Brain Research Bulletin, Vol. 22, pp. 759–762. Pergamon Press plc, 1989. Printed in the U.S.A. 0361-9230/89 $3.00 + .00

RAPID COMMUNICATION

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

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Received 7 February 1989

BANDERET, L. E. AND H. R. LIEBERMAN. *Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans.* BRAIN RES BULL **22**(4) 759–762, 1989.—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. Using a double-blind, placebo-controlled crossover design 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. Tyrosine significantly decreased symptoms, adverse moods, and performance impairments in subjects who exhibited average or greater responses to these environmental conditions. These results suggest that tyrosine should be evaluated in a variety of acutely stressful situations.

Tyrosine Environmental stressors Behavioral effects Mood Performance

ANIMALS that are acutely stressed exhibit characteristic neurochemical and behavioral changes (26,27). In certain brain regions turnover of norepinephrine increases and its absolute level declines. When these changes occur animals explore less, interact less with their environment, and seem debilitated (26,27). 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 cold exposure (5, 15, 16).

Tyrosine is a large neutral amino acid found in dietary proteins and is the precursor of norepinephrine, dopamine, and epinephrine (29). During stressful situations, highly active catecholaminergic neurons may require additional precursor so that catecholamine synthesis can keep pace with the increased amounts of neurotransmitters being released (20,29). Some of the behavioral deficits caused by acute stress may result from depletion of norepinephrine, and perhaps dopamine, in catecholaminergic neurons (10, 21, 26, 27). Specifically, noradrenergic neurons within the locus coeruleus are thought to influence attention, alertness, motor activity, and anxiety (10,21). Thus, tyrosine may 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 (26,27). In humans exposure to high altitude and the resulting hypoxia cause symptoms and adverse changes in performance and mood soon after ascent to altitude (1, 3, 22, 24). 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 time (14,17).

METHOD

Twenty-three male U.S. Army personnel, aged 18–20 years (median = 21), participated in this experiment. All were volunteers and gave their informed consent after they were fully apprised 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 generated in an altitude chamber 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 lower and higher 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

in counterbalanced orders for each of the three environmental conditions. Each environmental exposure (control condition, lessor stressor, or greater stressor) was 4.5 hr per day. At least 48 hr separated test sessions. Order of exposure to the environmental conditions was counterbalanced across the three groups of subjects who were studied, to control for order effects and adaptation across exposures. In addition, to further reduce order effects all subjects were briefly exposed to cold and hypobaric hypoxia a few days before testing began.

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. Each capsule contained 300 mg of tyrosine. Test sessions began at 7:00 a.m. The first dose of tyrosine (50 mg/kg) was given at 7:20 a.m., 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. The subjects had no difficulty ingesting the capsules. 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 (23). Just before, one hour and two and one-half hours after the start of each environmental exposure, blood pressure and pulse-rate were automatically assessed. Behavioral testing began at 8:40 a.m. and continued intermittently throughout the session.

We assessed symptoms, mood states, cognitive performance, reaction time, and vigilance since cold and high altitude environments produce a variety of adverse effects. Subjects rated their symptoms with the Environmental Symptoms Questionnaire (22). 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 (1, 8, 11, 18, 19, 25, 30). In addition, we designed a self-rated Catecholaminergic Effects Scale to evaluate behavioral changes that might result from the neurochemical consequences of administering supplemental tyrosine. The performance tasks employed required maintaining sustained attention, applying prior knowledge to problems, processing spatial and verbal information, performing mathematical calculations, and making decisions (2, 4, 7, 12). An addition task required summing problems with three 2-digit numbers. Another test involved coding a sequence of random numbers with nine symbols from a table. Map Compass Applications required conceptual understanding of the principles of land navigation but did not use compasses or terrain maps (3). A Number Comparison task required determinations if whether two numbers were the same or different. Pattern recognition problems consisted of a model histogram and eight samples. Finally, the Tower Task was a version of the Tower of Hanoi puzzle. Performance on each cognitive task was defined as number of problems correct per min. We also measured choice reaction time (23) and used a dual task vigilance test (13).

