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Treatment with Tyrosine, a Neurotransmitter Precursor, Reduces Environmental Stress in Humans

(s) L.E. Banderet and H.R. Lieberman

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DEPARTMENT OF THE ARMY
US ARMY RESEARCH INSTITUTE OF ENVIRONMENTAL MEDICINE
NATICK, MASSACHUSETTS 01760-5007

July 31, 1988

Health and Performance Division

Editor
Lancet
7 Adam Street
Adelphi, London WC2N 6AD
England

Dear Sir:

Enclosed is a manuscript "Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans", that we wish to submit for publication as a report in Lancet. In this paper we demonstrate that the amino acid tyrosine significantly reduces symptoms, adverse moods and performance impairments resulting from exposure to cold and high altitude. To the best of our knowledge this is the first study to show that this amino acid has beneficial effects on humans who are experimentally stressed.

Sincerely,

LOUIS E. BANDERET, Ph.D.
Research Psychologist
Health and Performance Division

HARRIS R. LIEBERMAN, Ph.D.
Research Scientist

Enclosure

TREATMENT WITH TYROSINE, A NEUROTRANSMITTER PRECURSOR, REDUCES ENVIRONMENTAL STRESS IN HUMANS

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SUMMARY

Acutely stressful situations can disrupt behavior and deplete brain norepinephrine and dopamine, catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. We investigated whether tyrosine (100 mg/kg) would protect humans from some of the adverse consequences of a 4.5 hour exposure to cold and hypoxia, conditions experienced in high mountainous regions. Tyrosine significantly decreased symptoms, adverse moods, and performance impairments in subjects who exhibited average or greater responses to these environmental conditions. This suggests that treatment with tyrosine should be evaluated in these and other acutely stressful situations for beneficial behavioral effects.

INTRODUCTION

Animals that are acutely stressed exhibit characteristic neurochemical and behavioral changes (1-2). In certain brain regions turnover of norepinephrine increases and its absolute levels decline. When these changes occur animals explore less, interact less with their environment, and seem debilitated (1-2). Tyrosine, given acutely or in the diet, protects rodents from both the neurochemical and the behavioral effects of acute stressors such as tail shock or a cold exposure (3-5).

Tyrosine is a large neutral amino acid found in dietary proteins and is the precursor of norepinephrine, dopamine, and epinephrine (6). During stressful situations, catecholaminergic neurons that are highly active may require additional precursor so that catecholamine synthesis keeps pace with the increased neurotransmitter being released (6-7). Some of the behavioral deficits caused by acute stress may result from depletion of norepinephrine, and perhaps dopamine, in catecholaminergic neurons (1,2,8,9). Noradrenergic neurons within the locus coeruleus are thought to influence attention, alertness, motor activity, and anxiety (8,9). Thus, tyrosine could protect against the adverse behavioral effects of acute stress by preventing depletion of norepinephrine in such neurons.

To determine whether tyrosine might have beneficial effects on humans who are exposed to acutely stressful conditions we employed a combination of environmental stressors -- cold and hypoxia. In rodents, acute cold exposure depletes central catecholamines and impairs various behaviors (1,2). In humans exposure to high altitude and the resulting hypoxia cause adverse changes in performance and mood soon after ascent to altitude (10-13). To our knowledge tyrosine's effects have not been previously evaluated

in experimentally stressed humans. In studies of normal subjects, not exposed to experimental stress, its administration resulted in small improvements in mood and reaction times (14,15).

METHODS

Twenty-three male U.S. Army personnel, aged 18-29 years (median = 21), participated in this experiment. All were volunteers and gave their informed consent after they were fully appraised of the potential risks and benefits of the study. The protocol was reviewed and approved by the appropriate institutional human use review committees. All volunteers were exposed twice to two levels of environmental stressors: 1) 15°C and 4200 m (450 torr) simulated altitude; and 2) 15°C and 4700 m (421 torr) simulated altitude. These conditions were simulated by reducing atmospheric pressure. The relative humidity was 30-50%; ventilation was 0.71 m^3/min. Such environments resemble conditions encountered by travelers to mountainous regions; the altitudes we selected were slightly higher and lower than Pikes Peak, Colorado. A control condition with normal temperature and pressure conditions [22°C and 550 m (710 torr) altitude] was also included. All subjects were tested with both placebo and tyrosine for each of the three environmental conditions. Each environmental exposure (control condition, lessor stressor, or greater stressor) was 4.5 h per day. At least 48 h separated test sessions.

