The Effects of Tyrosine on Cognitive Functions during Sustained Operations

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Abstract

The effect of supplementation of the amino acid L-tyrosine on cognitive task performance was assessed during a highly demanding two-week combat training course. A tyrosine group (10 subjects) received daily doses of a protein-rich drink (containing 2 g tyrosine), while a placebo group (11 subjects) received the same doses of a carbohydrate rich drink (containing no proteins). Cognitive task performance was evaluated immediately preceding the course, as well as at the end of the first week of the course. Although there were no group differences in task performance prior to the course, the tyrosine group clearly performed better than the placebo group on several cognitive performance tasks during the course. Overall, up to 40% of the cognitive performance decrement that was due to the impact of stress and fatigue, was counteracted by the supplementation of tyrosine. The findings suggest that tyrosine supplementation can be effective in preventing cognitive degradation in highly demanding military operational environments that include sustained operations, as well as physical and psychological stressors.

Introduction

It is a well documented fact that the psychological stress, as well as the fatigue that are implicated in sustained operations, may affect various aspects of cognitive functioning[1, 2]. This may cause a deterioration of the performance of information-processing and psychomotor tasks, which may, in turn, reduce operational effectiveness and compromise safety. A wide variety of measures have been employed to counteract the cognitive degradation, including stimulating and depressing drugs, as well as resource management, sleep and work/rest management, and physical fitness training. The present study focuses on a relatively new approach: the prevention of cognitive performance degradation through supplementary nutrition. The approach is based on observation that the amino acid L-tyrosine, which is a precursor of norepinephrine (NE), may enhance NE synthesis in the brain[3], and may thus prevent stress- and fatigue-induced NE depletion.

As has been well established, during exposure to stressful conditions, there is an increase in the release of peripheral as well as brain NE[4,5], and it has been shown that the transmission of nor-adrenergic neurons is increased during stress[3, 6]. Noradrenergic projections from the locus coeruleus, providing the main innervation to the frontal cortex and demonstrating increased electrical activity during stress [7, 8], play an important role in attention, alertness, motor activity and the regulation of emotional processes[9]. Accordingly, it has been found that the depletion of brain NE that results from the enhanced release during exposure to stressful conditions, may have a negative behavioral and cognitive impact. NE depletion has been observed to reduce explorative behavior and motor activity, and to induce behavioral depression in animals[10, 11]. In humans, clonidine-induced inhibition of NE release resulted in an increase in the number of lapses of attention, which could be reversed by the antagonist idazoxan[12].

Conversely, there is suggestive evidence that the detrimental effects of NE depletion may be counteracted by administration of tyrosine. In rats receiving a tyrosine-rich diet, neither NE depletion nor behavioral impairments were found after stress industion[10, 13]. In humans, similar results were obtained. Supplementation of 100 mg/kg tyrosine caused a reduction of the number psychomotor impairments and stress symptoms during exposure to cold and hypoxia, compared to a placebo[14]. Similarly, administration of 150 mg/kg tyrosine prevented the cold-induced impairment of short-term memory that was observed in a placebo group[15]. Furthermore, cognitive task performance during exposure to 90 dB noise was found to be superior in a group of subjects that was supplemented with 100 mg/kg tyrosine than in a placebo group[16]. The available evidence, therefore, strongly suggests that supplementation with tyrosine may serve to reduce the detrimental cognitive and behavioral effects of exposure to stress.

The feasibility of dietary tyrosine supplementation is suggested by the fact that protein-containing diets have been found to increase the plasma tyrosine/large neutral amino acids (LNAA) ratio and brain tyrosine levels. Plasma tyrosine concentration, expressed relative to the plasma concentrations of the same transport competitive

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amino acid (tyrosine/LNAA) reflects the amount of tyrosine available to the brain for catecholamine synthesis. In rats, the acute consumption of a high-protein meal has been observed to almost double the serum tyrosine level and the tyrosine/LNAA ratio[17, 18]. In humans, plasma tyrosine levels and the plasma tyrosine ratio were shown to increase significantly when a protein-rich diet was consumed[19]. In another study, oral protein (albumin) was found to increase the plasma tyrosine/LNAA ratio in healthy fasting females by 20-60%[20]. Finally, a protein-rich breakfast was found to cause a significant increase in cerebrospinal fluid tyrosine in patients suffering from normal pressure hydrocephalus[21].

