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Behavioral Effects of Tyrosine During Sustained Wakefulness

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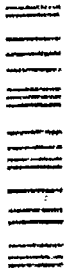
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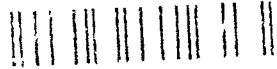## 51 HOVEY ROAD, PENSACOLA, FL 32508-1046

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ABSTRACT

The fatigue and cognitive performance deficits associated with sleep loss and stress, like that experienced during sustained flight operations and nighttime flying, have motivated the search for effective nonpharmacological countermeasures. The behavioral effects of the potential countermeasure tyrosine, an amino-acid precursor to dopamine and norepinephrine, were examined during an episode of continuous nighttime work involving one night's sleep loss. Volunteers performed nine iterations of a 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 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 these cases, the improvements were short-lived, never lasting more than two consecutive testing sessions and disappearing by the last testing session. The results of this study suggest that tyrosine is a relatively innocuous substance and, after further testing with other doses and administration schedules, may prove useful in counteracting performance decrements during episodes of sustained work coupled with sleep loss.

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ACKNOWLEDGMENTS

INTRODUCTION

Naval aviation is an inherently stressful, demanding, and dangerous occupation. Naval aviators face the challenges of flying complex aircraft for long durations and in all varieties of weather. Carrier-based aviators must launch and recover on small, pitching and rolling flight decks. Flying performance and the probability of mission success are enhanced by well-rested, unstressed crews operating at peak alertness. Unfortunately this is not always the case, even in peacetime, due to the frequent requirement of flying at night. Flying at night is more challenging than flying during the day because the reduction in perceptual information that occurs in the dark leads to increased reliance on instruments. This can transform an ordinary mission into a high-task-load situation at a time when the body is fatigued and the natural tendency is to sleep. Because aircrew are rarely physiologically adapted to a nighttime work and daytime sleep schedule, the problems of night flying, like those of the night shift work, are significant and real.

Perhaps the most negative consequence of nighttime flying is the misalignment that occurs between the sleep-wake schedule and the phase of the circadian pacemaker. In other words, an aviator must attempt to remain awake and alert during a night flight at a time when intrinsic circadian rhythms are operating to promote sleep. Later, after returning to the carrier, the aviator must attempt to sleep during the day when the pacemaker is operating to promote wakefulness. Civilian, night shift workers who routinely live and work in this state of misalignment experience many negative health and performance aftereffects (Monk & Folkard, 1992). Another problem of nighttime flying is the inevitable sleep deprivation that accompanies it. Aviators flying at night must operate on a schedule that would have them sleeping if they were not flying. There are few opportunities to lessen the impact of impending sleep loss with prophylactic naps or sleep-wake schedule manipulations before a night flight. Sleep duration is often sacrificed. Finally, aviators may begin night missions usually after being awake the entire day (15-18 h). This situation contrasts with that of daytime flying when aviators can launch fresh and alert after a full night's sleep. These perceptual and sleep-related problems combine to make flying at night more challenging and risky than flying during the day.

Circadian and sleep-related problems of misalignment, sleep loss, and shortened sleep duration increase the probability of fatigue. The adverse consequences in cognitive performance of forgoing sleep while working at night have been well documented in laboratory studies (see Dinges & Kribbs, 1991; Hockey, 1986; Holding, 1983; Johnson, 1982; Tilley & Brown, 1992, for reviews). 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 (Bills, 1931; Patrick & Gilbert, 1896; Warren & Clark, 1937; Williams, Lubin, & Goodnow, 1959). Although lapses may represent the most visible and profound effect of sleep deprivation, a number of investigators have suggested that sleep deprivation may lead to a generalized slowing of responses as well (Dinges & Kribbs, 1991; Kjellberg, 1977; Lisper & Kjellberg, 1972; Tharp, 1978; Williams et al. 1959). Regardless of the exact form these deficits take, any increase in lapses, slowing of response times, or other cognitive decrements occurring in naval aviators flying at night could lead to failures to correctly perceive and respond to critical visual and auditory events. In combat aviation, these failures can translate into failures to detect dangerous or unsafe conditions in the cockpit as well as potential ta. ·· .utside the cockpit. Furthermore, when coupled with sleep loss, the periods of boredom that often occur while on patrol, during return flights from combat, or during transoceanic flights can make microsleeps and lapses even more frequent.

