Tyrosine for Mitigating Stress and Enhancing Performance in Healthy Adult Humans, a Rapid Evidence Assessment of the Literature

Selasi Attipoe, MA; Stacey A. Zeno, MA*; Courtney Lee, MA†; Cindy Crawford, BA†; Raheleh Khorsan, PhD†; Avi R. Walter, BA†; Patricia A. Deuster, PhD**

ABSTRACT Background: Tyrosine, a precursor of catecholamine neurotransmitters, may help alleviate physical/cognitive performance decrements in humans under conditions of high physical/psychological stress. Objective: Determine whether supplemental tyrosine mitigates stress-induced decrements in cognitive and/or physical performance in healthy individuals using Samueli Institute's Rapid Evidence Assessment of the Literature methodology. Methods: Key databases (PubMed/MEDLINE, CINAHL, Embase, PsycInfo, and Agricola) were searched for randomized controlled trials from inception to October 2012. Scottish Intercollegiate Guidelines 50 criteria and Grading of Recommendation Assessment, Development, and Evaluation framework were used to assess the quality of individual studies and the overall literature pool, respectively. Controlled clinical trials were included later in the overall methodology. Results: 10 randomized controlled trials and 4 controlled clinical trials met our inclusion criteria. On the basis of the available evidence, no recommendation could be made for the effect of tyrosine on physical performance under stressful physical conditions. However, a weak recommendation in favor of tyrosine was made for cognitive stress as all studies showed a positive effect. Conclusions: This review indicates that the available evidence is insufficient to make confident recommendations on the effectiveness of tyrosine for mitigating stress effects on physical/cognitive performance. However, tyrosine may benefit cognitive performance and is worthy of further study.

INTRODUCTION

Tyrosine is a large, nonessential, neutral amino acid present in both animal and vegetable protein in various amounts.[1–5] Produced in the liver and to some extent the brain, L-tyrosine is synthesized via hydroxylation of phenylalanine, an essential amino acid. Furthermore, L-tyrosine is the precursor of the catecholamine (CA) neurotransmitters (dopamine [DA], norepinephrine, and epinephrine) through the action of tyrosine hydroxylase.[4] High levels of CA, especially noreprinephrine, in the blood are elicited by some form of physiological, psychological, and/or environmental stressors.[3–6] Depletion of norepinephrine has the potential to impair/compromise cognitive and physical performance.[1]

Interestingly, when tyrosine is systemically administered in pharmacologic amounts before acute exposure to stressful events, it has been shown to increase concentrations and release of CA with cellular firing in the brain.[7,8] Human studies have shown ingestion of such doses is associated with neurochemical, behavioral, and cognitive changes.[4,6,8] Notably, tyrosine supplementation has been shown to diminish cognitive and some behavioral deficits associated with stressful conditions.[4,5,9–12] In addition, the administration of tyrosine has been shown to improve performance on stress-sensitive attention tasks and attentional focus in the presence of acute exposure to cold.[4,5,9–14]

Nutritional agents that can maintain optimal performance during military operations are critical to the national force strength. Some persons are very sensitive to stressful conditions and exhibit exaggerated responses that could result in CA depletion.[15,16] Given that CA depletion during exposure to acute and chronic stress may compromise performance, providing stress-susceptible individuals supplemental tyrosine may prevent depletion of CA.[16–18]

In fact, the 1994 Institute of Medicine report concluded that tyrosine may enhance performance, but additional research is needed.[19] Since then, several trials have been conducted assessing the effectiveness of tyrosine; however, to date, there have been no comprehensive systematic reviews that assess the effectiveness of tyrosine for the mitigation of stress on cognitive or physical performance. Consequently, the aim of this systematic review using the Rapid Evidence Assessment of the Literature (REAL) process[20,21] was to determine if tyrosine may prevent such depletion, thereby improving either cognitive or physical performance under conditions of various stressors in healthy adults. To accomplish this objective, the authors: (1) surveyed the available literature on supplemental tyrosine; (2) examined and assessed the quantity, quality, and efficacy of studies on tyrosine across relevant stress outcomes as reported in the literature; and (3) identified gap areas that exist in the literature based on the overall literature pool evaluated.

*Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814-4799.

†Samueli Institute, 1737 King Street, Suite 600, Alexandria, VA 22314-2847.

doi: 10.7205/MILMED-D-14-00594

METHODS

Data Sources and Search Strategy

The databases PubMed/MEDLINE, CINAHL, Embase, PsycInfo, and Agricola were searched from their inception to October 2012 for randomized controlled trials (RCTs) with a tyrosine intervention and cognitive or physical outcomes. Authors explored MeSH within MEDLINE to strategize the most powerful search and also consulted with subject matter experts (SMEs) to ensure the correct key terms were being targeted. The following search string was used to search PubMed: "(tyrosine) and (stress or stress, psychological or stress, physiological or resilience, psychological or coping or performance or psychomotor performance or athletic performance or exercise)." Variations of the search strategy for the remaining databases are available upon request from the primary author.

Study Selection

Articles were included in the REAL if they met the following criteria: (1) RCT presented in the English language and involving human subjects; (2) healthy population with no preexisting diseases or conditions; (3) use of tyrosine supplement as an intervention; and (4) at least one cognitive or physical performance outcome. In addition, because tyrosine is often formulated/provided with other ingredients (i.e., dissolved in water, mixed with food), articles that combined tyrosine with nonactive ingredients (e.g., those that would not affect our outcomes of interest), were included.

Articles were excluded if they met at least one of the following criteria: (1) any study design other than a RCT, (2) population with preexisting conditions or diseases, (3) focus on an intervention other than tyrosine, (4) intervention consisting of tyrosine in combination with other active ingredients or drugs, (5) articles without at least one cognitive or physical performance outcome.

