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Effect of Tyrosine on Cognitive Function and Blood Pressure Under Stress

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DEIJEN, J. B. AND J. F. ORLEBEKE. *Effect of tyrosine on cognitive function and blood pressure under stress.* BRAIN RES BULL **33**(3) 319–323, 1994.—The effects of tyrosine on mood, performance, heart rate and blood pressure of 16 healthy young subjects were assessed. Subjects were tested on two separate days, one test session after ingestion of 100 mg/kg tyrosine and the other test session after placebo, in random order. While performing a number of stress sensitive tasks, subjects were exposed to a stressor consisting of 90 dB noise. Tyrosine was found to improve the performance on two cognitive tasks, which were performed 1 h after administration of the medication and which could be characterized as highly sensitive to stress. In addition, tyrosine decreased diastolic blood pressure 15 min after ingestion, while 1 h after ingestion diastolic blood pressure was the same with tyrosine and placebo. No effects on mood, systolic blood pressure and heart rate were found.

Tyrosine Cognitive performance Stress Blood pressure Heart rate Mood

IN animal studies "stress-induced" depression was found to coincide with depletion of norepinephrine (NE) in specific brain regions (28). Stressful events cause an increase in transmission of noradrenergic neurons, particularly in the frontal cortex, because these neurons are activated by stress (17,7,11). A main innervation to the frontal cortex is produced by noradrenergic projections from the locus coeruleus (LC). This structure shows an increased electrical activity during stress (1,24). The activity of noradrenergic neurons within the LC is thought to influence attention, alertness, motor activity and anxiety (22). Indeed, stress-induced NE depletion was found to impair performance. For instance, in animal studies it was found that explorative and motor behavior was impaired after NE depletion caused by cold-swim stress (5,19). In humans NE depletion caused irrepressible eye movements during smooth pursuit and visual search. The finding that catecholamine depletion increased the amplitude and frequency of saccadic intrusions during fixation and pursuit implied that brainstem neurones use catecholamines to suppress saccades (27). However, no other effects of NE depletion on human behavior are known. In addition, it is unclear if stressful events cause NE depletion in human brain. Apart from this, behavioral effects of stress in humans are well documented. The main cognitive effects of stress can be summarized as being (a) attentional narrowing, (b) increased speed in information processing paired with less accuracy and (c) a decrease in the capacity of short-term memory (14). Whether these behavioral stress effects are associated with NE depletion is still unclear. On the peripheral nervous system the physiological effects of stress can be summarized as being increased heart rate, blood pressure, muscle tonus, skin conductance and respiration rate. In addition biochemical changes take place, that is, increases in the concentration of catecholamines (12,9,13).

The precursor of norepinephrine, dopamine and epinephrine is the large neutral amino acid tyrosine, which is present in dietary proteins. Tyrosine reaches its maximum concentration in mice brain 1 h after oral ingestion, while 4 h after administration the baseline concentration is present again (26). There is evidence that tyrosine enhances catecholamine synthesis in particular noradrenergic neurons, when these neurons are physiologically active and firing frequently (10,21). With respect to dopamine, supplemental tyrosine in anaesthetized rats was found to enhance dopamine concentrations in the extracellular fluid of corpus striatum and nucleus accumbens. Thus, supplemental tyrosine increased dopamine release, even when the animals did not receive treatment to accelerate the firing of dopaminergic neurons (8,30).

In animal studies tyrosine was shown to prevent NE depletion and negative behavioral effects after stress induction (5,19). The possible beneficial effect of tyrosine on humans who are exposed to acutely stressful conditions was studied quite recently (4). Young male subjects were supplemented with 100 mg/kg tyrosine before exposure to cold and hypoxia. Tyrosine reduced stress-symptoms like headache, tension and fatigue and decreased performance impairments in subjects who were adversely affected by these environmental conditions. Performance measurements consisted of the assessment of vigilance, pattern recognition, choice reaction time and arithmetic skills.

It is clear that only limited evidence of the stress reducing effects of tyrosine in humans exist. Therefore, the present study was designed to investigate whether tyrosine reduces cognitive

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and physiological stress effects in humans exposed to a combination of mental and physical stressors.

METHOD

Subjects

Sixteen (9 males, 7 females) healthy young subjects participated in the study. They were aged between 23 and 35. The mean age was 27. Subjects did not use any form of medication, were not addicted to alcohol or drugs and had no sensory or motor handicaps which could influence the performance. They responded to a written invitation to take part in the study and were paid for participation.