Overlaid on the fatigue from flying at night and occasional boredom during uneventful patrols, is the transient but significant stress associated with carrier launches, critical periods of the mission (especially in combat), and carrier recoveries. Nighttime recoveries are more challenging and dangerous than daytime ones and therefore are inherently more stressful. High-stress levels have been associated with elevated levels of urinary catecholamines, reflecting increased secretion (Stone, 1975). This catecholamine secretion is considered part of a generalized stress response. Sleep deprivation appears to be similar to other stressors; the ensuing fatigue is nonspecific and is similar to other stress responses (Craig & Cooper, 1992). This view suggests that sleep deprivation could lead to increased catecholamine secretion, and eventually a selective reduction of

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catecholamines in the brain. The view that sleep deprivation is a stressor like any other, in terms of catecholamine secretion, is not universal (Froberg, Karlsson, Levi, & Lidberg, 1972). However, there is agreement that sympathoadrenal activity is altered with sleep deprivation when the deprivation is accompanied by *demanding tasks* (Craig & Cooper, 1992). With a heavy task load, sleep-deprived individuals may increase their level of stress by expending extra effort in an attempt to overcome fatigue-induced cognitive impairment. During nighttime flying, naval aviators experience a unique combination of demanding task activity and sleep loss, resulting in fatigue, stress, and possibly essential catecholamine reduction.

Given that nighttime flying is an operational necessity, what can be done to counteract the consequences of fatigue and stress? There are two general approaches. One approach uses pharmacological agents to enable the body to overcome the cognitive effects of fatigue by improving reaction times, reducing memory deficits, decreasing response lapses, and boosting alertness and mood. Several applied studies have shown that a variety of stimulants are effective in small doses, with a relatively small risk of physiological or behavioral side effects (Babkoff, Kelly, Matteson, Gomez, Lopez, Hauser, Naitoh, & Assmus, 1992; Johnson, Spinweber, Gomez, & Matteson, 1989; Newhouse, Penetar, Fertig, Thorne, Sing, Thomas, Cochran, & Belenky, 1992; Shappell, Neri, & DeJohn, 1992; Stanny, McCardie, & Neri, 1993a, 1993b). These alerting substances may have a role in naval aviation under well-defined circumstances--after the prescreening of aviators on the ground, with the consent of appropriate commanders, under the close supervision and control of the flight surgeon, and with the voluntary consent of the aviator.

In many circumstances, however, a pharmacological countermeasure is inappropriate. Therefore, the use of nonpharmacological countermeasures constitutes an alternative approach. Numerous nonpharmacological countermeasures are available, including exercise (e.g., Angus, Heslegrave, & Myles, 1985; Englund, Ryman, Naitoh, & Hodgdon, 1985), napping and sleep logistics (e.g., Angus, Heslegrave, Pigeau, & Jamieson,1987; Mullaney, Kripke, Fleck, & Johnson, 1983; Naitoh & Kelly, 1992), light manipulation (e.g., Comperatore, 1993; Kelly, Smith, & Naitoh, 1989), and dietary manipulations (e.g., Lieberman, Corkin, Spring, Growdon, & Wurtman, 1983; Lieberman, Corkin, Spring, Wurtman, & Growdon, 1985; Wurtman, 1982). Amino acids, in particular, have generated much interest and controversy regarding their effects on health and performance (Braverman, 1987; Dean & Morgenthaler, 1990). Tyrosine is one amino acid that has received recent attention as a potential countermeasure to stress (Ahlers, Salander, Shurtleff, & Thomas, 1992; Owasoyo, Neri, & Lamberth, 1992; Salter, 1989; Shurtleff, Thomas, Ahlers, & Schrot, 1993; Wurtman, 1986). 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 military operations involving sleep loss are presented elsewhere (Owasoyo et al., 1992).

