress in older adults. Using a similar oral dose of L-tyrosine and randomized placebo-controlled design, we hypothesized that older adults supplemented with tyrosine will exhibit a greater cutaneous VC response during 90 min of whole-body cooling, and the increased VC will correspond to a reduction in their decline in  $T_{ES}$ .

## METHODS

**Subjects.** Experiments adhered to the standards set by the Declaration of Helsinki and were approved by the Des Moines University Institutional Review Board. Voluntary written and verbal informed consent were obtained from 9 young ( $25 \pm 3$  yr, 2 women, 7 men) and 9 older ( $72 \pm 8$  yr, 4 women, 5 men) subjects. Older adults were given a Mini-Mental State Exam (score =  $29 \pm 1$ ) to test for cognitive impairment that may affect their ability to provide informed consent. The screening process consisted of a fasting blood draw and anthropometric measurements. Skinfold thickness was measured in duplicate at seven sites (chest, axilla, triceps, subscapula, abdomen, suprailium, thigh) for percent body fat calculation. All subjects were healthy, normotensive, nondiabetic, non-smokers, nonobese, normal cholesterol, and not taking any medications or vitamin supplements that may impact cardiovascular or thermoregulatory function (Table 1). Older women had not previously taken hormone replacement therapy. Young women ( $n = 2$ ) were taking oral contraceptives. Before each experiment, subjects abstained from alcohol and caffeine ( $>12$  h) and strenuous physical activity ( $>24$  h). Participants were instructed to eat a light breakfast devoid of tyrosine-rich food  $>3$  h before the experiment and then fast thereafter.

TABLE 1. Subject characteristics.

Variables	Young	Older
Age (yr)	$25 \pm 3$	$72 \pm 8^*$
Sex (F, M)	2, 7	4, 5
BMI ( $\text{kg} \cdot \text{m}^{-2}$ )	$25 \pm 3$	$26 \pm 4$
Sum of skinfolds (mm)	$105 \pm 27$	$114 \pm 16$
Body fat (%)	$21 \pm 4$	$25 \pm 2^*$
Resting MAP (mm Hg)	$82 \pm 7$	$89 \pm 6$
Glucose ( $\text{mg} \cdot \text{dL}^{-1}$ )	$85 \pm 5$	$99 \pm 6^*$
Total cholesterol ( $\text{mg} \cdot \text{dL}^{-1}$ )	$159 \pm 23$	$200 \pm 35^*$
HDL ( $\text{mg} \cdot \text{dL}^{-1}$ )	$59 \pm 11$	$69 \pm 17$
LDL ( $\text{mg} \cdot \text{dL}^{-1}$ )	$84 \pm 23$	$113 \pm 25$
Cholesterol ratio (total/HDL)	$2.7 \pm 0.6$	$3.1 \pm 0.9$

Values are mean  $\pm$  SD.

\* $P < 0.05$  vs young.

BMI, body mass index.

All participants recorded what they ingested for meals the evening before and the morning of the experiment and replicated these meals for the second experiment.

**Instrumentation.** Subjects arrived at the laboratory (room temperature =  $23^\circ\text{C}$ ) in the morning (8:00 AM to 1:00 PM) and were given either  $150 \text{ mg} \cdot \text{kg}^{-1}$  tyrosine or placebo in a double-blind, randomized crossover study design fashion (16). Investigators remained blinded through data acquisition and analysis. At least 48 h separated experimental days to ensure an adequate washout period. Tyrosine, or placebo, was compounded into small gel capsules (Buderer Drug Co; Sandusky, OH).