Although authors followed these predefined criteria, it was decided that in the event that only a small subset of RCTs (i.e., less than 15 RCTs) met the predefined inclusion criteria, a post hoc search would be conducted in PubMed for clinical controlled trials (CCTs) to help further inform conclusions. The same predefined search strategy as described above was used; however, the delimiter of CCT was applied instead. In contrast to RCTs that are randomized control trials, the gold standard for clinical trials, i.e., CCTs are clinical trials with comparative arms but no randomization. Any retrieved CCTs would be screened according to the inclusion criteria described above and included in the analysis.

Data Extraction and Quality Assessment

This review was conducted using a secure web-based systematic review management program known as Mobius Analytics SRS (Copyright 2003–2009 Mobius Analytics, Ottawa, Ontario), which automates article progression and management, eliminates data transcription, and reduces post-review data collation and errors.

Two investigators independently screened titles and abstracts for relevance based on the inclusion criteria predefined above. Any disagreements about inclusion were resolved either through discussion and consensus with a review manager or by one of the SMEs. All articles marked for inclusion were retrieved and included in the review phase, during which two reviewers performed quality assessments and data extraction; all work was cross-checked by a review manager. Methodological quality was independently assessed by using the Scottish Intercollegiate Guidelines Network (SIGN 50) checklist for RCTs, a validated and reliable assessment approach widely used in the literature.[22] Both reviewers were fully trained in the methodology and reviewed the articles in pairs until a sufficient kappa (>90%) was achieved, at which point they continued reviewing the remaining articles independently. All disagreements were resolved either through discussion and consensus, or by the SMEs.

The following descriptive data were extracted to characterize each included study: the population description, sample size, whether informed consent was obtained, description of the tyrosine and control interventions, the stressor used in each study, all cognitive or physical performance related outcomes and statistics, funding source, author's main conclusions, and whether power calculations and adverse events were reported.

The SMEs also collectively decided on key elements believed essential for authors to report when describing nutritional supplement interventions. These elements are essential to properly determine the "true" effect of a nutritional supplement, thereby enabling a better understanding and interpretation of the results, and providing the detail necessary for replication. The two elements included were a detailed description and preparation of the nutritional supplement and the nutritional status of the population to which the supplement was being administered.

Data Synthesis and Analysis

Once the quality assessment of the individual RCTs was completed, the SMEs performed a quality assessment of the overall literature pool for each stressor component category that emerged from the literature (i.e., exercise or environmental stressor); the assessment was made by using the Grading of Recommendation Assessment, Development, and Evaluation (GRADE)[23] an internationally accepted approach to grading the quality of evidence and strength of recommendations across studies. SMEs examined: (1) the confidence in the estimate of the effect for the overall literature pool for each category, (2) the overall magnitude of the effect, (3) safety, and developed recommendations based on the strength of the evidence for the overall tyrosine literature pool of included studies for each stressor component. SMEs were trained in the GRADE methodology by using a rulebook developed, tested, and agreed upon by the entire

team (available by contacting the primary author). SMEs performed the GRADE independently before discussing their answers together and coming to consensus, as guided by the review managers.

RESULTS

Our search yielded a total of 421 citations from database inception to October 2012 (Fig. 1). Of these, 10 RCTs fit the predefined inclusion criteria and were subsequently assessed using SIGN 50 criteria (Table I). RCTs were separated into two categories based on the stressor used in the study (i.e., environmental or exercise). Table II describes the characteristics and overall SIGN 50 quality score of the individual RCTs. Table III describes the GRADE of the overall literature pool.

Because of the limited RCTs found and included in this review, the authors agreed that a search and assessment of the CCTs could contribute to this review. A post hoc PubMed search conducted by applying the same search strategy as for the RCTs revealed 4 CCTs[3,5,8,12] that met the predefined inclusion criteria. Agreed upon and included CCTs were assessed for quality using SIGN 50 criteria for CCTs (Table I), and data extraction was performed just as the RCTs had been characterized. These four studies are included in Table I to share the quality and evidence as shown in these individual studies, but not included in the overall GRADE assessment.

Quality Assessment

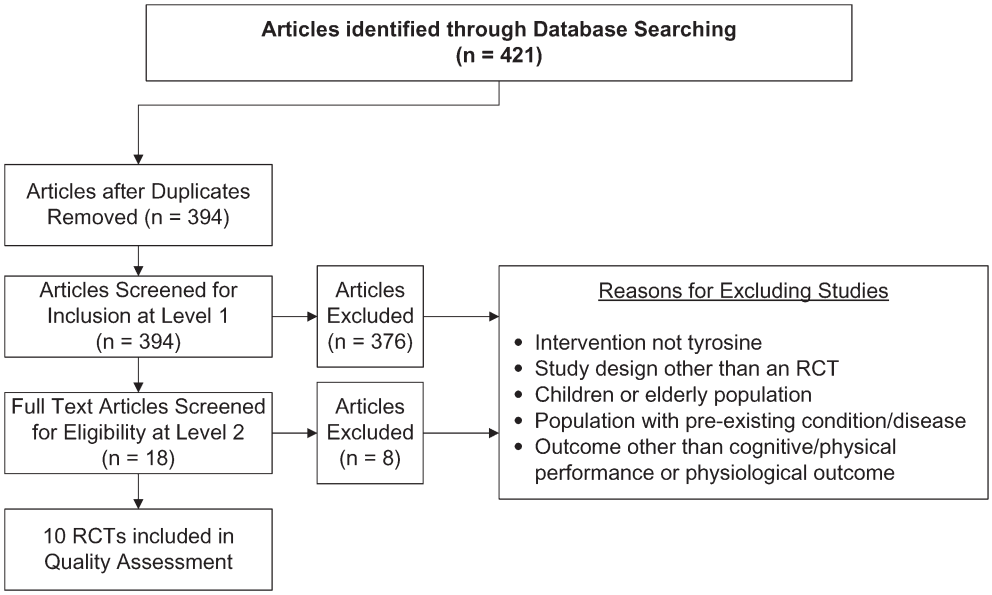
According to SIGN criteria (Table I), the majority (80%) of the 10 included RCTs were of poor (–) quality with only 2 high (+) quality[2,11] studies. The four included CCTs[3,5,8,12] were all high (++) quality for CCT design.