In addition to the potential benefit of tyrosine from increased catecholamine synthesis, the amino acid may also serve to assist in fighting fatigue indirectly. Tyrosine competes with other large, neutral, amino acids for transportation from blood to brain. The amount of tyrosine that enters the brain depends on the amount available relative to the sum of the other available amino acids (the tyrosine ratio). Elevating the tyrosine ratio by ingesting tyrosine may increase the amount of tyrosine that enters the brain at the expense of other competing amino acids such as tryptophan (Wurtman, Hefti, & Melamed, 1981). Tryptophan, a sleep promoter (Braverman, 1987), is a precursor of serotonin, which in turn is a precursor of melatonin. Melatonin also has known sleep-inducing effects (see Kelly et al., 1989, for a review). Tyrosine ingestion may reduce the levels of available tryptophan, limiting melatonin synthesis, and thereby indirectly reducing fatigue.

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 from both cold (Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994) and cold plus hypoxia in subjects most

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affected by these stressors (Banderet & Lieberman, 1989;). However, it failed to produce measurable effects on mood and performance in both rested (Lieberman et al., 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 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's sleep.

MATERIALS AND METHODS

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 told that they would receive either tyrosine and 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. Auditory stimuli were presented using Koss Pro 4AAA Plus headphones. The computers were linked by an Artisoft, Inc., LANtastic local-area network.

INSTRUMENTS

Three computer-administered objective performance tasks and two computer-administered subjective measures were performed repeatedly by the subjects throughout the experiment. Several physiological measures were also obtained at regular intervals. Each measure is described in detail below.

Compensatory tracking task. The compensatory tracking task is a measure of eye-hand coordination. It requires the subject to maintain the position of a small airplane-shaped cursor at the intersection of a large set of cross-hairs located in the middle of the video display. The cursor was manipulated using the trackball. Rolling the trackball away from the subject moved the cursor toward the bottom of the screen whereas rolling it toward the subject moved the cursor toward the top of the screen. Left and right movements of the trackball resulted in corresponding left and right movements of the cursor[1]. When not controlled by the trackball, the cursor continually drifted away from the center of the screen in a random direction. Thus, continuous movements of the trackball by the subject were required to compensate for the drift in the cursor. Task duration was 10 min.

High-event-rate vigilance task (running memory). The running memory task is a variant of the Continuous Performance Task (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) used by Williams et al.

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[1] This pattern of movement was chosen to mimic the type of control provided by an aircraft's flight stick, with forward movement of the stick resulting in a downward movement of the aircraft's nose and backward movement of the stick resulting in an upward movement of the nose. Such coupling between trackball and cursor is similar to controlling a remote vehicle or drone.

(1959) in their seminal analyses of the performance of sleep-deprived subjects on experimenter-paced tasks. The running memory task requires subjects to monitor a randomly ordered sequence of the upper case letters, "A" through "Z," presented individually for 50 ms in the center of the video display. The interstimulus interval was 1250 ms, measured from stimulus onset to stimulus onset. Subjects were required to decide whether each letter matched the immediately preceding letter in the sequence. A random 50% of all letters matched the immediately preceding one. Subjects responded by pressing a key with the first finger of one hand whenever a letter matched its immediate predecessor and another key with the first finger of the other hand when a letter differed from its immediate predecessor. Key assignments to dominant and nondominant hands were counterbalanced across subjects. A total of 480 stimuli was presented in each block of trials, requiring approximately 10 min to complete.