Tyrosine or placebo was administered double-blind, in gelatin capsules, in two equal doses. On a given test day about half of the subjects received tyrosine; the others received placebo. Test sessions began at 7:00 A.M. The first dose of tyrosine (50 mg/kg) was given at 7:20 AM, just before we exposed subjects to the environmental condition, the second dose (50 mg/kg), 40 min later. The total dose was about 80% of an adult's daily dietary

intake. Blood samples (<20 ml) were drawn just before the first dose of tyrosine or placebo, and 150 and 265 min later, and used for determination of plasma tyrosine concentrations (16). Just before, one hour and two and one-half hours after the start of the environmental exposures, blood pressure and pulse-rate were automatically assessed.

Cold and high altitude environments produce a variety of adverse effects. We assessed symptoms, mood states, cognitive performance, reaction time, and vigilance. Subjects rated their symptoms with the Environmental Symptoms Questionnaire (10). Mood states were evaluated with several standardized self-report questionnaires (the Clyde Mood Scale, Multiple Affect Adjective Check List, Profile of Mood States, Stanford Sleepiness Scale) that have been employed to evaluate a variety of psychoactive drugs, foods, environmental conditions, and behavioral disorders (11,17-22). In addition, we designed a Catecholaminergic Effects Scale to evaluate behavioral changes that might result from the neurochemical consequences of administering supplemental tyrosine. The performance tasks required sustained attention, applying prior knowledge to problems, processing spatial and verbal information, performing mathematical calculations, and making decisions (23-26). We also measured reaction time (27) and vigilance (28).

RESULTS

As expected, individual subjects responded differently to the stressors (29). To insure that tyrosine was evaluated in subjects substantially impaired by exposure to the environmental conditions, we limited our analyses to individuals most affected by exposure to the cold and high altitude environments. These individuals were identified, based upon their scores when they were treated with placebo, for each dependent measure and

level of environmental stressor. When a subject was exposed to an environmental stressor, his score (for each symptom, mood, and performance measure) was subtracted from his score for the control environmental condition. The subject was then classified as a responder to the environmental manipulation if his difference score was equal to or greater than the group mean. The scores of responders', on tyrosine versus placebo treatment, were compared for tyrosine effects with paired t-tests (two-tailed). T-tests were used for each level of environmental stressor rather than an overall analysis of variance because the number of individuals selected varied somewhat across environmental conditions and dependent measures.

Tyrosine significantly reduced many adverse behavioral effects produced by exposure to cold and hypoxia. Figure 1 shows treatment data from the Environmental Symptoms Questionnaire, Stanford Sleepiness Scale, and the Catecholaminergic Effects Scale. Tyrosine, compared to placebo, significantly reduced symptoms of headache, coldness, distress, fatigue, muscular discomfort, and sleepiness among those subjects who responded adversely to the environmental conditions during exposure to at least one level of the environmental stressors. Tyrosine was also beneficial as measured by the Catecholaminergic Effects Scale (Fig. 1).

Tyrosine also reduced adverse emotions experienced during exposure to the environmental stressors. Fig. 2 shows mood states from the Clyde Mood Scale, Multiple Adjective Affect Check List, and the Profile of Mood States. During exposure to the environmental stressors, tyrosine treatment reduced dizziness, confusion, fatigue, unhappiness, hostility, and tension. The subjects also reported that they could think more clearly. The performance of the subjects on many cognitive tasks was also impaired by exposure to the cold and high altitude conditions. Treatment with tyrosine reversed many of

these adverse effects (Fig. 3). Subjects, exposed to the lessor environmental stressor, completed more Addition, Coding, Map Compass Applications, Number Comparison, and Pattern Recognition problems correctly. They also had decreased Choice Reaction Time latencies and made fewer errors. Beneficial effects from tyrosine were also seen during the greater environmental stressor. Tyrosine increased the number of correctly completed Number Comparison and Pattern Recognition problems, increased vigilance, and significantly decreased latencies on the Choice Reaction Time task.