After oral ingestion of tyrosine or placebo, subjects donned a water-perfused suit that covered the entire body except for the face, feet, hands, and forearms. Then, subjects were in a semirecumbent position for the remainder of the experiment. An automated brachial cuff (Tango M2, Suntech Medical, Morrisville, NC) and lead II electrocardiogram (CT-1000 cardiometer; CWE Inc., Ardmore, PA) were placed for collection of blood pressure and heart rate, respectively. Mean skin temperature ( $T_{sk}$ ) was sampled by the unweighted average of copper–constantan thermocouples placed on the surface of the skin at six sites: calf, thigh, abdomen, chest, back, and upper arm. With all thermocouples in place, the suit was perfused with water to maintain baseline  $T_{sk}$  at  $34^\circ\text{C}$ . Then, a sterile thermistor within a 16-Fr feeding tube was fed through a naris to heart level, which was estimated as one quarter of the subjects standing height, for esophageal temperature measurements. Before placement, a benzocaine spray was used to anesthetize the posterior oropharynx. The participant was asked to swallow water to aid in advancing the probe down the esophagus. Lastly, multifiber integrated laser Doppler flowmetry probes placed within local heaters (moorVMS-laser Doppler flux [LDF] and moorVMS-HEAT, Moor Instruments) were attached to the surface of the nondominant ventral forearm to continuously measure red blood cell flux (LDF), an index of skin blood flow. Local heaters were set at  $33^\circ\text{C}$  throughout the experiment to ensure that any vasomotor changes were reflex in origin.

**Protocol.** After instrumentation and approximately 70 to 80 min postingestion of tyrosine or placebo, subjects began whole-body cooling. Thus, the beginning of cooling corresponded to when blood tyrosine concentration peaks after ingestion (16). The 90-min cooling protocol consisted of a primary ramp where  $T_{sk}$  was gradually reduced to  $30.5^\circ\text{C}$  over a 30-min period followed by a smaller secondary ramp in  $T_{sk}$  to approximately  $29.5^\circ\text{C}$  that occurred over a 60-min period. The water bath temperature was adjusted to ensure that skin temperature was the same between and within subjects. Bath temperature during the primary ramp was approximately  $5^\circ\text{C}$  to  $10^\circ\text{C}$  and approximately  $16^\circ\text{C}$  to  $18^\circ\text{C}$  during the secondary ramp. Bath temperature set point was changed and/or ice was periodically added to the bath to more precisely follow the same rate of change in skin temperature for each experiment. Blood pressure measurements were collected every approximately 5 min throughout the cooling bout. A survey to assess perception was given at baseline and at the end of cooling. At the end of cooling, subjects were rewarmed in the suit and deinstrumented.

The temperature perception survey consisted of two visual analog questions on a 164-mm scale that asked, “What is your level of discomfort with respect to body temperature that you feel at this time?” and “How cold do you feel at this time?”. The first question assessing discomfort was labeled at the 0, 41, 82, 123, and 164 mm point as “comfortable,” “slight discomfort,” “moderate discomfort,” “uncomfortable,” and “extremely uncomfortable,” respectively. The second question assessing cold perception was labeled at similar points as “normal temperature,” “noticeably cold,” “cold,” “frigid,” “painfully cold.”

**Data acquisition and analysis.** Data were collected at 1000 Hz and stored for offline analysis (LabChart v8 and PowerLab 16/35; ADInstruments, Bella Vista, NSW, Australia). The LDF and  $T_c$  were processed into 1-s averages every third second throughout the protocol. Mean arterial pressure (MAP) was calculated as the diastolic blood pressure plus one-third the pulse pressure. Absolute cutaneous vascular conductance (CVC) (calculated as  $LDF \cdot MAP^{-1}$ ),  $\% \Delta CVC_{BASELINE}$  (absolute CVC expressed as a percent change from baseline), and  $\Delta T_{ES}$  (change in  $T_{ES}$  from precooling baseline) were calculated for every 0.5°C drop in  $T_{sk}$  during the primary ramp and every 10 min during the secondary ramp. Calculated values were averaged over 3 min at each time/temperature point. For each of these dependent variables, a three-way mixed model ANOVA followed by Bonferroni *post hoc* analysis was conducted (SPSS version 24; SPSS, Chicago, IL) to detect drug treatment effects at different time/temperature points in the protocol between age groups. The slope of the decline in  $T_{ES}$  was determined using linear regression. Unpaired two-tailed Student's *t* tests were used for between age group comparisons for subject characteristics (Table 1) and variables within Table 2 (with the exception of absolute CVC). Paired two-tailed Student's *t* tests were used

for Table 2 variables for drug treatment comparisons and to determine differences between baseline and the end of the cooling bout. Statistical significance for all tests were set at  $\alpha = 0.05$ . Data are presented as mean  $\pm$  SEM except for subject characteristics and data illustrating individual subject changes with drug treatment that include group means and standard deviations.