Dichotic listening task (DLT). The DLT (Gopher & Kahneman, 1971) required subjects to identify and recall, in order, the numbers in a sequence of 11 letters and 5 numbers presented in a synthesized voice to one ear. The subjects were required to ignore a competing sequence of letters and numbers presented simultaneously to the opposite ear. At the beginning of each trial, a 500-ms, 1000-Hz tone was presented over both headphones as a ready stimulus. After a 1200-ms delay following the onset of the ready stimulus, the ear to which the subject was to attend was indicated by presenting the word "Left" or "Right" over both headphones. After a further 800-ms delay following the onset of the word "Left" or "Right," a sequence of 11 letters and 5 numbers was delivered to the target ear. The letters used were A-Z except W; the numbers used were 0-9. The order of the letters and numbers was randomized. As the letters and numbers were being delivered to the target ear, a different random sequence of 11 letters and 5 numbers was delivered to the nontarget ear. Whenever a letter was presented to one ear, a different letter was presented to the opposite ear. The letter delivered to the nontarget ear was constrained not to rhyme with the letter being presented to the target ear. Whenever a number was presented to one ear, a different number was presented to the other ear. The intervals between the onsets of the letter-number stimuli were 700 ms. The subject was told to ignore all letters presented to the target ear and all letters and numbers presented to the nontarget ear. At the end of each sequence, five underscore marks appeared on the video display. Subjects responded by typing the numbers heard in the target ear in order, on the computer keyboard. This caused the typed numbers to appear above the underscore marks on the display. Subjects were allowed 6.25 s to type their responses and correct errors before the next trial began. A total of 48 stimulus sequences were presented in each block of trials. Each sequence was approximately 19.45 s in duration, which yielded a task duration of approximately 15.56 min.

Visual Analog Scale (VAS). The VAS allows for the assessment of a customized set of subjective symptoms and states (DeJohn, Marr, Molina, McCardie, 1992). A sequence of adjectives (symptoms) appeared one at a time on the display above a horizontal line segment. The list of symptoms is included as Appendix A. The horizon line was labeled with "0" at the left end and "100" at the right. Subjects were instructed that "0" corresponded to no sensation of the symptom, while "100" corresponded to the most intense symptom sensation imaginable. An arrow appeared in the middle of the display below the line. The subject's task was to move the arrow, using the trackball, to the position on the line that corresponded to the intensity of the symptom experienced at that moment. The task required approximately 3.5 min to complete.

Stanford Sleepiness Scale (SSS). The SSS (Hoddes, Dement, & Zarcone, 1971; Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973) was used to assess subjects' sleepiness levels throughout the experiment. This scale, reproduced in Appendix B, appeared on the video display. Subjects entered on the keyboard the number of the sleepiness description that most closely corresponded to how they felt at that moment. The task usually took less than 30 s to complete.

Post-study questionnaire. The post-study questionnaire was a paper-and-pencil survey consisting of several questions regarding sleep latency and quality, and a question concerning whether the subject believed he had received tyrosine or the placebo.

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Physiological measures. Body temperature, systolic and diastolic blood pressure, and heart rate were monitored and collected throughout the experiment. Body temperature was measured using an IVAC digital oral thermometer. Blood pressure was assessed with standard Marshal sphygmomanometers and stethoscopes. Heart rate was monitored using Escort electrocardiogram telemetry units.

PROCEDURE

Testing environment. The experiment was carried out in the Sustained Operations Laboratory of the Naval Aerospace Medical Research Laboratory. The Sustained Operations Laboratory is a large windowless room configured with six subject workstations and a monitor's console. Each work station was separated from the others by a large partition, which prevented subjects from observing each other during testing. At each workstation was a computer, configured as described above. The laboratory was dimly lit by ceiling-mounted incandescent lights positioned so that illumination glare would not interfere with the perception of the video displays.