Procedure

Prior to testing subjects had been familiarized with the test battery in a practice session. In this session, which took about 0.5 h, shortened versions of all tests were presented. A few days after the practice session subjects were tested on 2 days at approximately 9:30 a.m., separated by a period of 10 days. Subjects were allowed to eat a light breakfast. On the first test session the random assignment to the different treatment conditions took place. Treatment consisted either of tyrosine or placebo. In the second session each subject was given the alternate treatment. The procedure was double-blind and on termination of the data collection subjects were informed as to the kind of treatment they had received on which occasion. Half the subjects received the placebo first, the other half the tyrosine treatment.

Subjects were examined individually in a quiet room. The test procedure as a whole took 1 h and started 20 min after ingestion of the tablets. Each task was preceded by a number of practice trials. The task only started after a preset criterion of a certain number of error-free trials had been reached. Just before and immediately after the test procedure, blood pressure and pulse-rate were assessed.

Dependent Measures

Perceptual-motor tasks.

Cognitrone. In the cognitrone program five display fields appear on the screen, four on top and one at the bottom. The figure displayed in the field below had to be compared with the four figures in the top field. If the figure below was identical to one of the four figures on top, the subject was instructed to push a "yes" button; if there were no identical figures, no response was needed. Each trial was followed by the next with a fixed intertrial interval of 1.8 s, this interval being the maximum response time. As a number of 200 trials were presented, the duration of this task was 6 min. The number of correct responses and reaction time were recorded. This program measures concentration and form perception (16).

Vienna determination unit. The determination apparatus is a complex, multiple-stimuli reaction unit. The unit allows presentation of optical stimuli colored white, yellow, red, green and blue, which are presented on ten different positions. The subject had to respond by pressing one of five reaction keys assigned to these colors. Two additional white lamps, which are set apart from the colored lamps, require stepping on the left or right pedal. Two acoustic stimuli (high tone, low tone) are assigned to two rectangular "tone" keys.

The version used in the present study consists of a practice phase and an endurance test. The practice phase is used to familiarize the subject with the different speeds at which stimuli may be presented. The test is started at a speed with a signal length of 3 s followed by an increase in presentation speed up to the point that the maximum stress tolerance (i.e., a 50% right performance) of the subject is reached. When the limit is reached the practice phase is discontinued.

The endurance test assesses "psycho-physical" stress tolerance. A number of 540 signals are presented at a speed at which the subject is only just able to perform 50% right, as was determined in the practice phase. In this way an extremely stressful situation is created which makes it possible to assess reactive stress tolerance, distribution of attention and resistance to panicking.

The determination apparatus has been found to be useful in simulating stress-situations, which require decisions under time-pressure.

At a medium speed level a 9.7% increase in heart rate has been found. At a higher speed level heart rate increased with 17.8%. In addition, systolic blood pressure increased with 14.3–20.5%, depending on speed level, while diastolic blood pressure increased 15% on average for both speed levels (29).

As all subjects reached an average speed in the endurance test comparable to the higher speed level mentioned above, the endurance test can be assumed to increase heart rate and blood pressure with the same or even higher percentages.

The duration of the endurance test is, depending on response speed of the subject, about 7 min.

Vigilance/peripheral perception (double task). A circle consisting of small rings is displayed on the screen. A point travels along the circular path from one ring to the next. Occasionally one ring is skipped and if this occurs, the subject has to press a button. The number of right and missed reactions in addition to reaction time are recorded. This vigilance task is an adapted version of the original "clock" test (20), which simulated the essentials of the radar operator's job. When performing this task, the peripheral perception of the subject is measured at the same time. The duration of this double task is 10.5 min.

Peripheral perception. On the central screen of the testing unit, the vigilance test, on which the subject has to fixate his eyes throughout the test, is presented. Occasionally light stimuli are moving from the periphery of the testing unit towards its centre. As soon as the subject perceives a light stimulus out of the corner of his eyes, a foot pedal has to be stepped on. This test is designed to test a person's ability to perceive and process peripheral visual information, with special emphasis on the timely perception of stimuli entering the visual field from both sides. Measurements were made of the number of right, wrong and missed reactions and of reaction time.

Stroop task. Four color words (white, red, black, and blue), randomly distributed on a sheet, were presented visually in one of these colors in an incongruent condition. This means that the color of the word presented did not match the color name (e.g., the word black displayed in blue color). Subjects were instructed to name as quickly as possible the color of the 80 words on the sheet. While performing this task, subjects were auditorily presented with random color names of 90 dB through a head phone. Recorded were number of errors and total response time. The duration of this task is about 1 min.

Short term memory.