RCTs

The majority of RCTs addressed an appropriate and clearly focused question either well (50%) or adequately (40%). Most of the articles poorly addressed several SIGN 50 criteria by not providing a full description of the randomization procedure (100%), not describing allocation concealment (90%), or whether it was even done, not demonstrating baseline similarities between the treatment and control interventions (60%), neither describing dropout rates nor indicating high dropout rates (70%), and not providing details about or performing intention to treat analyses (80%). Blinding was adequately addressed by most articles (90%). Half of the articles (50%) did not address whether there were confounding factors between groups other than the treatment itself, and as such, it is unclear whether one treatment received additional attention or treatment that could have swayed or biased the results. Finally, the majority of articles addressed the reported outcome reliability and validity either well (40%) or adequately (40%).

CCTs

CCTs were evaluated using a modified version of the SIGN 50 criteria for CCT study designs (Table I). Two CCTs[5,12] addressed an appropriate and focused research question well (50%), whereas the remaining two (50%)[3,8] did so adequately. Treatment and baseline differences were also adequately described by all four articles, as authors clearly indicated that the intervention under investigation was the



*Note the four CCT studies included in our REAL are not included in the Flow Chart as this search was conducted post hoc.

FIGURE 1. Flowchart of included studies.

TABLE I. SIGN 50 Checklist for RCT Study Design[21]

Section 1: Internal Validity[a]	
Item	Description
1.1	The study addresses appropriate and clearly focused question.
1.2[a]	The assignment of subjects to treatment groups is randomized.
1.3[a]	An adequate concealment method is used.
1.4[a]	Subjects and investigators are kept blind about treatment allocation.
1.5	The treatment and control groups are similar at the start of the trial.
1.6	The only difference between groups is the treatment under investigation.
1.7	All relevant outcomes are measured in a standard, valid and reliable way.
1.8	What percentage of subjects in each treatment arm dropped out before the study was completed?
1.9	All subjects are analyzed in the groups to which they were randomly allocated (intention to treat analysis).
1.1	Where the study is carried out at more than one site, results are comparable for all sites.
Each Item in Section 1 Is to Be Evaluated Using These Criteria:	
1. Well Covered	
2. Adequately Addressed	
3. Poorly Addressed	
4. Not Applicable (NA) Only for Question 1.10	
Section 2: Overall Assessment	
Score options: ++, +, – based on following (modifications to SIGN criteria in italics):	
++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study are thought very unlikely to alter. *Both a RCT and CCT receive this score if there are 0 criteria scored as poorly addressed.*
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions. *A RCT receives this score if 1–3 criteria are scored as poorly addressed. A CCT receives this score if 2 criteria are poorly addressed.*
–	Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter. *A RCT receives this score if more than 3 criteria are scored as poorly addressed. A CCT receives this score if more than 2 criteria are scored as poorly addressed.*

[a]Item not applicable/assessed for CCT studies.

only difference between groups and that there were no confounding factors and treatment and control groups were similar at baseline. In addition, the validity and reliability of primary outcomes were addressed either well (50%) or adequately (50%). Dropout rates and intention-to-treat analyses were poorly covered by all (100%) studies.

Effectiveness of Tyrosine

RCTs

Exercise Stressors: Two high (+)[2,24] and two poor (–)[25,26] quality studies, with a total of 47 participants, investigated the effect of tyrosine on physical performance under stressful conditions induced by either cycling trials[24–26] or a load carriage test.[2] Only one study[26] reported improvements in endurance capacity following tyrosine administration; the remaining studies found no differences between tyrosine and placebo. Although one study[24] reported no adverse events, such events were not discussed by the remaining studies. Because of the small sample sizes and power to detect an effect, as well as the limitations around the quality of these studies, further research is very likely to have an important impact on the confidence in the estimate of the effect. Thus, no recommendation can be provided as to whether tyrosine confers a beneficial effect on physical performance under stressful conditions induced by exercise at this time.

Environmental Stressors: Six studies,[4,9–11,13,14] all of poor (–) quality, examined tyrosine's effects on cognitive performance in which a total of 175 participants were exposed to stressful, environmental conditions (i.e., warm/cold exposure, noise, combat course, negative pressure, sleep deprivation). All studies showed favorable effects of tyrosine, citing improvements in memory,[9–11,13,14] attention,[9] perceptual motor skills,[10,13,14] reaction time,[4] as well as logical reasoning and mathematical processing.[13] Adverse events were only described in one study,[4] which reported no adverse events. Similar to the exercise studies, these studies also did not report on effect sizes, and because of these severe limitations in study quality, our confidence in the estimate of the effect is low. However, because all these studies did show positive effects, we give a weak recommendation in favor of tyrosine; more high-quality studies with larger sample sizes and power are needed to increase the confidence in the estimate of the effect.

Included CCTs

All four CCTs[3,5,8,12] were of high (++) quality according to the SIGN 50 criteria for assessing CCTs. They investigated tyrosine's effect on cognitive performance in a total sample of 77 participants, 57 of which were exposed to stressful conditions via either cold immersion[5,12] or simulated mountain temperatures/altitude.[3] The remaining study,[8] consisting of 20 participants, did not include a stressor. Two[5,12] of the four studies included military populations, and reported improvements in cognitive tasks assessing attention, reaction time, memory, and psychomotor function. The remaining two studies[3,8] also reported favorable results, citing improvements in auditory reaction time and a variety of other cognitive tasks relating to problem solving, attention, spatial and verbal processing, mathematical calculations, and decision making. Because GRADE only considers RCT study designs for making recommendations, the SMEs did not make any recommendations for the CCTs.