## RESULTS

Subject characteristics are presented in Table 1. Groups were well matched based upon resting mean arterial pressure and body mass index but older adults had higher % body fat ( $P = 0.027$ ). Although older adults had higher total cholesterol ( $P = 0.019$ ), there were no differences with respect to LDL, HDL cholesterol, or cholesterol ratio. Older adults exhibited higher fasting blood glucose ( $P < 0.05$ ) compared with young adults.

Values for thermoregulatory variables and perception data at baseline and at the end of whole-body cooling are summarized in Table 2. Cooling resulted in a decline in  $T_{sk}$  and CVC and an increase in MAP from baseline ( $P < 0.05$ ). In the older adults receiving placebo, there was a decline in  $T_{ES}$  from baseline during the 90-min cooling bout ( $P = 0.002$ ). Thus, the  $T_{ES}$  at the end of cooling was lower in the older placebo group than in the older tyrosine, young placebo, and young tyrosine groups ( $P < 0.05$ ). Furthermore, the decline in  $T_{ES}$  over time ( $T_{ES}$  slope) was greater in the older placebo group than the other three groups ( $P < 0.05$ ). Thus, compared with placebo, tyrosine supplementation in older adults attenuated the decline in  $T_{ES}$  and in the  $T_{ES}$  slope, and resulted in a lower CVC by the end of cooling ( $P < 0.05$ ). In young, tyrosine did not affect thermoregulatory variables during cooling ( $P > 0.05$ ). Responses to the

TABLE 2. Thermoregulatory responses and perception to whole-body cooling.

	BASELINE		COOLING	
	Placebo	Tyrosine	Placebo	Tyrosine
$T_{ES}$ (°C)				
Young	37.52 $\pm$ 0.05	37.57 $\pm$ 0.05	37.56 $\pm$ 0.10	37.55 $\pm$ 0.09
Older	37.45 $\pm$ 0.04	37.51 $\pm$ 0.05	37.16 $\pm$ 0.08***	37.44 $\pm$ 0.09***
$T_{ES}$ slope (°C·h <sup>-1</sup> )				
Young	—	—	-0.31 $\pm$ 0.07	-0.31 $\pm$ 0.04
Older	—	—	-0.52 $\pm$ 0.05**	-0.34 $\pm$ 0.06***
$T_{sk}$ (°C)				
Young	34.01 $\pm$ 0.01	33.98 $\pm$ 0.03	29.56 $\pm$ 0.02*	29.56 $\pm$ 0.05*
Older	34.00 $\pm$ 0.01	34.02 $\pm$ 0.02	29.56 $\pm$ 0.08*	29.60 $\pm$ 0.08*
MAP (mm Hg)				
Young	91 $\pm$ 2	92 $\pm$ 2	98 $\pm$ 3*	101 $\pm$ 3*
Older	96 $\pm$ 3	94 $\pm$ 3	104 $\pm$ 3*	102 $\pm$ 2*
CVC (flux·mm Hg <sup>-1</sup> )				
Young	0.30 $\pm$ 0.04	0.27 $\pm$ 0.04	0.19 $\pm$ 0.03*	0.16 $\pm$ 0.02*
Older	0.28 $\pm$ 0.03	0.24 $\pm$ 0.03	0.24 $\pm$ 0.03*	0.16 $\pm$ 0.02***
Discomfort (mm)				
Young	5 $\pm$ 1	3 $\pm$ 1	76 $\pm$ 9*	65 $\pm$ 13*
Older	24 $\pm$ 11	10 $\pm$ 5	94 $\pm$ 11*	70 $\pm$ 10*
Perception (mm)				
Young	3 $\pm$ 1	2 $\pm$ 1	80 $\pm$ 8*	67 $\pm$ 9***
Older	5 $\pm$ 2	5 $\pm$ 2	78 $\pm$ 12*	74 $\pm$ 8*