The aim of the present study was to assess whether supplementation of L-tyrosine would be effective in reducing the effects of stress and fatigue on cognitive functioning during sustained military operations. In addition to cognitive task performance, mood states were evaluated, in order to assess whether the tyrosine supplementation would also reduce the subjective effects of stress and fatigue.

The study was carried out among a group of cadets from the Netherlands Royal Military Academy who had to complete a combat training course (CTC) as part of their training program. The CTC encompassed a range of psychologically, as well as physically highly demanding conditions, including sustained operations and sleep loss.

Method

Subjects

Thirty-two cadets of the Royal Military Academy (Koninklijke Militaire Academie; KMA) volunteered to participate in the study. Sixteen subjects (Ss) were randomly assigned to a tyrosine group, and the remaining sixteen Ss were assigned to a placebo group. In the course of the CTC, eleven Ss dropped out due to injuries, etc., leaving a total of twenty-one Ss for analysis (tyrosine group: ten Ss; placebo group: eleven Ss). The tyrosine group included one female and 9 males aged between 19 and 26 years, with a mean age of (± SD) 22.8 (± 2.7). The placebo group consisted only of males, aged between 18 and 27 years, with a mean age of (± SD) 21.4 (± 2.8) years.

Each participant received $ 30.00 at the end of the study. The study protocol was approved by the Medical Ethical Committee of the Free University Hospital, and all Ss gave their written consent to participate.

Apparatus

Cognitive performance tasks. The cognitive performance tasks were presented via eight PC systems, equipped with a timer/response card (TNO), an A/D conversion card (Data Translation DT 2808), a response panel and a joystick. Four tasks from the Taskomat Battery[22] were employed: (1) a memory comparison task (MCT), (2) a tracking task (TT), (3) a continuous memory task (CMT), and (4) a double task (DT).

The MCT evaluates the speed and accuracy of short-term memory comparisons. During the MCT, stimulus trials (an arrangement of 1, 2 or 4 letters), were presented successively on the computer display. The Ss were required to monitor the stimuli for the occurrence of one out of four prespecified target letters, and to respond as fast as possible by pressing a "yes" button if a target letter was present, or a "no" button if this was not the case. After an incorrect response, the word "incorrect" was displayed. The interval between the response and the next trial was 500 ms. If a 1,000 ms deadline had elapsed without a response, the next trial was presented and a response omission recorded. The duration of the MCT was 8 min. The performance measures were the number of correct and incorrect responses.

The TT evaluates perceptual-motor skills. During the TT, a track moved upward in a variable direction on the display. The Ss had to horizontally move a gateway using the joystick, in order to keep the track in the middle of the gateway. The Ss could anticipate the direction of the movements of the track with a 'preview time' of 2,300 ms. The duration of the TT presentation was 7 min. (14 intervals of 30 sec.). The performance measure was the root mean square (RMS) of the distance between the track and the middle of the gateway. This measure was computed separately for each 30 s interval, as well as for the entire task period.

The CMT evaluates the accuracy of short-term memory rehearsal. During the CMT, stimulus trials containing arrangements of 1,2 or 4 letters were successively presented on the display. As was the case in the MCT, the Ss were required to press a 'yes' button when one out of four prespecified target letters was present (no 'no' button was employed in this task). In contrast with the MCT however, the Ss had to additionally count the number of times each of the four target letters was presented in the 7-min. task period, and to type in these numbers on the keyboard after completion of the task. Performance measures were the number of correct responses, and the number of incorrect counts.

During the DT, the TT and the CMT were presented simultaneously. The DT was presented for 7 min (14 intervals of 30 s each). The performance measures included the TT, as well as the CMT performance.

During the performance of the tasks, the Ss frequently suffered from lapses of attention, resulting in temporary interruptions in the execution of the tasks. In the TT (as well as in the DT), this caused them to occasionally leave the joystick in a fixed position. As a consequence, the variability of the RMS values in these tasks was not always associated with real variability in the task performance, but rather with variations in the distance of the track with respect to the (fixed) gateway. Hence, the RMS did not always accurately reflect task performance. This prob-

lem was resolved by employing another performance measure: task-interruption time (TIT). The TIT reflects the percentage of time on task the joystick was not moved. TIT was determined for each subject by counting the number of 30-s periods that the RMS exceeded a cut-off value of 50. The choice of this cut-off value was based on the observation that a failure to move the joystick almost invariably yields mean RMS values > 50[23].