Digit span. On the computer screen a series of 4 digits is presented, 1 each second. Afterwards the subject has to press the corresponding digits on the computer keyboard. After correct responding a series of 5 digits is presented. If the subject responds correctly, the series is lengthened to 6, and, in case of correct responses, to a maximum of 9 digits. At each span length a second trial is given if the first response is incorrect. After incorrect responding to two trials of the same span length, the forward procedure is ended. In addition, the subject has to respond to

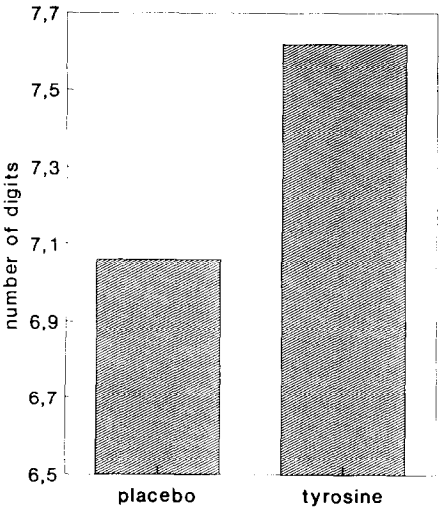

FIG. 1. Mean scores on the "Digit Span" task for the placebo and the tyrosine condition (SD placebo = 1.4; SD tyrosine = 1.4).

progressively longer series (3 to a maximum of 8) of digits in the reverse order from that presented on the computer screen. The "backward" test, apart from the reverse response order, is comparable to the forward procedure. The scores recorded are the numbers of digits entered correctly both forward and backward. The duration of this task is about 6 min.

Mood.

Adjective Check List (ACL) (23). The ACL assesses six groups of mental state aspects, that is, vigor, inertia, extraversion/introversion, feeling of wellbeing, irritability and anxiety. These mental state aspects are again subdivided into 14 subscales, that is, active, concentrated, inactive, tired, benumbed, extroverted/introverted, self-confident, elated, excited, sensitive, angry, anxious, depressed and dreamy. The subject has to agree or disagree with the adjectives presented on a monitor by pressing a "yes" or "no" button. Depending on the response speed of the subject, this task takes about 8 min.

Physical Stress Exposure

As environmental stressor, a continuous broad-band noise with a sound pressure level of 90 dB was induced through a headphone. This noise consisted of a mixture of the sounds of a swimming-pool, a factory, traffic and trains. Industrial continuous noise of 20 min. duration at sound levels of 75, 85 and 95 dB has been found to significantly increase diastolic blood pressure (5–12%), mean arterial pressure (3–7%) and total peripheral resistance (11–13%) in young healthy subjects (2,3). Thus, the induction of 90 dB noise can be assumed to be stressful, as indicated by substantial increases in hemodynamic indices. The noise was presented during the performance of all tasks, except during the Stroop task and the ACL.

Medication

The medication consisted of 100 mg/kg L-tyrosine (Country Life, Hauppauge, NY) or placebo. Subjects were given tablets containing 500 mg L-tyrosine and 10 mg vitamin B-6 or nonactive tablets of identical appearance in the placebo condition. L-tyrosine was administered in combination with vitamin B-6, because this vitamin supports the conversion of tyrosine into NE (18). The study medication was ingested under supervision of the investigator at 20 min before the start of the experiment.

Apparatus

Most cognitive tasks were presented by means of the "Vienna Test System," a computerized testing system which is connected to an Olivetti M24 Personal Computer, except the Digit Span was presented by an Olivetti M250 personal computer, and the Stroop test was presented by means of a stimulus sheet requiring verbal responses which were recorded by the investigator.

Data Analysis

All data from the cognitive tasks and the physiological measurements were analyzed by means of one-way (multivariate) analyses of variance with condition as repeated measurements factor.

RESULTS

Significant treatment effects were found for two tasks, that is, Digit Span and the Stroop task. With respect to Digit Span the number of correct responses was higher under tyrosine than under placebo ($F(1, 15) = 3.46$; $p < 0.05$). This effect was not found for the backward procedure of Digit Span, although the mean scores were also higher under the tyrosine condition. The results on Digit Span are shown in Fig. 1.

The data from the Stroop task revealed that subjects performed this task faster with tyrosine than with placebo ($F(1, 15) = 4.18$; $p < 0.03$), whereas the number of correct responses were the same for both treatments (see Fig. 2).

With respect to pulse rate and blood pressure, a significant decrease in diastolic blood pressure was found in the tyrosine condition preceding the behavioral testing ($F(1, 15) = 4.52$; $p < 0.03$). As medication was administrated 15 min before blood pressure was assessed, this finding indicates that a drop in diastolic blood pressure followed the ingestion of tyrosine after this period of 15 min. For the pretest measurements of systolic blood pressure and heart rate and for all posttest physiological measurements, no significant differences between tyrosine and placebo were found. The findings with respect to pretest blood pressure are depicted in Fig. 3.