Plasma tyrosine levels were significantly elevated during behavioral testing in subjects who received tyrosine. Mean baseline level of plasma tyrosine before treatment was 42.7 $\pm$ 3.3 nmoles/ml, averaged across all environmental conditions. Plasma tyrosine levels were 108.5 $\pm$ 5.1 nmoles/ml 150 min after ingestion of tyrosine and 98.6 $\pm$ 6.3 nmoles/ml after 265 min. Heart rate and blood pressure did not differ with tyrosine treatment.

DISCUSSION

In this study tyrosine reduced adverse behavioral effects caused by exposure to cold and hypoxia. It did not produce any apparent side effects. Tyrosine decreased symptom intensities, adverse moods, and performance impairments in subjects who responded adversely to the environmental conditions. We observed numerous positive effects of tyrosine with these measures at both levels of the environmental stressors. These results suggest that this nutrient may be useful for reducing the acute behavioral consequences of exposure to cold and high altitude.

Many behavioral functions, for example, anxiety (tension), vigilance, and attention, that we found to be improved by treatment with tyrosine are believed to be regulated, in part, by noradrenergic neurons in the locus coeruleus (1,2,8,9). Such beneficial effects are consistent with known

neurochemical changes resulting from administration of supplemental tyrosine to animals (3-5). For our analyses, we selected those subjects most affected the combination of environmental stressors to evaluate the treatment strategy. We hypothesized that unless a behavior (e.g. mood, performance) was impaired, it could not improve with treatment. This is consistent with the neurochemical rationale for treating animals with tyrosine to overcome neurotransmitter deficits (6). This approach is supported by the finding that catecholaminergic neurons only appear to be responsive to additional substrate when they are highly active (7). Perhaps stress-induced impairments in behavior are present in individuals with the greatest central deficits in catecholaminergic functioning.

Additional research is needed to determine whether tyrosine's beneficial effects will be present in other stressful circumstances. In such situations, our study suggests that beneficial effects of tyrosine will be observed in subjects most affected by environmental or other stressors.

ACKNOWLEDGEMENTS

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The investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on the use of Volunteers in Research. The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

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FIGURE CAPTIONS

Fig. 1. Effects of tyrosine treatment (mean $\pm$ sem) as measured by the Environmental Symptoms Questionnaire, Stanford Sleepiness Scale, and the Catecholaminergic Effects Scale. An asterisk(s) indicates the level of statistical significance ($p \leq 0.05$ = *; $p \leq 0.01$ = **). A high number on the Catecholaminergic Effects Scale indicates a more positive outcome.

Fig. 2. Tyrosine treatment effects (mean $\pm$ sem) as measured by factors from the Clyde Mood Scale, Multiple Affect Adjective Check List, and the Profile of Mood States (15). An asterisk(s) indicates the level of statistical significance ($p \leq 0.05$ = *; $p \leq 0.01$ = **; $p \leq 0.001$ = ***).

Fig. 3. Tyrosine treatment effects (mean $\pm$ sem) as measured by cognitive, reaction time, and vigilance tests. An asterisk(s) indicates the level of statistical significance ($p \leq 0.05$ = *; $p \leq 0.01$ = **).