Mood questionnaire. The Profile of Mood States (POMS) is a questionnaire that is designed to evaluate mood states[24, 25] that includes the following subscales: Depression, Anger, Fatigue, Vigor and Tension. In this study, the shortened Dutch version of the POMS was employed[26]. Responses are made by choosing from five response alternatives.

Procedure

Prior to the study, all cadets participating in the CTC had been had been informed about the goal and procedure of the study. Following this, volunteers were invited to participate in the study.

Two weeks prior to the commencement of the CTC, all Ss practised the cognitive performance tasks. The practice session, during which shortened versions of all tasks were presented, was held in a classroom of the KMA. At the end of the practice session, the mood questionnaire was distributed and instructions were given concerning its completion. The Ss were requested to send the completed questionnaires to the second author, using a stamped and addressed envelope, before the start of the training course.

The pre-test session, which was also held in a classroom of the KMA, took place one week prior to the CTC. The pre-test session had a duration of 45 min. The cognitive performance tests were presented in the following order: MCT (8 min), TT (7 min), CMT (7 min), and DT (7 min). In addition to the computer tests, blood pressure was determined, urine samples were taken, and a mood questionnaire was completed (not reported here).

On days 2-5 of the CTC, the drinks containing the tyrosine and placebo compounds were ingested between 0700 and 0800 h. On day 6 of the CTC (when the post-test session took place), the drinks were ingested between 0200 and 0300 h. All drinks were supplied by the group commanders, which made it possible to control compliance.

The post-test session took place on day 6 of the CTC, between 0500 and 0800 h. A classroom in the barracks, close to the training ground, served as the testing room. The protocol was similar to that used in the pre-test session.

Combat training course (CTC)

The aim of the CTC was to enhance stress tolerance and to increase operational effectiveness. During the two-week CTC, the Ss had to cope with a range of physically demanding and psychologically stressful conditions, including sleep deprivation and food rationing. During the CTC, the limits of physical endurance were reached. Stress was not only induced by the severity of the demands, but also by their unpredictability. The diet of the Ss was restricted and controlled throughout the CTC. The last meal before the post-test session was provided between 1900 and 2000 h (i.e., about 10-12 h before the last test and 6-8 h before the last experimental drink).

Supplementation

L-tyrosine was supplied in a 500-ml drink, consisting of orange juice in which 70 g of the diet powder PROTIFAR® (Nutricia, Zoetermeer, The Netherlands) was dissolved. This amount of PROTIFAR contains 42 g of proteins, including 2 g of tyrosine. In addition to tyrosine, 70 g PROTIFAR contains: alaline (1.5 g), arginine (1.5 g), aspartic acid (3.4 g), cysteine (0.4 g), glutamic acid (9.5 g), glycine (0.8 g), histidine (1.3 g), isoleucine (4.3 g), leucine (4.3 g), lysine (3.7 g), methionine (1.1 g), phenylalanine (2.1 g), proline (4.2 g), serine (2.6 g), threonine (1.9 g), tryptophan (0.6 g) and valine (2.7 g). The placebo group received a 500-ml mixture of orange juice, in which 67 g of FANTOMALT® (Nutricia) was dissolved. FANTOMALT is a diet powder consisting of 95% carbohydrates, and contains no protein. Both drinks contained the same amount of calories (255 kcal). The Ss were required to take one drink daily for a five-day period.

The group commander handed out the containers with the drinks. The containers were marked with a green of yellow spot; which colour each subject had to receive was marked on a list given to the group commander. Neither the group commanders, nor the Ss were aware which colour corresponded to which treatment[a].

