4-1994

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Abstract

The fatigue and cognitive performance deficits associated with sleep loss and stress have motivated the search for effective nonpharmacological countermeasures. The purpose of the present study was to examine the potential behavioral effects of tyrosine, an amino-acid precursor to dopamine and norepinephrine, during an episode of continuous nighttime work involving one night of sleep loss.

The adverse consequences in cognitive performance of forgoing sleep while working at night have been well documented in laboratory studies (see Tilley & Brown, 1992 for a review). Perhaps the most notable effects of sleep deprivation and fatigue are brief episodes of sleep ("microsleeps") that lead to lapses in responding in cognitive and perceptual tasks (Williams, Lubin, & Goodnow, 1959). Sleep deprivation appears to be similar to other stressors; the ensuing fatigue is nonspecific and is comparable to other stress responses (Craig & Cooper, 1992). This view suggests that sleep deprivation could lead to increased catecholamine secretion and, eventually, to a selective reduction of catecholamines in the brain.

Amino acids have generated much interest and controversy regarding their effects on health and performance. Tyrosine is one amino acid that has received recent attention as a potential countermeasure to stress (Owasoyo, Neri, & Lamberth, 1992). Tyrosine is a large, neutral amino acid found in dietary proteins. It is a precursor of the catecholamines dopamine and norepinephrine. Should the fatigue of sleep deprivation be stressful enough to result in significant brain catecholamine reduction, making tyrosine available might serve to increase catecholamine synthesis and thereby improve mood and performance. A more detailed description of the biochemistry and physiological role of tyrosine, a review of its effectiveness in animals and man, and a fully developed rationale for its use in continuous-work operations involving sleep loss are presented elsewhere (Owasoyo et al., 1992).

Previous studies of the effectiveness of tyrosine in counteracting stress and fatigue in humans have yielded mixed results. Tyrosine was found effective in counteracting adverse behavioral effects resulting

[1] This research was sponsored by the Naval Medical Research and Development Command under Project Number 62233N MM33P30.001-7001 Accession DN477519. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government. Volunteer subjects were recruited, evaluated, and employed in accordance with the procedures specified in Department of Defense Directive 3216.2 and Secretary of the Navy Instruction 3900.39 series. These instructions are based upon voluntary informed consent and meet or exceed the provisions of prevailing national and international guidelines. Trade names of materials and/or products of commercial or nongovernment organizations are cited as needed for precision. These citations do not constitute official endorsement or approval of the use of such commercial materials and/or products.

from hypoxia and cold in subjects most affected by these stressors (Banderet & Lieberman, 1989). However, it failed to produce measurable effects on mood and performance in both rested (Lieberman, Corkin, Spring, Wurtman, & Growdon, 1985) and sleep-deprived subjects (J. French, personal communication, October 1993). The inconclusive nature of these findings, along with tyrosine's established role as a precursor to the catecholamines, its possible role in decreasing brain levels of the sleep-inducing substance tryptophan, and its relative safety make it worthy of further study as a countermeasure to fatigue and stress. The present study examined the effects of tyrosine on cognitive performance and subjective fatigue during a period of sustained wakefulness involving the loss of one night of sleep.

Method

Subjects

Twenty male, U.S. Marines, ranging in age from 21 to 27 years ($M = 24.5$) and ranging in weight from 66.66 kg to 99.34 kg ($M = 80.36$) volunteered for the experiment. All were college graduates awaiting initial flight training. The subjects had current flight physical examinations and underwent medical screening by a flight surgeon before the experiment. Subjects were fully informed as to the purpose of the experiment and were advised that they would receive either tyrosine or a placebo. Subjects were also informed that they were free to withdraw any time during the experiment without prejudice.

Apparatus

All cognitive performance and subjective tasks were administered on six, Intel 486DX/33-based IBM PC-compatible desktop computers equipped with Panasync 1381i SVGA color displays, Microspeed PC-Trak trackballs, and Systems Research Laboratory Labpak input-output modules with DigiTalker speech synthesis cards. Koss Pro 4AAA Plus headphones were used for the dichotic listening task. The computers were linked by an Artisoft, Inc., LANtastic local-area network.