FIG. 1

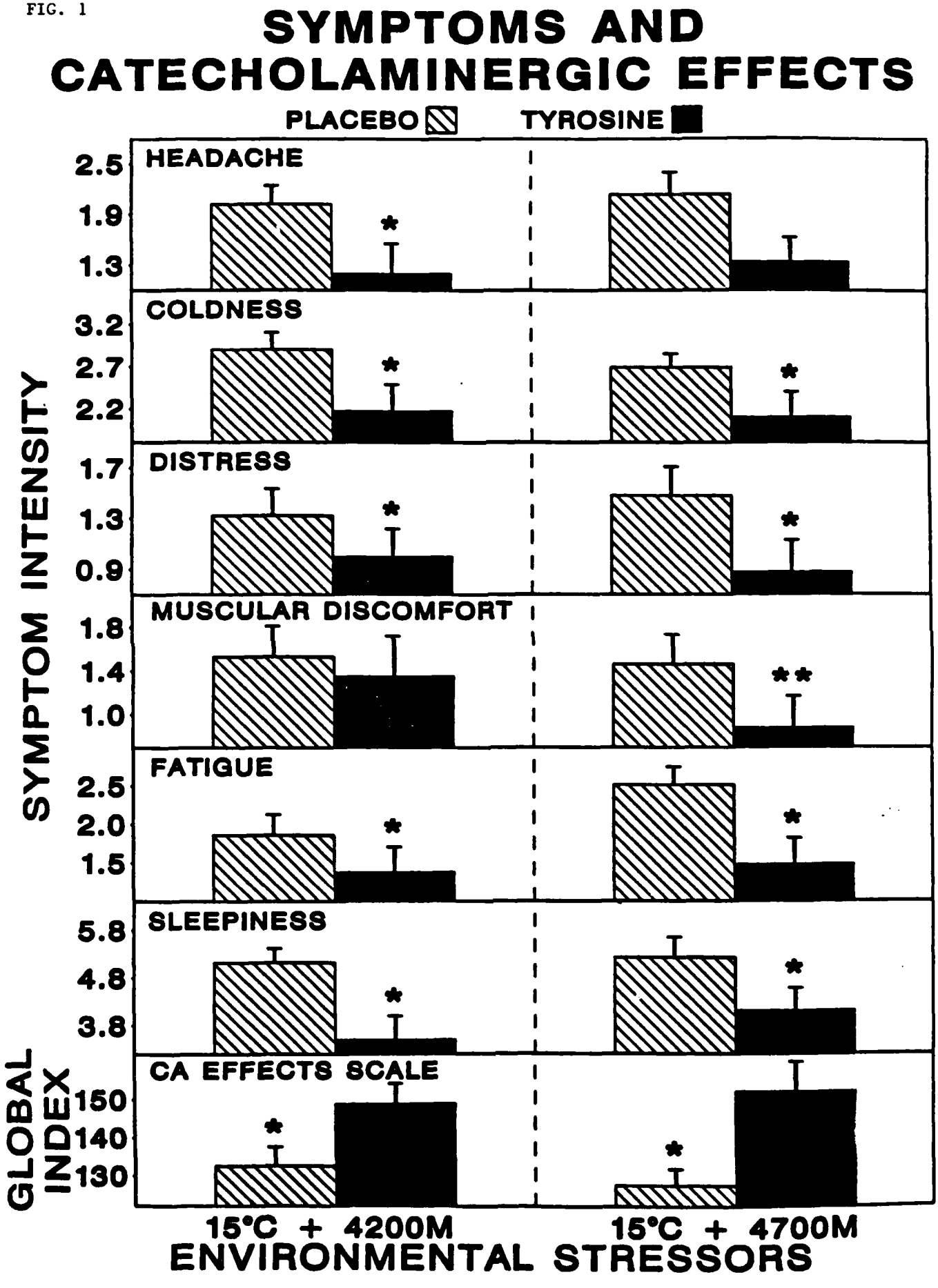