Data analysis

With respect to the MCT, the numbers of correct and incorrect responses (excluding omissions) were averaged across all trials, resulting in a correct and an incorrect score for each subject. Average RMS tracking scores during the TT and the DT were determined by averaging the squared 30-s interval values, and by subsequently computing the root of the average. Average RMS scores were

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[a] *This unusual mode of administration was dictated by dose and dosage form restrictions imposed by the RNLA medical supervisor, who allowed only administration of tyrosine as naturally occurring in food. Hence, the L-tyrosine was not supplemented in pure form in this study, but in protein-rich powder (PROTIFAR) which contains, in addition to tyrosine, other amino acids. However, it should be stressed that none of these are known to be precursors of NE. Likewise, the placebo was not a pure placebo administration. However, it should be emphasised that FANTOMALT does not contain any amino acids and may therefore be assumed not to influence NE synthesis. A second restriction was that the investigators were not allowed to determine plasma amino acid levels.*

computed for each of the 14 30-s intervals, as well as for the entire 7-m task period (with the exception of the first and the last interval). CMT performance could not be assessed. This was due to the fact that, probably due to excessive fatigue, a majority of the Ss had forgotten the target letters during the task performance, thereby making any assessment of the counts useless.

Differences in the treatment effects between the tyrosine group and the placebo group were evaluated by one-way Analyses of Covariance (ANCOVA), with Group as the independent factor, and the pre-test score as the covariate. The RMS tracking scores during the successive 14 intervals were analysed via repeated-measures ANCOVA's with Group as the independent factor and Interval as the repeated measurement factor. Owing to the absence of any variation in TIT values during the pre-test session, only the TIT values of the post-test session were analysed, using one-way Analyses of Variance. Because several earlier studies had found tyrosine supplementation to improve cognitive performance during stress exposure[14, 15, 16], it was hypothesised that similar effects would be found in the present study. Accordingly, statistical tests were one-tailed, except for the 14 RMS scores. Because no specific hypotheses had been formulated with regard to the POMS scores, two-tailed statistical tests were employed for these variables.

Results

Cognitive task performance

During post-test, the cognitive task performance of the tyrosine group appeared to have been less affected by the fatigue and stress induced by the CTC than that of the placebo group. On the MCT, the number of correct responses was higher in the tyrosine group than in the placebo group ($F(1,18) = 4.11$, $p < 0.05$; see Figure 1).

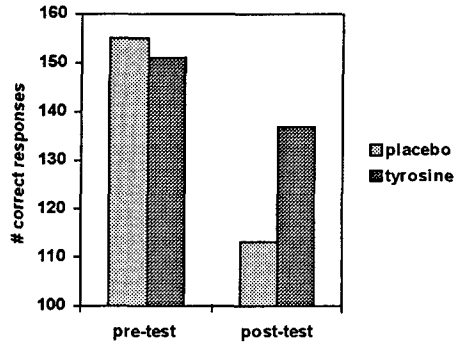

Figure 1. Memory comparison task: mean number of correct responses for the placebo (n = 11) and tyrosine (n = 10) groups during pre-test and post-test.

On the other hand, the difference in the number of MCT errors of both groups did not reach significance (see Figure 2).

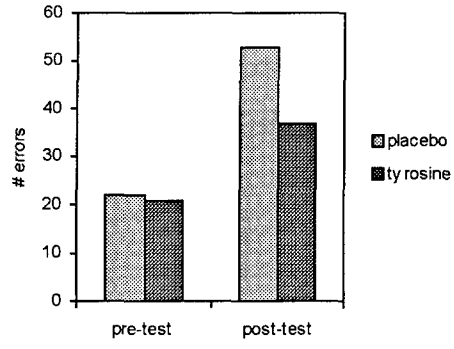

Figure 2. Memory Comparison Task: mean number of errors for the placebo and tyrosine groups during pre-test and post-test.

During the post-test, the tyrosine group also had a better RMS tracking score on the TT than the placebo group ($F(1,18) = 6.14$, $p < 0.05$; see Figure 3).

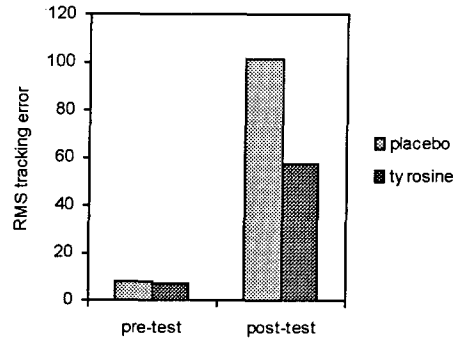

Figure 3. Tracking Task: mean root mean square (RMS) tracking scores for the placebo and tyrosine groups during pre-test and post-test.