Training. Subjects trained on the computer tasks over a 4-d period, beginning Monday morning and ending Thursday morning. Training consisted of eight sessions, each lasting approximately 40 min. The presentation order of the computer tasks was VAS, SSS, tracking, running-memory, and DLT. By the end of training, subjects had completed eight VAS and SSS measures, eight 10-min tracking sessions, 3,840 running memory trials, and 384 DLT trials.

Testing. Subjects were run in groups of 4, 6, 3, 4, and 3, with subjects in both tyrosine and placebo conditions participating in each session. The experiment began on the Thursday evening following the completion of training. Conditions during the experiment were the same as during training, with the following exception. During the experiment, subjects were exposed to a moderate intensity (70-dB A), low-frequency (150-Hz cutoff) noise that resembled the muffled rumble of a jet aircraft engine. The noise was employed as a realistic environmental stressor at a sound intensity selected to be low enough to avoid arousal effects. The noise was omitted during training to ensure that subjects could concentrate fully on learning the cognitive tasks.

Testing began at 1930 Thursday and proceeded until 0820 Friday morning. The order and duration of tasks and breaks within each 90-min experimental block are shown in Table 1. Subjects completed nine blocks of tasks during the experiment. During the short (5-min) breaks, subjects were allowed to stand and use the bathroom. During the long (40-min) breaks, body temperature, blood pressure, and heart rate were recorded and subjects were provided caffeine-free snacks. Subjects were restricted to the laboratory and an adjacent corridor during the experiment.

Tyrosine (Ajinomoto Company, Inc.) was simultaneously administered to 10 randomly selected subjects during the long breaks that followed the fourth and fifth testing blocks (i.e., at 0130 and 0300). At both times, tyrosine was administered in doses of 75mg/kg of body weight, resulting in a total administration of 150mg/kg. This dose was chosen because previous work in humans has shown 100-150 mg/kg to increase the plasma tyrosine ratio two- to threefold (Glaeser, Melamed, Growdon, & Wurtman, 1979). Tyrosine was administered in a split dose because its half-life is relatively short, at 2-3 h (A. Dollins, Massachusetts Institute of Technology, personal communication, July, 1992). Two smaller, spaced doses would therefore serve to maintain plasma levels for a longer time. Ten randomly selected subjects in the placebo group received 150mg/kg of cornstarch. The cornstarch, like the tyrosine, was divided into two doses and administered during the long breaks following the fourth and fifth testing sessions at 0130 and 0300, respectively. Cornstarch was chosen as the placebo because it is a relatively inert and tasteless substance. Each dose of cornstarch or tyrosine was mixed with approximately 113 g of banana-flavored yogurt and administered to the subjects in a double-blind procedure. Previous testing with research staff indicated that cornstarch mixed with 113 g of banana

yogurt is indistinguishable in taste, texture, and appearance from tyrosine mixed with the same quantity of banana yogurt.

Table 1. Experimental Task Order and Duration (min).

Test	Duration	Cumulative duration
VAS/SSS	04	04
Tracking	10	14
Break	05	19
Running memory	10	29
Break	05	34
DLT	16	50
Break	40	90

After completing the final testing session, subjects were asked to rest (and, if possible, sleep) for 6 h in the laboratory dormitory. At the end of this post-experiment recovery period, each subject filled out the post-study questionnaire and received a final medical screening by a flight surgeon.