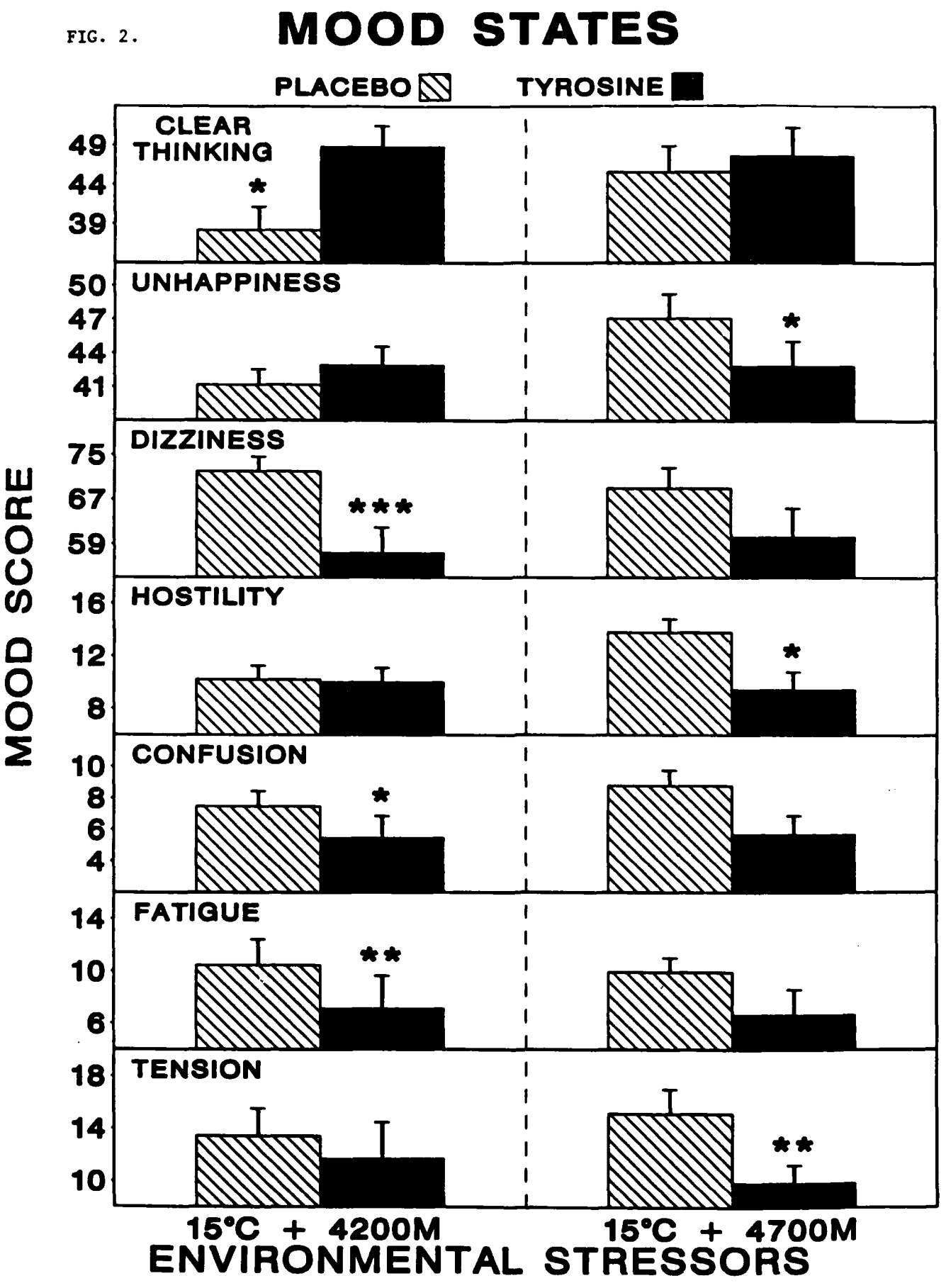