The mean RMS values for the 14 successive 30-s intervals of the TT are presented in Figure 4. The ANCOVA yielded a marginally significant interaction between Groups and Intervals ($F(13,234) = 1.64$, $p = 0.08$). This suggests that,

as the TT progressed, the tyrosine group performed increasingly better than the placebo group.

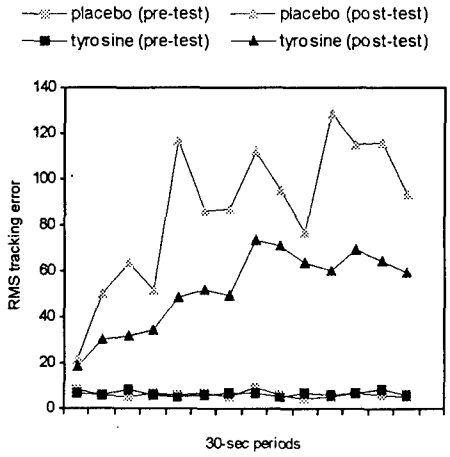

Figure 4. Tracking task: mean root square (RMS) tracking scores for each 30-s period for the placebo and tyrosine groups during pre-test and post-test.

The results concerning the percentage of task interruption time (TIT) in the TT are presented in Figure 5. The post-test TIT for the tyrosine group was lower than that for the placebo group ($F(1,18) = 5.10$, $p < 0.05$), suggesting that the tyrosine group suffered less from lapses of attention than the placebo group.

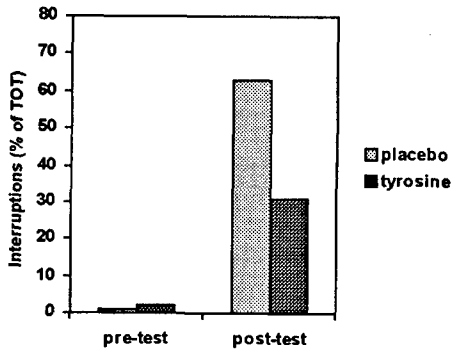

Figure 5. Tracking task: mean percentage of task interruption time (TIT) for the placebo and tyrosine groups during pre-test and post-test.

With respect to the DT, no significant difference emerged between the RMS tracking scores of both groups during the post-test (see Figure 6).

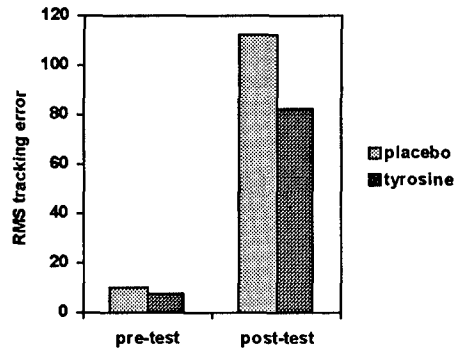

Figure 6. Double task: mean root mean square (RMS) tracking scores for the placebo and tyrosine groups during pre-test and post-test.

In contrast, the ANCOVA on the 14 separate interval values yielded a significant interaction between Groups and Intervals ($F(13,234) = 2.16$, $p < 0.05$; see Figure 7), indicating that, compared to the post-test performance of the placebo group, the post-test performance of the tyrosine group improved over time.

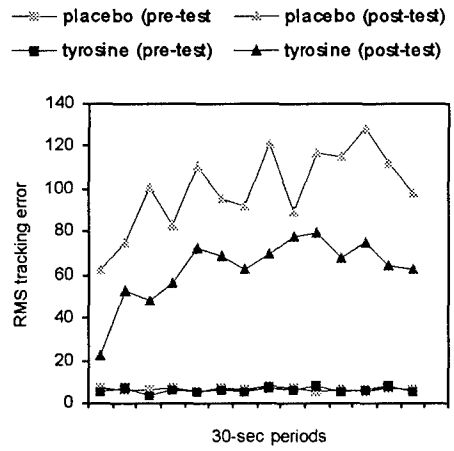

Figure 7. Double task: mean root mean square (RMS) tracking scores for each 30-s period for the placebo and the tyrosine groups during pre-test and post-test.