RESULTS

As expected, individual subjects were affected differently by exposure to the stressors (6). To insure that tyrosine was evaluated in subjects substantially impaired by exposure to the environmental conditions, we limited our analyses to those individuals most affected by exposure to the cold and high altitude environments. These individuals were identified, based upon their responses 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 this difference score was equal to or greater than the group mean. The scores of the responders, on tyrosine versus placebo treatment, were compared for tyrosine effects with paired t-tests (two-tailed). It was necessary to employ t-tests for each level of environmental stressor rather than an overall analysis of variance across conditions because the individuals selected varied somewhat across environmental conditions.

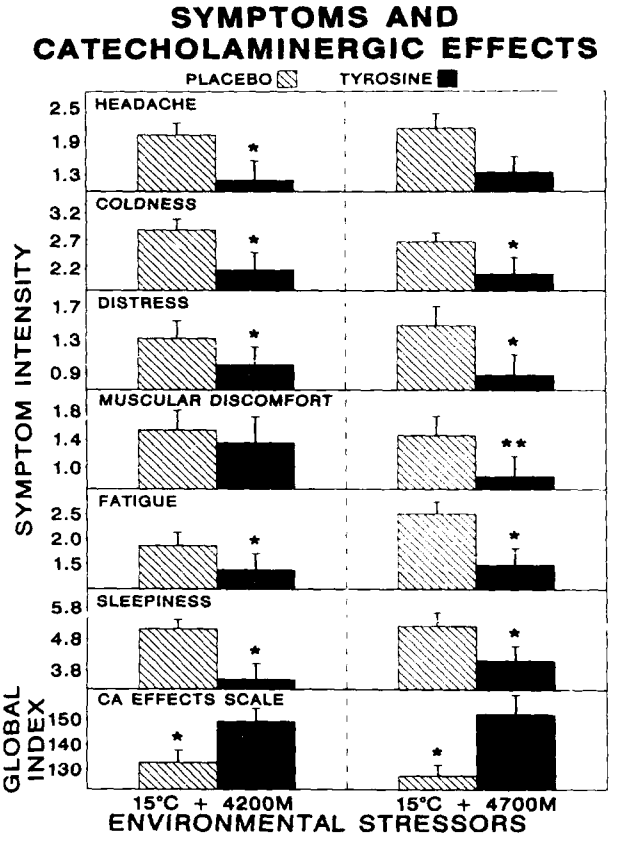

FIG. 1. Effects of tyrosine treatment (mean ± sem) as measured by the Environmental Symptoms Questionnaire, Stanford Sleepiness Scale, and the Catecholaminergic Effects Scale. An asterisk(s) indicates the level of statistical significance ($*p \leq 0.05$; $**p \leq 0.01$). A high number on the Catecholaminergic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

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 stressors. These effects were observed for both levels of environmental stressors, except for headache and muscular discomfort. 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. Figure 2 shows mood states from the Clyde Mood Scale, Multiple Adjective Affect Check List, and the Profile of Mood States. During exposure to the

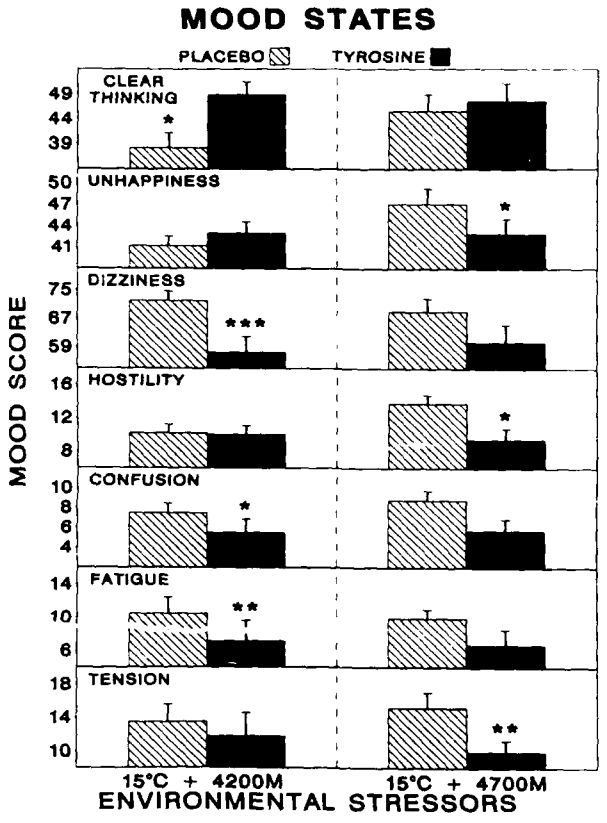

FIG. 2. Tyrosine treatment effects (mean ± sem) as measured by factors from the Clyde Mood Scale, Multiple Affect Adjective Check List, and the Profile of Mood States (15). An asterisk(s) indicates the level of statistical significance (*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$).