Values are group mean  $\pm$  SEM.  $T_{ES}$ , slope of the  $T_{ES}$  decline with cooling, absolute CVC, discomfort with respect to cold, and perception of cold values in young ( $n = 9$ ) and older ( $n = 9$ ) subjects at baseline and at the end of the 90 min cooling bout.

\* $P < 0.05$  vs baseline condition.

\*\* $P < 0.05$  vs young.

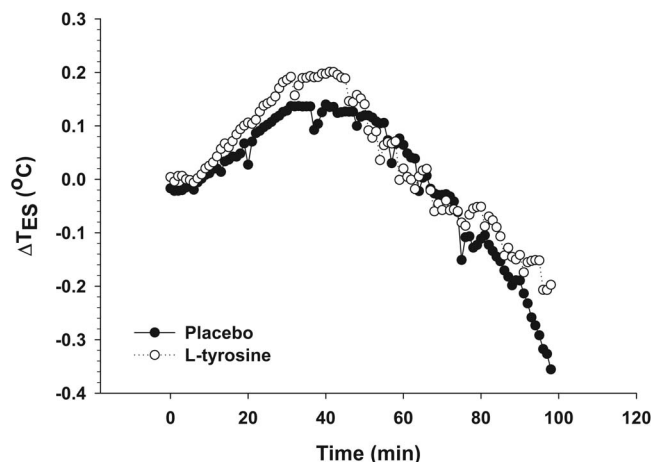
\*\*\* $P < 0.05$  vs placebo.

temperature perception survey indicated that, compared to baseline, whole-body cooling resulted in greater discomfort with respect to body temperature and increased perception of cold in both age groups ( $P < 0.05$ ). The mean score using the visual analog scale indicated that the cooling stimulus elicited “moderate discomfort” and was considered “cold.” In tyrosine or placebo conditions, there were no differences in discomfort or cold perception with age ( $P > 0.05$ ). Compared to placebo, tyrosine supplementation reduced perception of the cold in young adults ( $P = 0.007$ ).

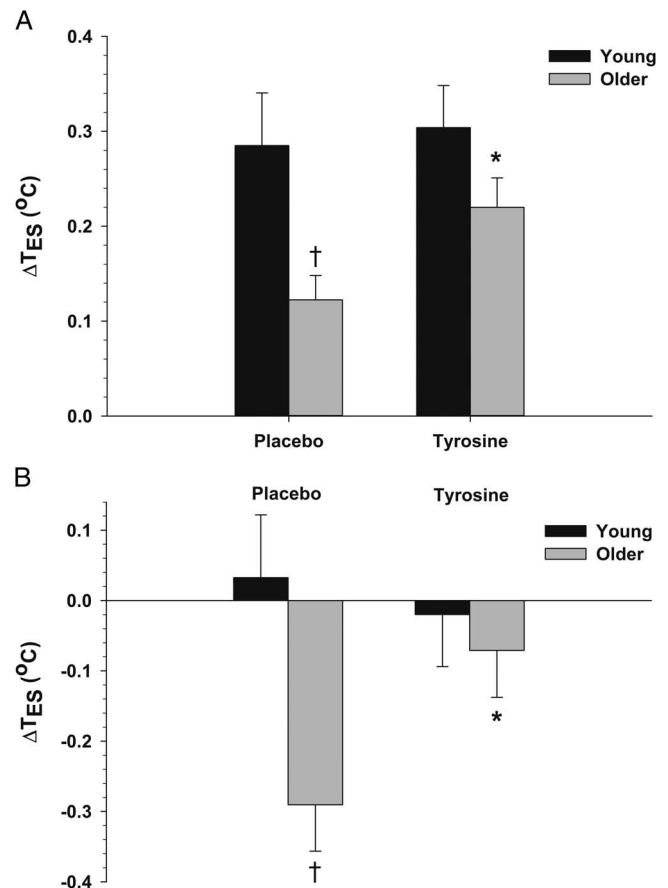
A representative tracing of the  $T_{ES}$  response to whole-body cooling in an older adult is depicted in Figure 1. The mean compensatory increase in  $T_{ES}$ , typically observed approximately 30 min into cooling, is shown in Figure 2A. Compared with young (Y), the peak increase in  $\Delta T_{ES}$  was blunted in older (O) adults ( $Y = 0.29 \pm 0.05$ ,  $O = 0.12 \pm 0.03$ ;  $P = 0.016$ ). Tyrosine supplementation augmented the peak ( $O = 0.22 \pm 0.03$ ;  $P = 0.017$ ) so that it was similar to that of young ( $Y = 0.30 \pm 0.04$ ;  $P = 0.140$ ). By the end of the 90-min cooling bout (Fig. 2B), there was a greater overall reduction in  $\Delta T_{ES}$  in older adults ( $Y = 0.03 \pm 0.09$ ,  $O = -0.29 \pm 0.07$ ;  $P = 0.010$ ). Tyrosine attenuated the  $\Delta T_{ES}$  reduction to whole-body cooling in older adults ( $O = -0.07 \pm 0.07$ ;  $P = 0.004$ ) so that it was similar to that of young ( $Y = -0.02 \pm 0.07$ ;  $P = 0.617$ ).