Instruments

Three computerized objective performance tasks and two computerized subjective measures were performed repeatedly by the subjects throughout the experiment. The three performance tasks were an eye-hand coordination task (compensatory tracking), a vigilance task (running memory), and an auditory perception task (dichotic listening; DLT). The computerized subjective tests were the Stanford Sleepiness Scale (SSS; Hoddes, Dement, & Zarcone, 1971) and a visual analog scale (VAS), which assessed subjective symptoms associated with sleep loss (fatigue, boredom, depression, etc.). Several physiological measures were also obtained at regular intervals. These measures were body temperature, systolic and diastolic blood pressure, and heart rate. A post-experimental questionnaire was used to assess the effects of tyrosine on the quality of recovery sleep, as well as subjects' abilities to accurately guess whether they had received the tyrosine treatment.

Procedure

Subjects trained on the computer tasks over a 4-day period, beginning Monday morning and ending Thursday morning. Training consisted of a total of 8 sessions, each lasting approximately 40 min. The presentation order of the computer tasks was VAS, SSS, tracking, running-memory, and DLT. During the testing phase, subject performed 9 iterations of the battery of cognitive and subjective tasks for approximately 13 h, beginning at 1930 and ending at 0820 the following morning. Subjects remained awake throughout the day on which the experiment began and were awake for approximately 24 h by the

end of testing. Six hours after the start of the experiment, one-half of the subjects received 150 mg/kg tyrosine in a split dose while the other half received a cornstarch placebo in a double-blind procedure. The effects of the tyrosine on performance during the second 6 h of testing were then assessed.

Results

Tests of significance were performed using split-plot analyses of variance (ANOVAs) with drug treatment (tyrosine or placebo) as the between-groups factor and time (nine test administrations) as the repeated factor. The significance levels of repeated-measures F ratios with two or more numerator degrees of freedom were corrected for nonsphericity effects using the procedure of Huynh and Feldt (1976).

Performance Measures

Compensatory Tracking. The Euclidean distance (in pixels) between the cursor and the center of the cross-hair was measured continuously. The root-mean-squared (RMS) value of this distance was calculated at 1-min intervals. The first minute of each tracking session was treated as a task-adaptation period; the RMS values from minutes 2-9 were averaged to produce a global tracking score.

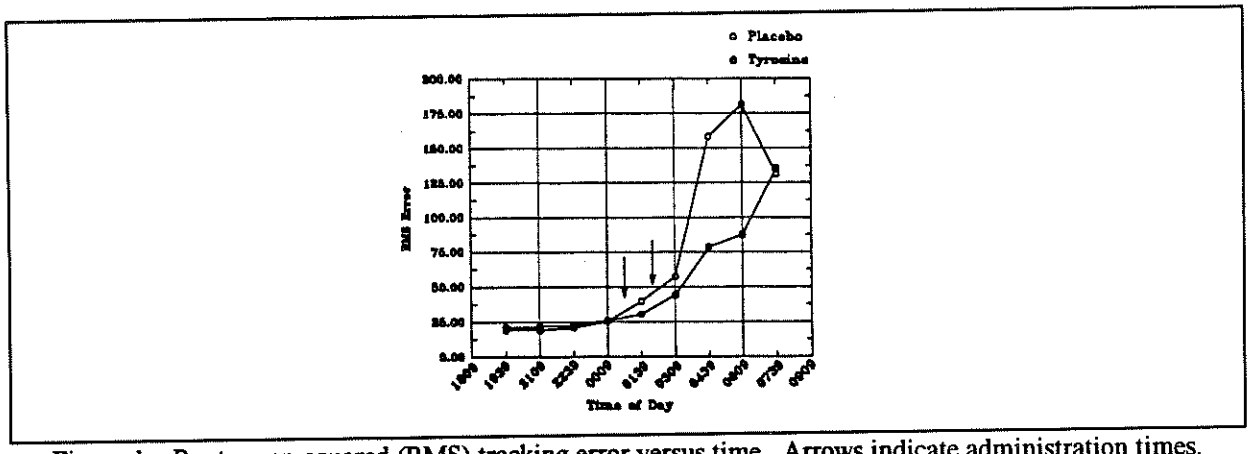

Figure 1. Root-mean-squared (RMS) tracking error versus time. Arrows indicate administration times.