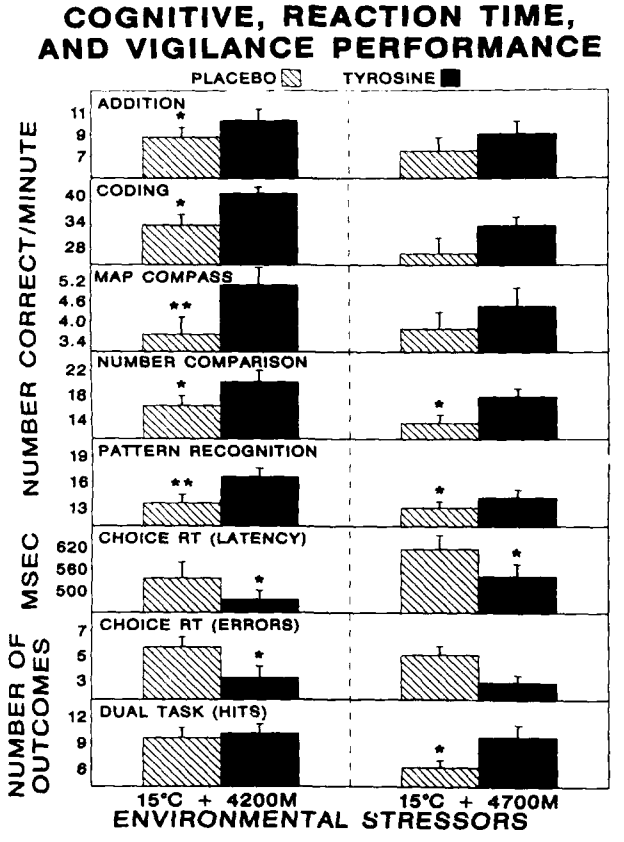

FIG. 3. Tyrosine treatment effects (mean ± sem) as measured by cognitive, reaction time, and vigilance tests. An asterisk(s) indicates the level of statistical significance (*$p \leq 0.05$; **$p \leq 0.01$).

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, when exposed to the lesser 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 ± 3.3 nmoles/ml, averaged across all environmental conditions. Plasma tyrosine levels were 108.5 ± 5.1 nmoles/ml 150 min after ingestion of tyrosine and 98.6 ± 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 improved following treatment with tyrosine are believed to be regulated, in part, by noradrenergic neurons in the locus coeruleus (10, 21, 26, 27). These beneficial effects are consistent with known neurochemical changes resulting from administration of supplemental tyrosine to animals (5, 15, 16). It is also possible that the effects observed could be attributable to other metabolites of tyrosine, such as tyramine. However, this amine is not detectable in the plasma of animals after they are given large doses of tyrosine (100 mg/kg) (9).

For our analyses, we selected those subjects most affected by 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; i.e., unless a deficit exists supplemental tyrosine will have little benefit (29). This is supported by in vitro data demonstrating that catecholaminergic neurons only appear to be responsive to additional substrate when they are highly active (20). Perhaps

stress-induced impairments in behavior are present in individuals with the greatest central deficits in catecholaminergic functioning. Additional research will be necessary to determine whether tyrosine's beneficial effects will be present in other stressful circumstances.

ACKNOWLEDGEMENTS

We acknowledge the statistical assistance of Mr. R. V. Spring and Dr. B. Chew. We also recognize the contributions of Ms. B. L. Shukitt, Ms. G. Garfield, Dr. R. P. Francesconi, Dr. R. F. Goldman, Major T. M. Rauch, Colonel D. D. Schnakenberg, Lt. Colonel G. F. Meadors III, the Altitude Research Division of USARIEM and the 23 test subjects. NASA grant NAG 2-210 and NIH grant 5R01-AG 04591 supported the Massachusetts Institute of Technology efforts. A report describing the initial results of this project was presented at a NATO conference, "Biochemical Enhancement of Performance," Lisbon, September 1986. 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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