Individual participant  $\Delta T_{ES}$  responses to whole-body cooling across drug treatment is summarized in young (Fig. 3A) and older adults (Fig. 3B). Group mean and standard deviation are also illustrated. In older adults, tyrosine supplementation reduced the core temperature decline with whole-body cooling ( $P < 0.05$ ).

The reflex cutaneous VC response, represented as a percent change in CVC from baseline, for every  $0.5^\circ\text{C}$  drop in  $T_{sk}$  and at the end of 90-min whole-body cooling is shown in Figure 4. Compared with young placebo (Fig. 4A), the VC response was blunted in the older placebo group (Fig. 4B;  $P < 0.05$ ). Tyrosine supplementation augmented the reflex VC response in older adults ( $P < 0.05$ ) so that the VC was similar in magnitude



**FIGURE 1**—Representative tracing depicting changes in  $\Delta T_{ES}$  from baseline during the whole-body cooling bout after ingestion of placebo or tyrosine in an older adult.

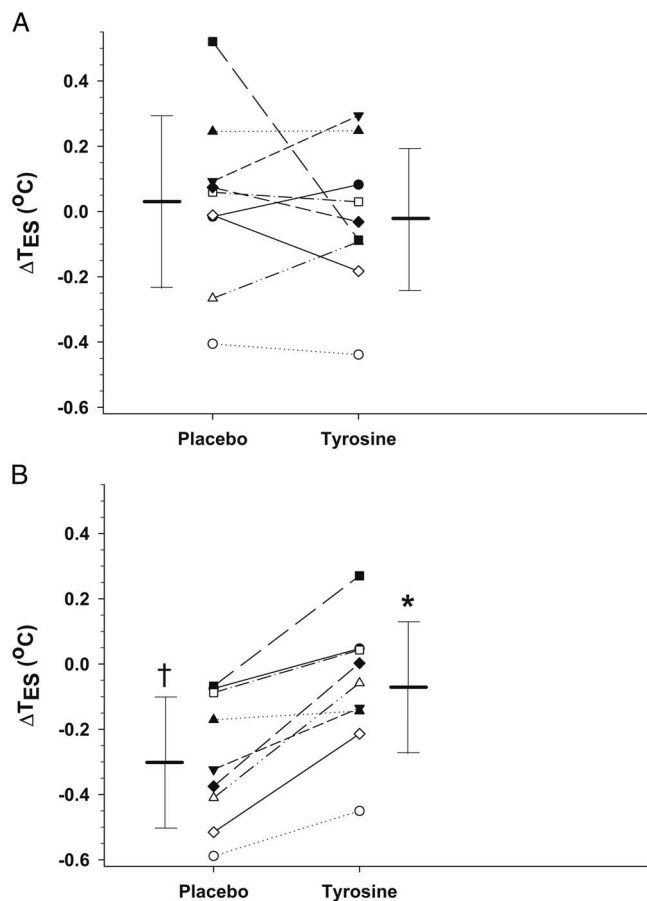


**FIGURE 2**—Group mean change in  $\Delta T_{ES}$  from baseline during whole-body cooling ( $T_{sk} = 29.5^\circ\text{C}$ ) after placebo or oral L-tyrosine supplementation. Panel A corresponds to the peak compensatory increase in temperature, reflecting metabolic heat production, occurring approximately 30 min into cooling. Panel B shows the nadir in temperature occurring at the end of the 90 min cooling bout. L-tyrosine attenuated the decline in core temperature during cooling in older adults. \* $P < 0.05$  vs placebo, † $P < 0.05$  vs young.