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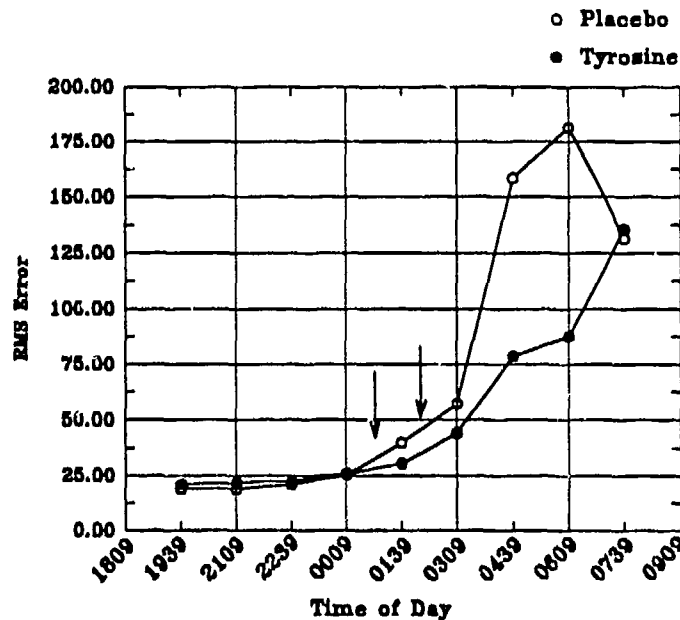
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Figure 1. *Root-mean-squared (RMS) tracking error versus time in pursuit tracking. Arrows indicate administration times.*

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 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.

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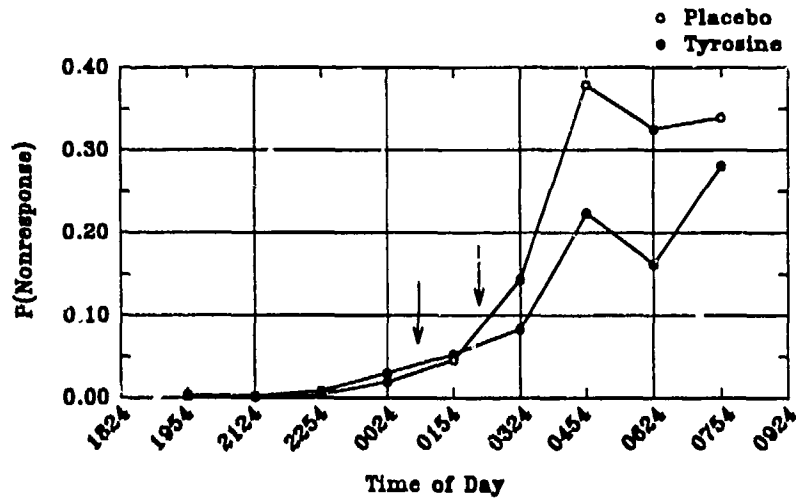
Figure 2. *Nonresponse probability (P(Nonresponse)) versus time in running memory. Arrows indicate administration times.*

Dichotic listening task. 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.

Figure 3 shows P(C) versus time in the DLT for the placebo and tyrosine groups. 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. The 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.

Figure 3. *Percentage correct responses verses time in Dichotic Listening. Arrows indicate administration times.*