Nutritional Elements and Adverse Events

Overall, more than half of the RCTs and CCTs (64%) addressed the background diet of the population, but only 43% of the studies reported on the bioavailability of tyrosine ingested by the participants. Only a small percentage (14%)

TABLE II. Characteristics of Included Studies Investigating Tyrosine in Healthy Populations

Citation	Population Description	Sample Entered/Completed	Supplement	Control	Stressor	Relevant Outcomes	Author's Main Conclusions	Quality Score
				Exercise (n = 4)				
Struder[24]	10 Endurance-Trained Male Cyclists, Mean Age 26 ± 2	10/10	TYR Drink: PLA Postbreakfast, 10 g L-Tyrosine Pretrial and 60 Minutes Postexercise	PLA: Postbreakfast, Pretrial and After 60 Minutes of Exercise Paroxetine: 20 mg Postbreakfast, PLA Pretrial and 60 Minutes Postexercise BCAA Mixture: PLA Postbreakfast, 14 g BCAA Pretrial, 7 g BCAA 60 Minutes Postexercise	Cycling Trial: Cycle Ergometer Exercise Until Exhaustion	Time to Exhaustion	TYR Does Not Significantly Affect Physical Performance	+
Tumilty et al[26]	8 Healthy Males, Mean Age 32 ± 11[c]	Overall (8/8)	TYR Drink: PLA + 150 mg/kg Body Mass TYR During the PreCycling Test	PLA: 500 mL Tap Water + 20% Sugar-free Lemon Squash	Cycling Test: Heavy Cycle Ergometer Exercise in Heated Chamber Until Exhaustion	Cycling Trial, Subjective Exertion	TYR Increases Endurance Capacity in the Heat in Moderately Trained Subjects (p = 0.0006)	–
Chinevere et al[25]	9 Male competitive cyclists, mean age 25 ± 1[bc]	Overall (9/ND)	TYR Drink: 5 mL/kg Body weight Solution With L-Tyrosine (25 mg/kg Body weight) at 30 Minutes Intervals From 60 Minutes Pre-exercise Until End of 90 Minutes Trial	PLA: 5 mL/kg Body Weight of Water + Aspartame Polydextrose: 70 g/L Polydextrose + TYR: 70 g/L Polydextrose + 2 mg/kg Body Weight of L-Tyrosine (25 mg/kg Body Weight) at 30-Minutes Intervals, Beginning 60 Minutes Before Exercise	90 Minute Cycling Trial	Oxygen Uptake, Perceived Exertion	TYR Does Not Significantly Affect Oxygen Uptake or Perceived Exertion at Any Time During a 90 Minutes Cycling Trial	–

(continued)

TABLE II. Continued

Citation	Population Description	Sample Entered/Completed	Supplement	Control	Stressor	Relevant Outcomes	Author's Main Conclusions	Quality Score
Sutton et al[2]	20 Healthy Male Subjects, Mean Age 32 ± 1[c]	Overall (20/20)	TYR Food: 70 g Applesauce With 150 mg/kg L Crystalline TYR at 30 minutes Pre-Exercise	PLA[e]: 70 g Applesauce With 7 g Microcrystalline Cellulose at 30 Minutes Pre-exercise	Load Carriage Test: With Loads of 30% Body Weight, Subjects Exercise 120 Minutes or Until Exhaustion	Borg Scale, Maximal Voluntary Contractions, Maximum Number of Stairs in 1 Minute, Pull-ups	TYR Does Not Significantly Affect Endurance, Muscle Strength or Anaerobic Power in Healthy Men	+
				Environmental Stressors (n = 6)				
Deijen et al[10]	16 (9 Male/ 7 Female) Healthy Subjects, Mean age 27[b]	Overall (16/16)	TYR Pill: 100 mg·L-Tyrosine and 10 mg Vitamin B-6 Taken 20 Minutes Pre-experiment	PLA[e]: Nonactive Tablets of Identical Appearance	Noise: Continuous Broadband Noise Played During all Tasks Except Stroop Task	Cognitrone, Vienna determination Unit, Vigiliance/Peripheral perception, peripheral perception, Stroop Task	TYR Improves Short-term Memory ($p < 0.05$) but Has No Post-test Effects on Pulse Rate or Blood Pressure. Supplementation also Improves Perceptual Motor Skills on the Stroop Task ($p < 0.03$) but Not on the Other Perceptual Motor Skill Tasks	–
Dollins et al[4]	22 Healthy male subjects, mean age 28 ± 5[c]	Overall (22/20)	TYR Pill: 50 mg/kg TYR at 0748 and 0900	PLA[e]: Cellulose capsules at 0748 and 0900	Low Body Negative Pressure (LBNP): 2 × 39 Minutes Sessions During Which Subjects Were Tested While Pressure Applied to Lower Half of Their Body Via LBNP Chamber	Pulse pressures, Dual Vigilance Task, 4-Choice Visual Reaction Time	TYR Does Not Significantly Affect Dual Vigilance, but it Does Improve Reaction Time ($p < 0.01$) and Cardiac Output, as Measured by LBNP Tolerance and Pulse Pressure ($p < 0.05$)	–
Magill et al[13]	76 Healthy Male subjects, Mean Age Range 18–35[c]	Overall (76/ND)	TYR Pill: 150 mg/kg in 500 mg Capsules at 1530	D-Amphetamine: 20 mg in 500 mg Capsules at 1530 Phentermine: 37.5 mg in 500 mg Capsules at 1530 Caffeine: 300 mg/70 kg in 500 mg Capsules at 1530	Sleep Deprivation Day: Subjects Not Permitted to Sleep During Night 2 and Day 3; Subjects Remained Awake Until 2330 on Day 4	Performance Test Battery, Visual Scanning Task, Running Memory Task, Logical Reasoning Task, Mathematical Processing, Stroop Task, 4-choice Serial Reaction Time Task, Time Wall Task, Pursuit Tracking	TYR Improves Some Aspects of Cognitive and Motor Performance Including Memory ($p < 0.01$), Logical Reasoning ($p = 01$), Mathematical Processing ($p = 0.003$) and Visual Vigilance ($p < 0.03$) After Sleep Deprivation	–