to that of young adults ( $T_{sk} \leq 32.5^\circ\text{C}$ ;  $P > 0.05$ ). Compared to young, the initial VC to cooling ( $T_{sk} > 32.5^\circ\text{C}$ ) remained attenuated in tyrosine-supplemented older adults ( $P < 0.05$ ). Tyrosine did not affect the cutaneous VC response in young adults ( $P > 0.05$ ).

## DISCUSSION

The novel finding from this study was that oral L-tyrosine supplementation improved  $T_c$  maintenance during acute cold stress in older adults. During whole-body cooling, the  $T_{ES}$  pattern consisted of a compensatory increase that occurred from the onset of cooling and peaked approximately 30 min into the cooling bout (Fig. 1). The peak compensatory increase was blunted in older adults. After peak, there was a steady decline in  $T_{ES}$  until the end of the 90-min cooling bout. Both the slope of the  $T_{ES}$  decline and the  $T_{ES}$  drop from baseline were significantly greater in older adults. However, after oral ingestion of L-tyrosine, both the magnitude of the reflex cutaneous VC response and the pattern of  $T_{ES}$  during cooling was similar



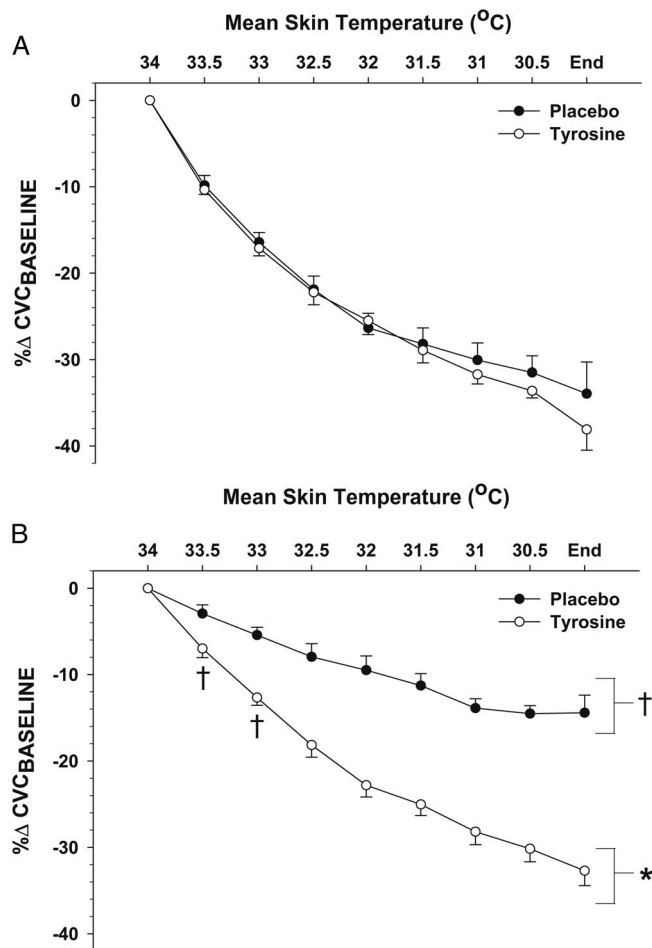
**FIGURE 3**—Individual subject responses to the change in  $\Delta T_{ES}$  from baseline at the end of 90 min whole-body cooling ( $T_{sk} = 29.5^{\circ}\text{C}$ ). The effect of oral L-tyrosine supplementation is shown in young (panel A) and older adults (panel B). Data are represented as group mean  $\pm$  SD. \* $P < 0.05$  vs placebo, † $P < 0.05$  vs young.