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SUBJECTIVE MEASURES

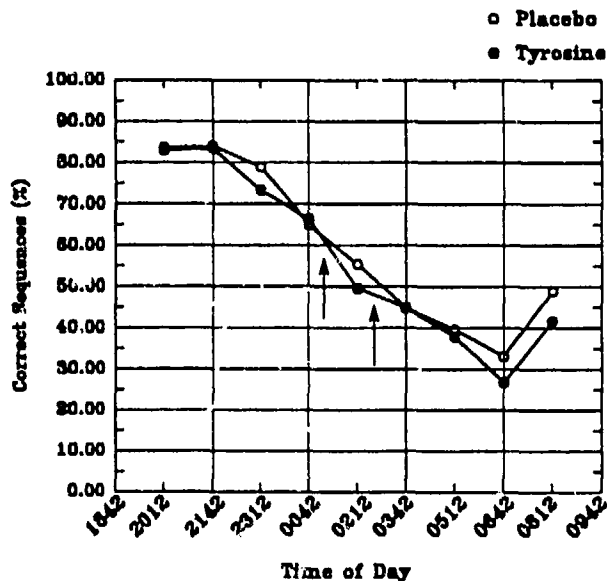**Stanford Sleepiness Scale.** Figure 4 shows the SSS ratings versus time in the placebo and tyrosine groups. Sleepiness ratings increased steadily during the night. This effect of time on sleepiness ratings was highly significant, $F(8, 144) = 84.30$, $p < .0005$. Mean sleepiness ratings were similar for the tyrosine and placebo groups through 0434 . As with tracking efficiency and running-memory lapse probability, group sleepiness ratings differed slightly 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.
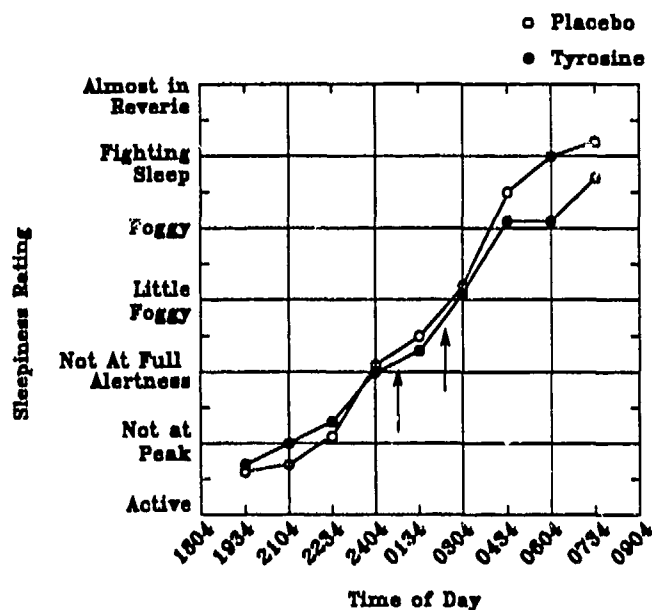
Figure 4. *Stanford Sleepiness Scale ratings versus time. Arrows indicate administration times.*

Visual Analog Scale. Table 2 is a list of symptoms that were significantly affected by time. The pattern of results for the VAS resembled that for the SSS shown in Fig. 4. The tyrosine and placebo 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. Subjects' responses on the post-study questionnaire indicated that they 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 twenty percent of the subjects in the placebo group guessed that they had received tyrosine, X^2 (1, $N = 20$) < 1.0. There were no significant differences between groups in responses to items related to sleep latency, sleep quality, or the need for more sleep on awakening.

Table 2. VAS Symptoms Significantly Affected by Sustained Wakefulness.

Symptom	Direction of change from first to last Block
Fatigue	Increase
Boredom	Increase
Sleepiness	Increase
Depression	Increase
Headache	Increase
Hostility	Increase
Restlessness	Increase
Alertness	Decrease
Attention	Decrease
Euphoria	Decrease
Talkativeness	Decrease

PHYSIOLOGICAL MEASURES

The results of the ANOVAs performed on mean systolic and diastolic blood pressure revealed no significant changes attributable to time or tyrosine treatment. 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. An examination of group means revealed that 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 Dinges & Kribbs (1991) and 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 a decrease in subjective alertness and attention.

Tyrosine administration was associated with a significantly smaller performance decline in the tracking task. Tyrosine also yielded nonsignificant trends in the direction of reduced lapses in the running memory task, reductions in subjective sleepiness, and reductions in the intensities of several fatigue-related symptoms. In all 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 effects are consistent with the view that the half-life of tyrosine is relatively short.