Figure 1 shows tracking performance versus time in the placebo and tyrosine groups. Lower RMS error scores correspond to better performance. Tracking performance in both groups can be seen to decrease steadily during the night. Averaged across both groups, the reduction in performance with time was highly significant, $F(8, 144) = 21.29$, $p < .0005$. As Fig. 1 indicates, the two groups performed at similar levels during the trials before tyrosine was administered. Following tyrosine administration, the placebo group's performance continued to worsen. Although the tyrosine group's performance also worsened, the performance of the tyrosine group declined much less than that of the placebo group and remained better than that of the placebo group until the final test block. This separation in performance resulted in a significant Groups x Time interaction, $F(8, 144) = 2.99$, $p = .04$. Analyses of the simple main effects associated with this interaction revealed that the difference in tracking scores between groups was significant at 0439 h, $F(1, 18) = 4.46$, $p = .049$, and 0606 h, $F(1, 18) = 4.47$, $p = .043$. No other between-groups differences were found.

Running Memory. Three scores were computed for the running memory task. The first score, proportion of correct responses, P(C), was the sum of the number of correct responses divided by the

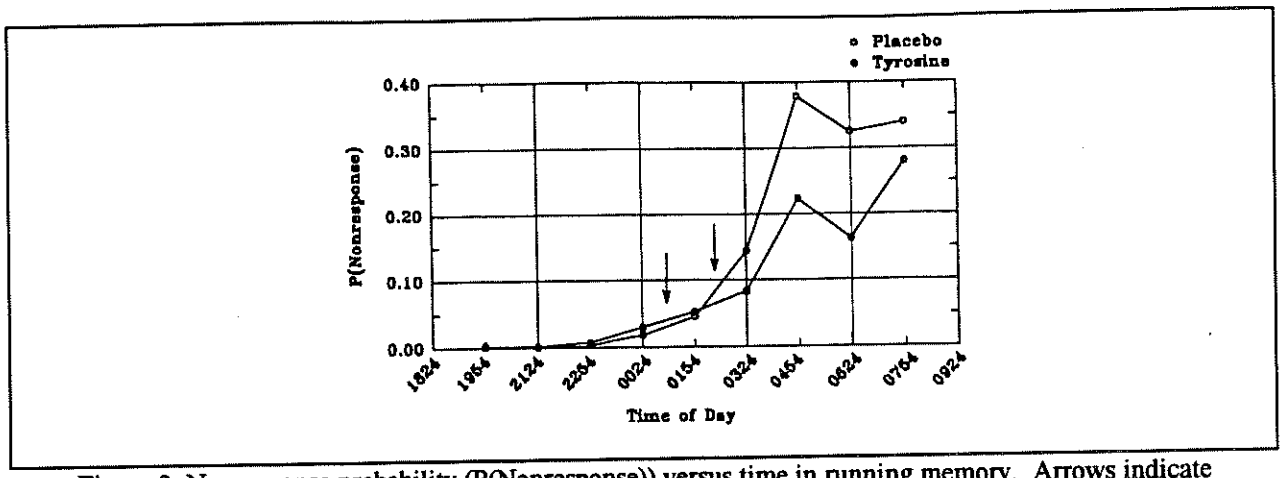

Figure 2. Nonresponse probability (P(Nonresponse)) versus time in running memory. Arrows indicate administration times.

number of responses made during the block. The second score, reaction time (RT), was the average time (in milliseconds) required to make a correct response. The last score, the proportion of lapses or nonresponses, P(N), was the proportion of stimuli to which subjects failed to respond during the 1250-ms interval available for responding.

Each running-memory dependent measure was analyzed using the ANOVA model described previously. The P(C) analysis revealed a significant main effect of Time, $F(8, 144) = 18.50$, $p < .00005$. The RT analysis also indicated the presence of a significant effect of Time, $F(8, 144) = 20.36$, $p < .00005$. An examination of group means revealed that P(C) decreased steadily during the night while mean RT increased. No significant differences between treatment groups were found in either P(C) or RT.

Figure 2 shows P(N) versus time. In both groups, the proportion of lapses increased systematically during the night. This overall increase in lapses, averaged across groups, was highly significant, $F(8,144) = 17.46$, $p < .00005$. Nonresponses were very similar across groups through 0154 h. As in the tracking task, there was a noticeable separation of the tyrosine- and placebo-group means at 0454 and 0624 h. In this case, however, the differences at 0454 and 0624 failed to reach significance.