The DT task-interruption values of both groups are presented in Figure 8. There emerged a marginally significant Groups effect ($F(1,19) = 2.78$, $p = 0.06$), indicating that the placebo group tended to suffer more from attentional lapses during post-test than the tyrosine group.

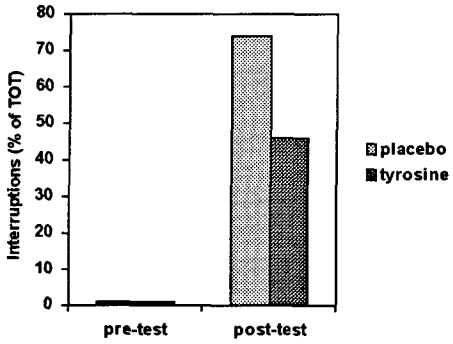

Figure 8. Double task: mean percentage of task interruption time (TIT) for the placebo and tyrosine groups during pre-test and post-test.

Questionnaire

The mean scores for both groups during pre-test and post-test, as well as the results of the ANCOVA's, are presented in Table 1[b]. During the post-test, there were no significant differences between the groups on any of the scales. However, t-tests revealed that there were several differences in the pre-test and post-test POMS values, suggesting effects that were due to the demands of the CTC. During post-test, the Fatigue score was higher than during pre-test (pre-test: 3.9 ± 3.0; post-test: 14.3 ± 5.2; $t(12) = -7.82$, $p < 0.001$). On the other hand, the Vigor score was lower during post-test (pre-test: 12.5 ± 4.6; post-test: 8.1 ± 4.7; $t(12) = 4.34$, $p = 0.001$). In addition, the post-test Tension score was higher than the pre-test value (pre-test: 2.6 ± 2.9; post-test: 5.1 ± 2.1; $t(12) = -2.65$, $p = 0.02$).

TABLE 1
QUESTIONNAIRE SCORES OF THE PLACEBO (n = 7) AND TYROSINE (n = 6) GROUPS DURING PRE-TEST AND POST-TEST

POMS Subscale	Group	Pre-test	Post-test	ANCOVA
Depression	Placebo	0.28	2.14	n.s.
	Tyrosine	3.33	2.50	
Fatigue	Placebo	3.71	14.00	n.s.
	Tyrosine	4.17	14.67	
Vigor	Placebo	14.43	8.71	n.s.
	Tyrosine	10.33	7.33	
Anger	Placebo	2.71	6.00	n.s.
	Tyrosine	5.67	6.67	
Tension	Placebo	2.42	5.71	n.s.
	Tyrosine	2.83	4.50	

[b] *Only 13 questionnaires (placebo group: 7; tyrosine group: 6) were returned by the Ss.*

Discussion

The aim of this study was to examine whether daily supplementation of a tyrosine-rich drink during a highly demanding combat training course (CTC) would reduce the effects of stress and fatigue on cognitive task performance and mood.

During the post-test session, which took place six days after the start of the CTC, and five days after the tyrosine supplementation began, the tyrosine group was found to perform not only better on a cognitive task (the memory comparison task (MCT)), but also on a perceptual-motor motor task (the tracking task (TT)). Only on the double task (DT), no significant difference between the overall RMS tracking scores of the two groups emerged (although the difference between the means of both groups was in the expected direction). However, as is suggested by the significant finding concerning the RMS values for the separate 30-s periods, there was a difference in the performance of both groups on the post-test DT, although this apparently emerged only gradually in the course of the task. The absence of a difference in the overall RMS tracking scores can probably be explained by increased error variances that were due to a reduced motivation associated with the time of presentation of the DT (it was the last task that was presented).

These findings seem to be supportive of the hypothesis that supplementation of tyrosine might serve to reduce the detrimental effects of stress and fatigue on cognitive performance during highly demanding sustained operations. During post-test, the performance on the MCT and the TT was better in the tyrosine group than in the placebo group. Moreover, there were indications that the performance difference between the groups increased as the tasks continued. Furthermore, the percentage of time the Ss were unable to perform the TT was larger in the placebo group than in the tyrosine group. There was a tendency in the same direction in the DT. This strongly suggests the supplementation of tyrosine may be effective in preventing attentional lapses due to fatigue.