(continued)

TABLE II. Continued

Citation	Population Description	Sample Entered/Completed	Supplement	Control	Stressor	Relevant Outcomes	Author's Main Conclusions	Quality Score
				PLA: 250 mg Cellulose in 500 mg Capsules at 1530		Task, Visual Vigilance Task, Trials (B) Task, Long-Term Memory Task		
Deijen et al[10]	33 Healthy Cadets (32 Male/ 1 Female), Mean Age 23 ± 3 (TYR) and 21 ± 3 (PLA)[bc]	Overall (32/21) TYR (16/10) PLA (16/11)	TYR Drink: 500 mL/kg Body Weight Solution (Orange Juice + 70 g of PROTIFAR Diet Powder) Daily for 5 Days	PLA: 500 mL Mixture (Orange Juice + 67 g FANTOMALT Diet Powder) Daily for 5 Days	Military Training Combat Course: 2-week Course, Including Sleep Deprivation and Food Rationing, Aimed to Increase Stress Tolerance and Improve Operational Effectiveness	MCT, Tracking Task, Double Task, Blood Pressure	TYR Improves Systolic Blood Pressure (p = ND), Memory ($p < 0.05$) and Perceptual Motor Skills ($p < 0.05$)	–
Shurtleff[11]	8 Healthy Males, Mean Age 28 ± 2	Overall (8/ND)	TYR Food/Warm: 150 mg/kg Body Weight of Mixture (42 g Applesauce + L-Crystalline TYR) Before Entering Warm Chamber	PLA/Warm: Mixture (42 g Applesauce + 5 mg Microcrystalline Cellulose) Before Entering Warm Chamber	Warm Exposure: Subjects Placed in 22°C Environmental Chamber Cold Exposure: Subjects Placed in 4°C Environmental Chamber	Delayed Match-to-Sample	TYR Effectively Protects Against the Effects of Cold Stress on Short-term Spatial Memory and Pattern Recognition (p = 0.0001).	–
			TYR Food/Cold: 150 mg/kg Body Weight of Mixture (42 g Applesauce + L-Crystalline TYR) Before Entering Cold Chamber	PLA/Cold: Mixture (42 g Applesauce + 5 mg Microcrystalline Cellulose) Before Entering Cold Chamber				
Neri et al[9]	20 Male U.S. Marines, Mean Age 25[b]	TYR (10/10) PLA (10/10)	TYR Food: 150 mg/kg TYR + 113 g Banana-Flavored Yogurt at 4th and 5th Testing Blocks	PLA: 150 mg/kg Cornstarch + 113 g of Banana-Flavored Yogurt at 4th and 5th Testing Block	Noise: Moderate Intensity, Low Frequency Noise Resembling Jet Aircraft Engine	Compensatory Tracking Task, High-Event-Rate Vigilance Task, Dichotic Listening Task	TYR Results in Significantly Smaller Performance Declines on Hand–Eye Coordination ($p < 0.05$) and Running Memory	–

(continued)

TABLE II. Continued

Citation	Population Description	Sample Entered/Completed	Supplement	Control	Stressor	Relevant Outcomes	Author's Main Conclusions	Quality Score
							Tasks ($p < 0.05$) But Has No Such Effect on Selective Auditory Attention and Pulse Rate	
				CCTs ($n = 4$)				
Banderet[3]	23 U.S. Male Army Personnel, Aged 18–20[c]	Overall (23/ND)	TYR Pill: 50 mg/kg Capsule Given at 0720[a], 20 Minutes After the Test Session Began, Second Administration at 0800[a]	PLA[e]: ND	Greater Stressed Environment (GSE): 15°C and 4,700 M Simulated Altitude Lesser Stressed Environment (LSE): 15°C and 4,200 M Simulated Altitude Control: Normal Temperature and Pressure (22°C and 550 m Simulated Altitude)	Addition Task, Coding Task, Map Compass Task, Number Comparison Skills, Pattern Recognition Task, Dual Task Vigilance Test, Reaction Time	Compared to PLA, TYR Improved Scores on Number Comparison ($p < 0.05$) and Pattern Recognition Tasks ($p < 0.05$) and Choice Reaction Latency Times ($p < 0.05$) During Exposure to Both Greater and Lesser Stress Environments. Additionally, TYR Improved Scores on Addition ($p < 0.05$), Coding ($p < 0.05$), Map Compass Applications ($p < 0.01$), During Exposure to Lesser Environmental Stressors, as well as Vigilance ($p < 0.05$) During Exposure to a Greater Environmental Stress	+
Lieberman[8]	20 Healthy Male Subjects, Mean Age 24[d]	Overall (20/ND)	TYR Pill: 100 mg/kg Ingested at 0700 After 12 Hours of Fasting	TYR Placebo[e]: Matched in Appearance to One of the Amino Acids Tryptophan Pill: 50 mg/kg Ingested at 0700 After 12 Hours of Fasting	None	Simple Auditory Reaction Time, Two-Choice Visual Reaction time, Grooved Pegboard Test, Thurstone Tapping Test	Compared to PLA, TYR Showed Significant Improvement in Auditory Reaction Time ($p < 0.05$) But Not on Any Other Performance Tests	+

(continued)