SYMPTOMS AND
CATECHOLAMINERGIC EFFECTS
PLACEBO
TYROSINE
SYMPTOM INTENSITY
HEADACHE
2.5
1.9
1.3
COLDNESS
3.2
2.7
2.2
DISTRESS
1.7
1.3
0.9
MUSCULAR DISCOMFORT
1.8
1.4
1.0
FATIGUE
2.5
2.0
1.5
SLEEPINESS
5.8
4.8
3.8
GLOBAL INDEX
CA EFFECTS SCALE
150
140
130
15°C + 4200M
15°C + 4700M
ENVIRONMENTAL STRESSORS

FIG. 2.


MOOD STATES
PLACEBO
TYROSINE
CLEAR THINKING
49
44
39
*
UNHAPPINESS
50
47
44
41
*
DIZZINESS
75
67
59
***
HOSTILITY
16
12
8
*
CONFUSION
10
8
6
4
*
FATIGUE
14
10
6
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TENSION
18
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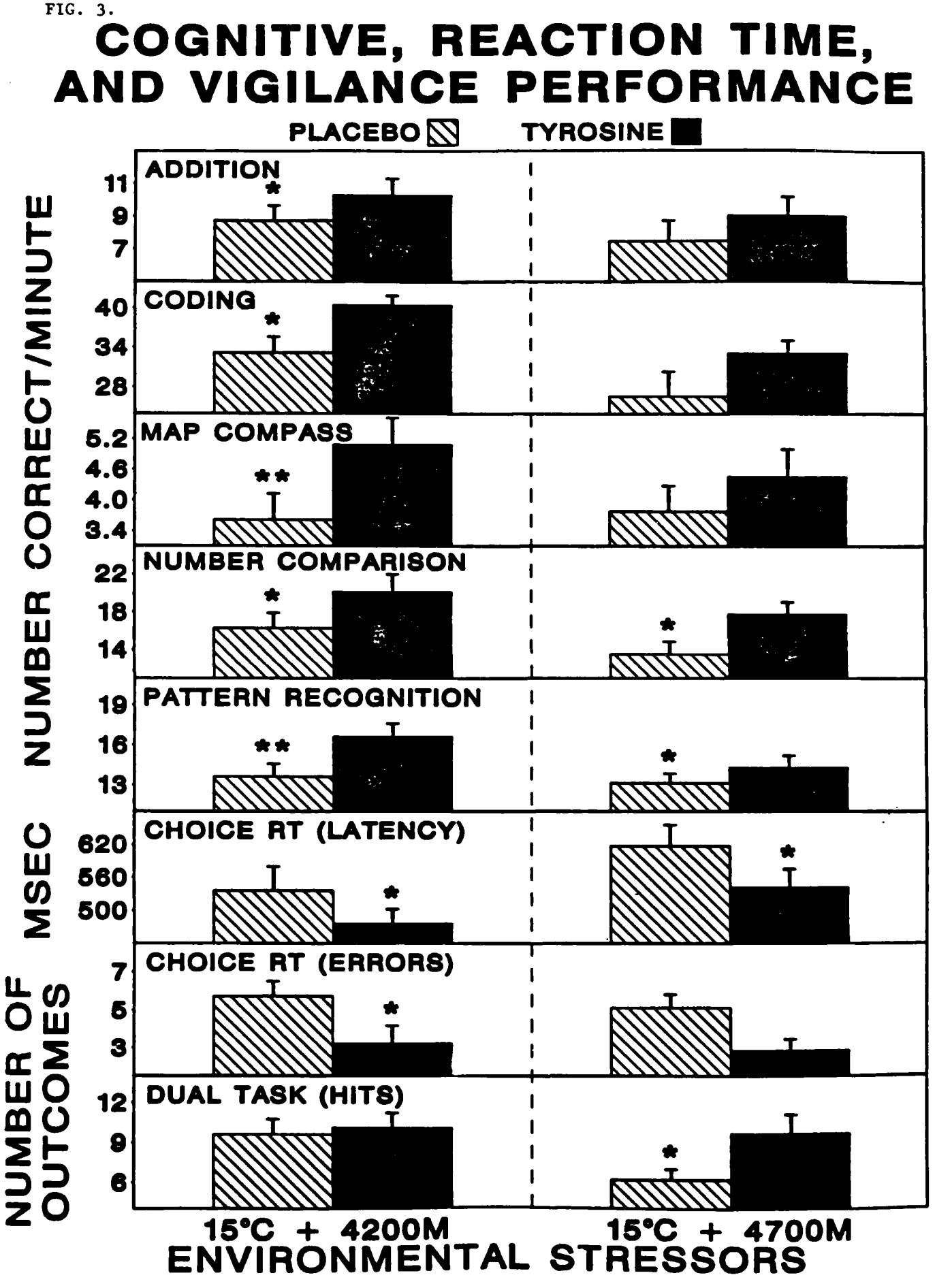
MOOD SCORE
15°C + 4200M
15°C + 4700M
ENVIRONMENTAL STRESSORS

FIG. 3.


COGNITIVE, REACTION TIME, AND VIGILANCE PERFORMANCE
PLACEBO
TYROSINE
NUMBER CORRECT/MINUTE
MSEC
NUMBER OF OUTCOMES
ADDITION
11
9
7
CODING
40
34
28
MAP COMPASS
5.2
4.6
4.0
3.4
NUMBER COMPARISON
22
18
14
PATTERN RECOGNITION
19
16
13
CHOICE RT (LATENCY)
620
560
500
CHOICE RT (ERRORS)
7
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3
DUAL TASK (HITS)
12
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6
15°C + 4200M
15°C + 4700M
ENVIRONMENTAL STRESSORS