Dichotic Listening (DLT). Two scores were calculated for the DLT. The first score, P(C), was the proportion of trials in which all items in the string were recalled in correct order. The second score, the proportion of nonresponses, P(N), was the proportion of trials on which subjects failed to respond during the allotted 6-s response interval.

In both groups, performance remained high during the first few hours of testing. By 0042, however, performance in both groups had declined noticeably. Performance continued to decline, reaching a minimum at 0642, and then improved in the final block of trials. ANOVA revealed that the effect of time on performance was significant, $F(8, 144) = 30.40$, $p < .005$. No significant between-group effects were found. Analyses performed on P(N) revealed a similar pattern of results.

Subjective Measures

Stanford Sleepiness Scale. Sleepiness ratings increased steadily during the night. This effect of time on sleepiness ratings was highly significant, $F(8, 144) = 84.30$, $p < .0005$. Mean sleepiness ratings were similar for the tyrosine and placebo groups through 0434. As in the case of tracking efficiency and running-memory lapse probability, there was a slight separation in group sleepiness ratings between 0434

and 0604. The tyrosine group's sleepiness ratings remained stable during these two sessions; in contrast, the placebo groups's sleepiness ratings continued to increase. Consequently, the mean sleepiness rating in the tyrosine group was lower by one step on the scale than the mean rating in the placebo group at 0604. These effects, however, failed to reach statistical significance.

Visual Analog Scale. The pattern of results for the VAS resembled that for the SSS. Both groups showed a similar pattern of responses on the VAS until the seventh and eighth sessions (0400 and 0600, respectively). At that time, the tyrosine group reported less fatigue, boredom, and depression, and more attention and alertness than the placebo group. However, none of these between-groups differences reached statistical significance.

Post-Study Questionnaire. Responses on the post-study questionnaire indicated that subjects were unable to reliably guess which substance they had received. Forty percent of the subjects in the tyrosine group correctly guessed that they had received the substance whereas 20% of the subjects in the placebo group guessed that they had received tyrosine, X^2 $(1, N = 20) < 1.0$. No significant differences were found between groups in responses to items related to sleep latency, sleep quality, or the need for more sleep upon awakening.

Physiological Measures

No significant changes in systolic and diastolic blood pressure were found. There were significant main effects of time for mean oral body temperature and mean pulse rate, $F(8, 144) = 22.59$, $p = .005$, and $F(8, 144) = 6.52$, $p < .0005$, respectively. Body temperature and pulse rate steadily decreased during the night. No between-groups differences in oral body temperature or pulse rate were found.

Discussion

Performance on the three cognitive tasks employed in this experiment declined steadily throughout the course of the night. These results are consistent with those from other sleep-deprivation studies reviewed by Tilley & Brown (1992). Specifically, decreases in psychomotor performance, vigilance, and auditory attention, and increases in RTs and response lapses were observed. Thus, the experimental paradigm successfully induced levels of fatigue high enough to produce measurable performance decrements. Accompanying the performance decline were substantial increases in subjective sleepiness and fatigue and decreases in subjective alertness and attention.

The tracking-task performance of tyrosine subjects declined less during the night than that of placebo subjects. Tyrosine administration was also associated with nonsignificant trends toward reducing a) lapses on a high-event-rate vigilance task, b) subjective sleepiness, and c) the intensities of several fatigue-related symptoms. In all of these cases, the improvements were short-lived, never lasting more than two consecutive testing sessions, and disappearing on all tasks by the last testing session. Additional doses of tyrosine would be necessary to determine whether the slowing of the performance decline could be extended throughout the period of enforced wakefulness. These data suggest that, for any behavioral effects of tyrosine to be sustained, it might be necessary to administer the substance repeatedly during continuous work episodes. The effects of tyrosine on tracking, lapses, and sleepiness ratings occurred approximately 1.5-2.0 h after the second administration and appear to have lasted only a few hours. The timing and brief duration of these possible tyrosine effects are consistent with the view that the half-life of the compound is relatively short. In sum, tyrosine appears to be a innocuous substance and, after further

testing with other doses and administration schedules, it may prove useful in counteracting performance decrements during sleep loss.

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