TABLE II. Continued

Citation	Population Description	Sample Entered/Completed	Supplement	Control	Stressor	Relevant Outcomes	Author's Main Conclusions	Quality Score
				Tryptophan PLA: Matched in Appearance to One of the Amino Acids				
Mahoney[5]	19 Healthy Military Males and Females (Gender Ratio = ND), Mean age 21 ± 3[c]	Overall (19/ND)	TYR Food/Cold: 150 mg/kg TYR in Nutrient Bar (9.3 mg TYR) Before Each Cold and Thermo-Neutral Immersion	ThermPLA[e]: Nutrient Bar Matched to TYR Bar's Taste/Texture Before Each Thermoneutral Immersion ColdPLA: Nutrient Bar Matched to TYR Bar's Taste/Texture Before Each Cold Immersion	Cold Immersion: Subjects Seated and Immersed to the Chest in Circulated Water (10°C) for 90 Minutes Thermoneutral Immersion: Subjects Seated and Immersed to the Chest in Circulated Water (35°C) for 90 Minutes	Visual Vigilance, Delayed Match-to-Sample, 4-Choice Reaction Time	TYR Alleviates Cold-induced Decrements in Working Memory ($p < 0.05$) But Not Visual Vigilance or Reaction Time	+
O'Brien[12]	15 Enlisted Soldiers (14 M/1 F), Mean Age 20 ± 2[c]	Overall (15/ND)	TYR Food/Cold: 150 mg/kg of Body Weight TYR in Energy Bar With TYR Before Cold Immersion	WarmPLA[e]: Nutrient Bar Matched to TYR Bar's Taste/Texture Before Warm Immersion ColdPLA: Nutrient Bar Matched to TYR Bar's Taste/Texture Before Cold Immersion	Warm Immersion: Subjects Immersed to the Chest in Circulated Water (35°C) for 90 Minutes Cold Immersion: Subjects Immersed to the Chest in Circulated Cold Water for 90 Minutes	Match-to-Sample, Complex Reaction Time, Serial Addition/Subtraction, Visual Vigilance Task, Logical Reasoning, Repeated Acquisition, Psychomotor and Physical Performance Test Battery	TYR Effectively Mitigates Cold-induced Tasks of Marksmanship (p = ND), and Visual Attention and Choice Reaction Time ($p < 0.05$).	+

PLA, placebo; TYR, tyrosine; BCAA, branched chain amino acids; ND, not described; CCTs, Clinical Controlled Trials; ThermPLA, Thermoneutral Placebo Bar; ColdPLA, Cold/Placebo Bar; WarmPLA, Warm/Placebo Bar; MCT, Memory Comparison Task. [a]Power achieved. [b]Power not achieved. [c]Informed consent obtained. [d]Informed consent not obtained. [e]Crossover design.

addressed the population's baseline exposure to tyrosine (i.e., level of tyrosine present at the beginning of the study).

Because tyrosine was administered in a variety of ways, including by pill, mixed in food (i.e., yogurt, applesauce), or as a drink mixture, the authors also examined whether studies included information regarding the preparation and analysis of the tyrosine supplement for these delivery methods. Preparation of tyrosine was only described by 29% of the studies; as expected, no studies described the preparation of pills, but a fair number of studies described the preparation of either food (29%) or drink (50%) mixtures. No studies described whether analyses of the tyrosine supplement were conducted.

Only 20% of RCTs[4,11] discussed adverse events, both of which stated that "no adverse events occurred." Similarly, 25% of CCTs reported no adverse events[5]; the remaining 75%[3,8,12] did not discuss adverse events.

DISCUSSION

Results from this systematic review indicate that the available evidence is not sufficient to make sound recommendations on the effectiveness of tyrosine for mitigating stress-induced decrements in physical or cognitive performance. However, this review does offer suggestions for future research.

It has been suggested that tyrosine may have beneficial effects in situations of extreme stress and little or no effect under conditions of mild stress.[5] Accordingly, of the four studies that investigated the effect of tyrosine on physical performance, only one low-quality study[26] (results may reflect bias) showed improved exercise tolerance in trained individuals exposed to a moderately hot environment. The other three studies[2,24,25]—carried out in temperate environments—showed no improvements in physical performance. Thus, future research should consider the potential effects of environmental settings (i.e., temperature), as it is possible that the stress imposed by exercising under thermoneutral conditions is insufficient to deplete CA neurotransmitters and/or their precursor, whereas the combined effect of strenuous physical activity under adverse environmental conditions is sufficient. Additional studies would be needed to confirm this effect.

In contrast to physical performance, all six studies investigating the effects of tyrosine on cognition while exposed to stressful conditions showed favorable effects on several psychological parameters. Stressors ranged from sleep deprivation and extreme climate conditions to military combat training, all of which have been shown to significantly increase CA levels. Although these results seem compelling and practically relevant, we cannot make strong recommendations because all studies were low quality according to the SIGN criteria. Future research should follow specific guidelines to ensure they are producing high methodological quality reports.

Because this review had so few RCTs, CCT study designs were included post hoc. These studies[3,5,8,12] were high quality and reported improvements in cognitive tasks assessing attention, reaction time, memory, and psychomotor function. Because GRADE only considers RCT study designs for making recommendations, the CCTs were not used to make any recommendations. However, the military may want to consider these trials and build upon the available knowledge as three of these studies[3,5,12] involved the military population. If tyrosine supplementation can be shown to be beneficial under stressful conditions, it will be especially relevant to military personnel who experience performance and cognitive decrements during stressful missions and adverse scenarios such as, but not limited to, sleep deprivation, intense combat, and exposure to extreme heat, extreme cold, or high-altitude environments.[27]

The divergent findings may reflect the extent of CA neurotransmitter activity. Stress increases CA neurotransmitter activity, particularly in the frontal cortex,[28] and under normal conditions, tyrosine hydroxylase catalyzes tyrosine synthesis: this enzyme appears to be the rate-limiting factor for CA synthesis in the brain.[29] However, tyrosine availability may be rate limiting under extremely stressful conditions when CA are being depleted because of rapid and continuous neuron firing.[1,4] Hence, maintaining an abundant supply of tyrosine may prevent CA depletion in the brain, which would explain why increasing tyrosine availability under nonstressful conditions does not yield any beneficial effect: CA must be depleted to demonstrate any effect of tyrosine.[11] Whether this is the mechanism explaining the beneficial effect of tyrosine remains to be determined.