These findings can be accounted for by the action of tyrosine which, as a precursor of NE, serves to prevent the depletion of NE in the brain[14, 15, 16]. However, this interpretation is complicated by a number of methodological complications that were due to the restrictions imposed by the RNLA medical supervisor. First, the possible influence of tyrosine on noradrenergic brain activity could not be directly evaluated by assessing plasma amino acid levels. Second, the dose of tyrosine that was administered in this study (2 g) was considerably lower than the standard dose

of 100-150 mg/kg (i.e., ± 6-12 g)[14, 15, 16]. Probably of more importance is the fact that the tyrosine was not administered in a pure form, but in a protein-rich mixture. As a consequence, several large neutral amino acids (LNAA's) were present in high quantities in the mixture, in particular (iso)leucine, phenylalanine and valine. There is no doubt that these LNAA's have competed with the tyrosine to cross the blood-brain barrier, and it can not be ruled out that they had an additional influence on brain functioning. However, it should be emphasised that stress- and fatigue-induced depletion of NE can only effectively be prevented by a precursor of NE, i.e., by L-tyrosine. Hence, it seems highly likely that the tyrosine, and not the LNAA's, was the most crucial factor in the observed reduction of the negative effects of stress and fatigue on cognitive performance.

Another issue that needs to be addressed is the possibility that the placebo drink had an adverse effect on cognitive functioning. Because the protein-rich drink had a high calorie value, it was decided to employ a placebo drink consisting of carbohydrates containing an equivalent amount of calories. Although this was not a real, and certainly not an ideal placebo, it was assumed that this drink, which could not affect NE synthesis, would have no effect on cognitive functioning. However, it has been suggested that carbohydrate consumption may result in a relative increase in LNAA TRP, which may be followed by an increased serotonin synthesis and release, and which may adversely affect cognitive functioning[3]. However, the studies that have examined the relationship between brain serotonin and carbohydrate meals have only employed rats, no humans[27]. Indeed, it is well established that carbohydrate meals raise brain tryptophan and serotonin in rats with empty stomachs. However, a recent review on animal and human studies concludes that any effects of carbohydrate meals on human brain serotonin are likely to be negligeble[27]. Furthermore, regarding dietary effects on behavioral measures, several studies[28, 29, 30] did not find any effect of carbohydrate meals on mood and performance. Hence, these studies do not seem to support the suggestion that the placebo drink did impair cognitive functioning.

The present study provided no evidence that supplementation of tyrosine was effective in reducing the effects of the stress and fatigue on subjective well-being. However, when evaluating this apparent discrepancy between the objective and subjective findings, it should be emphasised that only 13 out of the 21 Ss returned the questionnaires. Hence, the subjective data that were obtained could, unfortunately, hardly be regarded as representative. The only firm conclusion that can be drawn from these data would seem to be that the CTC did indeed, as expected, cause a substantial increase in fatigue and tension, as well as a decrease in vigor. As such, the subjective data may serve to underpin the fact that the CTC indeed posed considerable demands on the cadets.

Although the possibility that other amino acids than tyrosine might have contributed to the observed effects cannot entirely be ruled out, the present findings do seem to support the hypothesis that supplementation of tyrosine may serve to reduce cognitive impairment due to psychoenvironmental stress and fatigue. As such, they confirm earlier findings, obtained in laboratory studies. Moreover, they also strongly suggest that tyrosine supplementation can be effective in preventing cognitive degradation in highly demanding military operational environments that include sustained operations, as well as physical and psychological stressors. In particular, the results seem to indicate that not only the efficiency and speed of short-term memory operations can, to some degree, be protected against deterioration due to factors like stress and fatigue, but also, and maybe more importantly, that the degree to which these factors cause lapses of attention, can be considerably reduced. Overall, the cognitive impairment that was caused by the CTC in the placebo group appeared to be reduced by the supplementation of tyrosine by up to 40%.

Finally, it should be emphasised that, due to several methodological constraints, this study had a preliminary character. Hence, the present findings need replication in order to be draw definite conclusions concerning the efficacy of tyrosine supplementation in operational environments. First, it is necessary to evaluate the effects of tyrosine supplementation without the dose and dosage form restrictions that were imposed on the present study. Furthermore, it should be noted that the tasks that were employed addressed only quite basic aspects of cognitive functioning. Subsequent studies should therefore also include tasks that involve higher-order cognitive functions, including decision-making processes.

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