to that of young adults. However, the perception of cold stress and associated discomfort was not different with tyrosine compared with placebo in older adults. Collectively, these data indicate that sufficient L-tyrosine bioavailability is necessary to optimally maintain  $T_c$ . Considering that older adults are uniquely susceptible to hypothermia (4–6), the increased  $T_c$  maintenance afforded by tyrosine supplementation may be a practical strategy to reduce cold-related deaths.

L-tyrosine is the amino acid substrate required for catecholamine production in adrenergic nerve terminals (25). Increased sympathetic activity primes the rate-limiting enzyme, tyrosine hydroxylase (TH), for hydroxylation of L-tyrosine (17). This reaction is facilitated by tetrahydrobiopterin ( $\text{BH}_4$ ), an essential cofactor that reduces TH to its active ferrous form (26). Oral supplementation or intradermal administration of either  $\text{BH}_4$  or L-tyrosine augments the cutaneous reflex VC response in older adults (11,12,15,16). However, it seems unlikely that L-tyrosine limits NE production due to the following reasons: 1) tyrosine is abundantly supplied from exogenous ( $\sim 3\text{--}4\text{ g}\cdot\text{d}^{-1}$  from dietary protein) and endogenous sources ( $\sim 2\text{--}3\text{ g}\cdot\text{d}^{-1}$  from the liver), 2) the  $K_m$  for TH is below resting tyrosine concentrations (27), and 3) blood tyrosine is unaffected with age (28). Nevertheless, the L-tyrosine pool within the nerve terminal

that is in the immediate vicinity of TH may indeed become limited during a state of increased sympathetic activation (18). This is particularly relevant if the axonal pool of L-tyrosine is diminished by oxidative and nitrosative stress in age skin, thereby converting tyrosine to byproducts (e.g., 3-nitrotyrosine and tyrosyl radical) that cannot participate in catecholamine biosynthesis (19–21). Thus, axonal tyrosine may become depleted in older adults during times of increased sympathetic activation (e.g., cold exposure), resulting in reduced NE biosynthesis and release and blunted end-organ responses.

Our data is consistent with other reports indicating that the magnitude of the cutaneous VC response to whole-body cooling in age skin is about half that of young (10–13,15,16). The underlying mechanism of VC is altered with age, shifting away from contributions from redundant cotransmitter pathways ( $\sim 40\%$  of reflex VC in young) (10,29), such as ATP or neuropeptide Y (30,31), to relying upon a blunted noradrenergic response (10,15). Thus, the greater reliance upon NE to elicit reflex VC in older adults may increase the demand for L-tyrosine during cold stress. However, there is a marked reduction in skin sympathetic nerve activity during cooling in older adults (32,33).



**FIGURE 4**—Group mean change in CVC from baseline ( $\%\Delta\text{CVC}_{\text{BASELINE}}$ ) during whole-body cooling in young (panel A) and older subjects (B). Oral L-tyrosine supplementation augmented the reflex cutaneous VC response in older adults. \* $P < 0.05$  vs placebo, † $P < 0.05$  vs young.

Despite the reduction in the neural stimulus for “priming” TH, the lack of substrate appears to remain a limiting factor in the reflex VC response. This is supported by our current and previous work demonstrating that oral ingestion of L-tyrosine augmented the cutaneous VC response to cooling in older adults (16).