In addition, the divergent findings could be explained by the timing and amount of tyrosine ingested. Currently, no optimal dose or timing has been established for tyrosine supplementation. However, the serving size/dose utilized in many of the studies reviewed were consistent: either 150 mg/kg of tyrosine (or approximately 10 g of tyrosine for a 70 kg individual)[2,5,9,11–13,24–26] or 100 mg/kg of tyrosine (or approximately 7 g of tyrosine for a 70 kg individual).[3,4,8,10] These doses have been found to increase normal plasma tyrosine levels two- to three-fold, and have shown physiologic effects under stressful environmental conditions.[4] Importantly, the timing of tyrosine administration varied considerably across studies. However, it seems that the effects of tyrosine are realized after 60 and up to 300 minutes[9–11,13] after ingestion; plasma levels peak at about 120 minutes. Accordingly, future studies should strongly consider administering tyrosine approximately 2 hours before performance tasks and begin to use uniform dosing across studies.

Additional recommendations for future studies are as follows. First, researchers should report adverse events, even if there are none. Many of the studies reviewed failed to report adverse events, perhaps because tyrosine is an essential amino acid and researchers do not believe they need to document safety. Tyrosine supplements are most likely safe, but safety should be fully addressed and reported to make strong recommendations according to the GRADE criteria. Second, future studies should consider delivering tyrosine in forms other than drinks. In this review, four out of the 14 studies delivered tyrosine in liquid form. However, since tyrosine is

TABLE III. GRADE Analysis: Quality of the Overall RCT Literature Pool Assessing Tyrosine for the Enhancement of Cognitive/Physical Performance

Category	Number of Participants Completed (Number of Studies)	Confidence in Estimate of Effect GRADE	Magnitude of Estimate of Effect GRADE	Safety GRADE	GRADE Recommendation
Exercise	47 (4)	C	ND	+2	No Recommendation
Environmental Stressors	175 (6)	C	ND	+2	Weak Recommendation in Favor

Four major domains comprise the core of the modified GRADE methodology: Confidence in the Estimate of the Effect was categorized into the following groups using predefined criteria: (1) A (High; further research is very unlikely to change confidence in the estimate of effect): several high-quality RCTs with consistent results or in special cases, or one large, high quality, multicenter RCT; (2) B (Moderate; further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate): one high-quality RCT or several RCTs with some limitations; (3) C (Low; further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate): one or more RCTs with severe limitations; (4) D (Very Low; any estimate of effect is very uncertain): expert opinion, no direct research evidence or one or more RCTS with severe limitations. Magnitude of the Effect was categorized into 5 levels of none (<0.2), small (0.2–0.5), moderate (0.5–0.8), large (>0.8), or not described (ND). Authors did not describe or report effect size for this review's outcomes of interest because of the lack of author reporting). Safety Grade is dependent on the frequency and severity of adverse events and interactions. Safety was categorized into one of the following grades: +2: appears safe with infrequent adverse events and interactions; +1: appears relatively safe but with frequent but not serious adverse events and interactions; 0: safety not well understood or conflicting; −1: appears to have safety concerns that include infrequent but serious adverse events and/or interactions; or −2: has serious safety concerns that include frequent and serious adverse events and/or interactions. Strength of the Recommendation can be determined using the following categories and criteria: Strong recommendation in favor of or against: very certain that benefits do, or do not, outweigh risks and burdens; No recommendation: no recommendations can be made or; Weak recommendation in favor of or against: benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks.

only moderately soluble in water, tyrosine pills or tyrosine mixed in a meal or sauce may be more effective modes of delivery. Third, studies should explore effects in other target groups such as women and the military. Studies conducted in women could reveal gender differences if present; no current study has done so. High-quality studies in the military population are also needed as positive findings would be extremely beneficial to this group. Fourth, future studies should strive to assess indirect and/or direct measurement of influences on the central and peripheral nervous system to elucidate mechanisms whereby tyrosine supplementation exerts its effects. For instance, Deijen et al[14] assessed 3-methoxy-4-hydroxyphenylglycol (MHPG) concentration in urine to determine the direct influence of tyrosine on noradrenergic brain activity. Their rationale was that since "60% of the MHPG concentration is of central origin, a larger MPHG concentration in the tyrosine group than in the placebo group would be indicative of a tyrosine-induced increase in NE metabolism."[14] Fifth, future studies could explore other nutrients and enzymes that may affect the synthesis of CA. For example, the effect of tyrosine on CA synthesis is upstream relative to other nutrients (e.g., phenylalanine, ascorbic acid). Consequently, because tyrosine is also abundant in the average diet, supplementation of other nutrients to decrease stress should be explored. Finally, all researchers need to ensure their studies comply with strict criteria such as CONSORT, SIGN 50, and Cochrane guidelines to provide systematic reviews and meta-analysis high-quality data for stronger recommendations. The small number of RCTs included in this review demonstrates the need, not only for strong study designs and methodology that can address the research gaps but also for more RCTs that have sufficient power to produce an effect.

A limitation of the REAL process is that it only searches and evaluates RCT and systematic review study designs accessible in a standard set of current English electronic databases. Although the subsequent inclusion of only English literature and exclusion of gray literature may be seen as a limitation, research has shown that doing so does not seriously compromise the implications for the majority of interventions and claims.[30]

In summary, this REAL demonstrated that tyrosine as an intervention to improve cognitive or physical performance cannot be recommended at this time because of the limited number of high-quality studies available. Although it appears highly probable that tyrosine may have favorable effects on cognition during periods of sustained and severe stress, future high-quality studies with adequate dosing are needed to document this possibility.

ACKNOWLEDGMENTS

The authors thank Viviane Enslein, BA, for assistance in preparation of the manuscript. This work was supported by the Defense Health Program and USUHS, Human Performance Resource Center, G191FL.