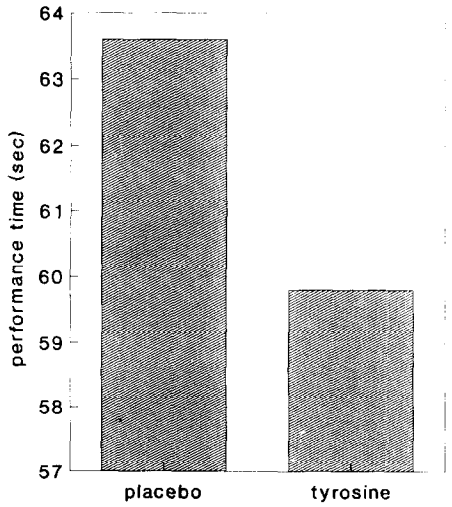

FIG. 2. Mean performance time on the "Stroop" task for the placebo and the tyrosine condition (SD placebo = 9.7; SD tyrosine = 9.4).

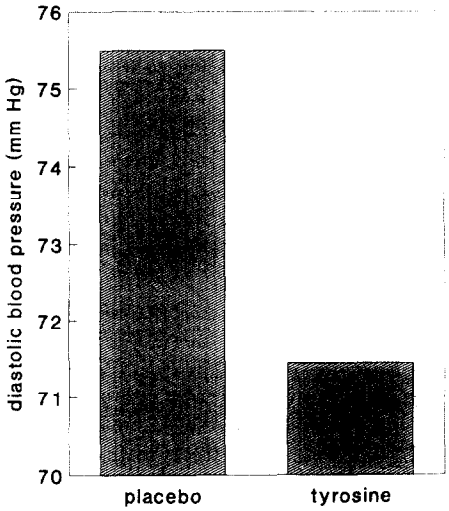

FIG. 3. Mean diastolic blood pressure 15 min after placebo or tyrosine ingestion (SD placebo = 7.6; SD tyrosine = 7.2).

DISCUSSION

The present results indicate that the administration of tyrosine improved the performance on Digit Span and on the Stroop test. In addition, a decrease in diastolic blood pressure was seen 15 min after administration of tyrosine. The performance on these two cognitive tasks took place at the end of the test session which had a length of about 1 h. This means that an improvement on only those tasks, which were performed at about 70 min after ingestion, was found. As is mentioned in the introduction, the maximum concentration of tyrosine in mice brain is reached 1 h after oral administration (26). Assuming that the same is true for humans, it means that the performance of these tasks took place when brain tyrosine had reached its maximum concentration. In the study on humans exposed to environmental stress (4), only the data were analyzed of those subjects who were adversely affected by the stressors. They hypothesized that only behavior which was impaired by the stressor could be improved by treatment with tyrosine. Although in the present study no subjects were selected for analysis, a positive effect was found. Both the Digit Span and the Stroop task have been found to be very sensitive to stress induction in particular. As is stated in the introduction, a decrease in the capacity of short-term memory is one of the main, well documented, cognitive stress effects. In addition, the Stroop task is an experimental paradigm which requires a large mental load because the task demands the resolution of a conflict between two competing tendencies. Although the source of the effect is explained by different mechanisms as perceptual conflict, conceptual encoding, response interference or a combination of these factors, robust responses have been found in neuronal activity of the brain. In a recent study regional blood flow was measured using positron emission tomography (PET) during the performance of the Stroop task (23). A robust activation of the anterior cingulate cortex was found during the performance of the Stroop test. In addition to this response a complex distributed array of foci of activity was found.

As in the present study, an additional auditory stressor was used (random names of colors presented loudly through a headphone); this task may be assumed to be highly stress inducing. Thus, the combination of the test presentation at the right time (about 1 h after tyrosine ingestion) and the high degree of stress sensitivity of the tasks may explain why tyrosine improved the performance of, in particular, these two tasks.

Because of practical limitations, blood pressure was only measured just before and immediately after the test administration, and not during the tasks. Therefore, no data are available of the blood pressure during task performance. With respect to the available data, it was found that diastolic blood pressure was lower with tyrosine than with placebo, but this effect was only present 15 min after administration. At the end of the test session the diastolic blood pressure was the same for both conditions. This means that the drop in systolic blood pressure is temporary and is absent more than 1 h after ingestion. Indeed, in animal studies tyrosine was found to reduce blood pressure in hypertensive rats (25,31), but also to elevate blood pressure in animals with haemorrhagic shock (6). It would be worthwhile to investigate further if tyrosine may be useful in treating hypertensive subjects.

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