Reflex peripheral VC is important to  $T_c$  maintenance (4,13). This is clearly evident from the placebo trial demonstrating an impaired reflex cutaneous VC response in the older group. It was only in this trial that whole-body cooling consistently resulted in a decline in  $T_{ES}$  by approximately 0.3°C. The accompanying VC response was not only blunted but appeared to plateau approximately 25 min into the 90-min cooling bout. After tyrosine supplementation, cutaneous VC was augmented in older adults, thereby resulting in  $T_{ES}$  pattern that was similar to young adults. This finding was evidenced by the increase in  $T_{ES}$  that peaked approximately 30 min into cooling followed by a significant decrease in the slope of the decline in  $T_{ES}$ . Thus, it appears that the increase in the VC response after L-tyrosine ingestion was the principal contributor to the improvement in  $T_c$  maintenance in older adults. As such, increasing L-tyrosine concentration by a supplement or change in diet may be a practical strategy for older adults to improve thermoregulatory function in the cold and minimize hypothermia risk.

Tyrosine supplementation did not alter the perception or discomfort experienced with the cooling stimulus in older adults. Regardless of age or drug, the cooling bout was generally considered “cold” and elicited “moderate discomfort.” Although there are studies to the contrary, thermal sensitivity seems to gradually decline with age (7,14). Thus, older adults may have an increased threshold in which temperature changes elicit changes in behavior (e.g., adjusting the thermostat, putting on a coat, etc.) (14). However, the reduced sensitivity may occur to a greater extent in the distal extremities or in response to warm stimuli (14,34). Despite the different rates of change in  $T_{ES}$  between the placebo and tyrosine trials in older adults, there was no accompanying change in perception or discomfort during cooling. This finding is consistent with recent work, indicating that the rate of change in skin temperature, which was similar between experimental groups and trials, is the primary driver of thermal perception and behavior (35,36).

Oral ingestion of L-tyrosine has been investigated in young adults during cold exposure (22–24). In soldiers, tyrosine supplementation has been demonstrated to improve mood as well as cognitive and psychomotor function during prolonged cold stress (22–24). This is consistent with the current study indicating a modest reduction in cold perception with tyrosine. Additionally, ingestion of L-tyrosine had an acute effect of preventing a decline in cognitive function in response to other

stressors that include hypoxia, orthostatic stress, and extended wakefulness (37–39). In the current study, examining older adults, acute ingestion of approximately 1.5 to 2 times the normal daily intake of L-tyrosine augmented the cutaneous VC response and contributed to improved  $T_c$  maintenance during cooling. Collectively, these studies represent an acute effect of tyrosine supplementation that is not apparent at resting baseline but during elevated sympathetic activation. The effect of chronic L-tyrosine supplementation in older adults on stressors, such as cold exposure, is unknown.

**Limitations.** A limitation of this study is that the cooling stimulus was not prolonged or severe enough to elicit a decline in  $T_c$  in young adults. Thus, it is possible that L-tyrosine may affect thermoregulatory function in the young, but this could not be discriminated with the current protocol. A second limitation is that neither oxygen consumption nor shivering activity, via electromyography, was measured in this study as a means to characterize the role of metabolic heat production on the  $T_c$  response before and after tyrosine supplementation. However, visible shivering did not occur until the end of the 90-min cooling bout. Thus, it is unlikely that shivering thermogenesis contributed significantly to the age-related differences in the  $T_c$  response.

## CONCLUSIONS

In summary, acute oral L-tyrosine supplementation in older adults augmented cutaneous VC and prevented the decline in  $T_c$  during whole-body cooling. As a result, the VC and  $T_c$  responses were not different between the young placebo controls and the older adults that ingested tyrosine. These data suggest that the axonal pool of tyrosine available for catecholamine biosynthesis is limited in older adults during cold stress. As such, L-tyrosine may be a supplementation strategy to improve sympathetic function and  $T_c$  maintenance during cold stress in older adults.

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