REFERENCES

1. Owasoyo JO, Neri DF, Lamberth JG: Tyrosine and its potential use as a countermeasure to performance decrement in military sustained operations. Aviat Space Environ Med 1992; 63(5): 364–9.
2. Sutton EE, Coill MR, Deuster PA: Ingestion of tyrosine: effects on endurance, muscle strength, and anaerobic performance. Int J Sport Nutr Exerc Metab 2005; 15(2): 173–85.
3. Banderet LE, Lieberman HR: Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. Brain Res Bull 1989; 22(4): 759–62.

4. Dollins AB, Krock LP, Storm WF, Wurtman RJ, Lieberman HR: L-tyrosine ameliorates some effects of lower body negative pressure stress. Physiol Behav 1995; 57(2): 223–30.
5. Mahoney C, Castellani J, Kramer F, Young A, Liberman H: Tyrosine supplementation mitigates working memory decrements during cold exposure. Physiol Behav 2007; 92: 575–82.
6. Lieberman HR: Nutrition, brain function and cognitive performance. Appetite 2003; 40(3): 245–54.
7. Wurtman RJ, Hefti F, Melamed E: Precursor control of neurotransmitter synthesis. Pharmacol Rev 1980; 32(4): 315–35.
8. Lieberman HR, Corkin S, Spring BJ, Wurtman RJ, Growdon JH: The effects of dietary neurotransmitter precursors on human behavior. Am J Clin Nutr 1985; 42(2): 366–70.
9. Neri DF, Wiegmann D, Stanny RR, Shappell SA, McCardie A, McKay DL: The effects of tyrosine on cognitive performance during extended wakefulness. Aviat Space Environ Med 1995; 66(4): 313–9.
10. Deijen JB, Orlebeke JF: Effect of tyrosine on cognitive function and blood pressure under stress. Brain Res Bull 1994; 33(3): 319–23.
11. Shurtleff D, Thomas J, Schrot J, Kowalski K, Harford R: Tyrosine reverses a cold-induced working memory deficit in humans. Pharmacol Biochem Behav 1994; 47: 935–41.
12. O'Brien C, Mahoney C, Tharion W, Sils I, Castellani J: Dietary tyrosine benefits cognitive and psychomotor performance during body coping. Physiol Behav 2007; 90: 301–7.
13. Magill RA, Waters WF, Bray GA, et al: Effects of tyrosine, phentermine, caffeine D-amphetamine, and placebo on cognitive and motor performance deficits during sleep deprivation. Nutr Neurosci 2003; 6(4): 237–46.
14. Deijen JB, Wientjes CJ, Vullinghs HF, Cloin PA, Langefeld JJ: Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. Brain Res Bull 1999; 48(2): 203–9.
15. Petrides JS, Gold PW, Mueller GP, et al. Marked differences in functioning of the hypothalamic-pituitary-adrenal axis between groups of men. J Appl Physiol 1997; 82(6): 1979–88.
16. Singh A, Petrides JS, Gold PW, Chrousos GP, Deuster PA: Differential hypothalamic-pituitary-adrenal axis reactivity to psychological and physical stress. J Clin Endocrinol Metab 1999; 84(6): 1944–8.
17. Lehnert H, Reinstein DK, Strowbridge BW, Wurtman RJ: Neurochemical and behavioral consequences of acute, uncontrollable stress: effects of dietary tyrosine. Brain Res 1984; 303(2): 215–23.
18. Leyton M, Young SN, Pihl RO, et al: Effects on mood of acute phenylalanine/tyrosine depletion in healthy women. Neuropsychopharmacology 2000; 22(1): 52–63.
19. Marriott BM (editor): Food Components to Enhance Performance: An Evaluation of Potential Performance-Enhancing Food Components for Operational Rations. Washington, DC, The National Academies Press, 1994.
20. Lee C, Crawford C, Wallerstedt D, et al: The effectiveness of acupuncture research across components of the trauma spectrum response (tsr): a systematic review of reviews. Syst Rev 2012; 1: 46.
21. York A, Crawford C, Walter A, Walter J, Jonas W, Coeytaux R: Acupuncture research in military and veteran populations: a rapid evidence assessment of the literature. Med Acupuncture 2011; 23(4): 229–36.
22. Network SIG: SIGN 50: A guideline developer's handbook. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network, 2008. Available at http://www.sign.ac.uk/pdf/sign50.pdf; accessed October 4, 2014.
23. Group GW: Grading of Recommendations Assessment, Development and Evaluation (GRADE). Available at www.gradingworkinggroup.org; accessed September 28, 2010.
24. Struder HK, Hollmann W, Platen P, Donike M, Gotzmann A, Weber K: Influence of paroxetine, branched-chain amino acids and tyrosine on neuroendocrine system responses and fatigue in humans. Horm Metab Res 1998; 30: 188–94.
25. Chinevere TD, Sawyer RD, Creer AR, Conlee RK, Parcell AC: Effects of L-tyrosine and carbohydrate ingestion on endurance exercise performance. J Appl Physiol 2002; 93(5): 1590–7.
26. Tumilty L, Davison G, Beckmann M, Thatcher R: Oral tyrosine supplementation improves exercise capacity in the heat. Eur J Appl Physiol 2011; 111(12): 2941–50.
27. Beck TW, Housh TJ, Malek MH, Mielke M, Hendrix R: The acute effects of a caffeine-containing supplement on bench press strength and time to running exhaustion. J Strength Cond Res 2008; 22(5): 1654–8.
28. Cenci MA, Kalen P, Mandel RJ, Bjorklund A: Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate-putamen: a microdialysis study in the rat. Brain Res 1992; 581(2): 217–28.
29. Fernstrom JD: Effects on the diet on brain neurotransmitters. Metabolism 1977; 26(2): 207–23.
30. Watt A, Cameron A, Sturm L, et al: Rapid versus full systematic reviews: validity in clinical practice? ANZ J Surg 2008; 78(11): 1037–40.