Several factors might account for the modest effects of tyrosine on the performance indexes other than tracking error. First, the physiological effects of the continuous-work manipulation, although sufficient to impair performance and mood, may nevertheless have been too small to significantly reduce brain catecholamine levels. Feedback mechanisms evidently buffer catecholamine-transmitter supplies against fluctuations in precursor levels (see review by Wurtman et al., 1981). Conditions that deplete the transmitter reserves of catecholaminergic neurons, notably high rates of impulse activity, are associated with increases in the conversion of tyrosine to norepinephrine. A longer period of sleep deprivation, perhaps with additional stressors, might deplete catecholamine transmitters sufficiently that increases in tyrosine would yield increases in catecholamine synthesis and, thus, improvements in mood and performance. Second, the tyrosine dose(s) used in the present experiment may simply have been too low or administered too infrequently to be effective. Higher doses administered over longer periods might produce stronger and longer-lasting effects. Third, some of the tasks we used may have been too insensitive to detect effects of tyrosine on performance. This seems possible, inasmuch as the effects of food constituents on performance tend to be subtle and difficult to demonstrate empirically (Lieberman et al., 1983). More subjects might be required to obtain adequate power with these tasks.

Nonetheless, the findings do indicate that tyrosine had a significant effect on a psychomotor task of substantial relevance to aviation. Indeed, in some circumstances, the apparently brief duration of the effect may afford advantages relative to those of longer-acting stimulants, such as the amphetamines. Amphetamines can potentially interfere with the onset, duration, and quality of sleep (Hart & Wallace, 1975; Hartmann & Cravens, 1976), even after substantial sleep deprivation (Newhouse et al., 1989; Penetar et al., 1991). There was no indication that tyrosine interfered with subjects' recovery sleep in this study. Of additional importance, tyrosine did not produce any physiological side effects. In contrast to results obtained in continuous-performance studies of d-amphetamine (Newhouse, Belenky, Thomas, Thorne, Sing, & Fertig, 1989) and d-methamphetamine (Stanny et al., 1993a), tyrosine did not increase heart rate or blood pressure; nor did it significantly alter oral body temperature. None of the subjects reported any negative feelings or symptoms attributable to tyrosine administration.

In conclusion, the results of this study, though mixed, are promising. They suggest that tyrosine is a relatively innocuous substance that might prove useful in counteracting performance decrements during episodes of sustained work coupled with sleep loss. Further studies are needed to determine whether tyrosine's effects might be enhanced under more stressful conditions and/or with different doses and timing of administration.

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[2]Publications with AD numbers are available from the Defense Technical Information Center, Cameron Station, Alexandria, VA 22314-6145, (202) 274-7633.

APPENDIX A

Visual Analog Scale Items

Fluttering Heart
Dizzy
Ill at ease
Euphoric (feeling that all is well)
Overstimulated
Restless
Shaky
Headache
Diarrhea
Constipated
Abdominal Cramps
Dry mouth
Unpleasant Taste
Itchy
Fatigued
Depressed
Anxious
Hostile
Jumpy
Talkative
Hungry
Difficulty urinating
Urinating frequently
Sleepy
Rapid breathing
Alert
Able to focus attention
Bored

APPENDIX B

Stanford Sleepiness Scale

1. Feeling active and vital; alert; wide awake
2. Functioning at a high level, but not at peak; able to concentrate
3. Relaxed; awake; not at full alertness; responsive
4. A little foggy; not at peak; let down
5. Fogginess; beginning to lose interest in remaining awake; slowed down
6. Sleepiness; prefer to be lying down; fighting sleep; woozy
7. Almost in reverie, sleep onset soon; lost struggle to remain awake

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13. ABSTRACT (Maximum 200 words)

The fatigue and cognitive performance deficits associated with sleep loss and stress, like that experienced during sustained flight operations and nighttime flying, have motivated the search for effective nonpharmacological countermeasures. The behavioral effects of the potential countermeasure tyrosine, an amino-acid precursor to dopamine and norepinephrine, were examined during an episode of continuous nighttime work involving one night's sleep loss. Volunteers performed nine iterations of a 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 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 these cases, the improvements were short-lived, never lasting more than two consecutive testing sessions and disappearing by the last testing session. The results of this study suggest that tyrosine is a relatively innocuous substance and, after further testing with other doses and administration schedules, may prove useful in counteracting performance decrements during episodes of sustained work coupled with sleep loss.

14. SUBJECT TERMS

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