UMENTATION PAGE

Form Approved
OMB No. 0704-0188

2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
1994	Journal article

4. TITLE AND SUBTITLE
Tyrosine reverses a cold-induced working memory deficit in humans

5. FUNDING NUMBERS
PE - 63706
PR - M0095
TA - 004
WU - 1008

6. AUTHOR(S)
Shurtleff D; Thomas JR; Schrot J; Kowalski K; Harford R

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Naval Medical Research Institute
Commanding Officer
8901 Wisconsin Avenue
Bethesda, Maryland 20889-5607

8. PERFORMING ORGANIZATION REPORT NUMBER
NMRI 94-56

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Naval Medical Research and Development Command
National Naval Medical Center
Building 1, Tower 12
8901 Wisconsin Avenue
Bethesda, Maryland 20889-5606

10. SPONSORING/MONITORING AGENCY REPORT NUMBER
DN246556

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS
cold stress; tyrosine;working memory; catecholamines; matching-to-sample

15. NUMBER OF PAGES
7

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Pergamon

Pharmacology Biochemistry and Behavior, Vol. 47, No. 4, pp. 935–941, 1994

0091-3057/94 $6.00 + .00

Tyrosine Reverses a Cold-Induced Working Memory Deficit in Humans

DAVID SHURTLEFF,[1] JOHN R. THOMAS, JOHN SCHROT, KATHLEEN KOWALSKI AND ROBERT HARFORD

Thermal Stress Adaptation Program, Naval Medical Research Institute, 8901 Wisconsin Avenue, Bethesda, MD 20889-5607

Received 12 July 1993

SHURTLEFF, D., J. R. THOMAS, J. SCHROT, K. KOWALSKI AND R. HARFORD. *Tyrosine reverses a cold-induced working memory deficit in humans.* PHARMACOL BIOCHEM BEHAV 47(4) 935–941, 1994. – Acute exposure to cold stress has been shown to impair short-term, or working, memory, which may be related to reduction in, or disruption of, sustained release of brain catecholamines. Administering a supplemental dose of the catecholamine precursor tyrosine may alleviate cold stress-induced memory impairments by preventing cold-induced deficits in brain catecholamine levels. The present experiment determined whether administration of tyrosine would prevent a cold-induced working memory deficit, using a computer-based delayed matching-to-sample (DMTS) memory task. Eight male volunteers performed the DMTS task for 30 min at an ambient temperature of either 4°C (cold) or 22°C following a 30-min preexposure period and 2 h after ingesting 150 mg/kg of L-tyrosine or placebo. Subjects demonstrated a decline in matching accuracy on the DMTS task as delay interval increased, such that matching accuracy following a 16-s delay between sample and comparison stimuli was lower than that following a delay of 2 or 8 s. Consistent with previous research, and relative to 22°C exposure sessions, matching accuracy during 4°C exposure sessions was reduced significantly following placebo administration, which is attributed to the effect of cold exposure on short-term, or working, memory. Administration of tyrosine significantly improved matching accuracy at the longest delay interval most affected by cold exposure, such that matching accuracy in the cold following tyrosine was at the same level as matching accuracy following placebo or tyrosine administration at 22°C. Tyrosine administered prior to 22°C exposure had no effect on DMTS performance. Plasma norepinephrine levels and diastolic and systolic blood pressure were significantly elevated just prior to performing the DMTS task and following 30 min of acute cold exposure, indicating that the cold exposure produced a typical stress response. Tyrosine was effective in protecting against the effects of cold stress on DMTS performance, possibly by preventing cold stress-induced reduction in brain catecholamine levels.

Cold stress Tyrosine Working memory Catecholamines Matching-to-sample

ACUTE exposure to environmental stressors is associated with a variety of biochemical changes and behavioral and cognitive deficits. The biochemical changes that occur during exposure to acute stress include the increased release and often subsequent reduction in the levels of the central nervous system (CNS) catecholamines norepinephrine (NE) (8,14,18,22, 25,36) and dopamine (DA) (8,11,17,23,31). The inability of CNS catecholaminergic neurons to sustain neurotransmitter release during acute exposure to stressful conditions has been related to impaired motor behavior in rats (25) and is hypothesized to result in deficits in cognitive function (4,29,32,34).

In terms of cognitive impairment, recent research has demonstrated that exposure to acute *cold* stress impairs performance on a delayed matching-to-sample (DMTS) task. This finding has been attributed to the effect of cold on short-term, or working, memory (1,29,32,34). This deficit in DMTS performance may be related to cold stress-induced increases in CNS NE and DA activity, which result in an overall reduction in neurotransmitter release. The inability of these neurons to sustain normal levels of release during exposure to cold stress could be responsible for observed deficits in cognitive function, such as impaired working memory. Previous research does, in fact, suggest DA and NE are involved in short-term, or working, memory. Reductions in NE and DA CNS levels associated with biochemical lesions, for example, have been shown to impair DMTS performance (2,9). It is also likely that a reduction or a disruption in NE and DA release may impair DMTS performance by negatively affecting the release

[1] To whom requests for reprints should be addressed

of acetylcholine, a neurotransmitter important in working memory (10).

Because stressful conditions may disrupt the sustained release of DA and NE, administration of the amino acid tyrosine, a necessary precursor for catecholamine biosynthesis, should be effective in protecting against some of the adverse, stress-induced biochemical deficits in DA and NE, and thus prevent or reduce stress-induced behavioral and cognitive deficits. Tyrosine may protect against these debilitating effects of stress by allowing for the repletion of NE and DA in CNS regions responsible for normal cognitive and behavioral functions. In fact, it has been shown that tyrosine administration can increase the rate of NE synthesis in the CNS of rats during acute exposure to an ambient temperature of 4°C (14) and prevent shock-induced NE reduction in the hippocampus, a CNS region implicated in working memory (25). The increased firing rate of CNS neurons and the continued release of catecholamines under these stressful conditions activate tyrosine hydroxylase, which induces an increase in tyrosine utilization and catecholamine biosynthesis (21).

Providing supplemental tyrosine during exposure to stress has been shown to ameliorate cognitive and behavioral deficits caused by stressful conditions. Recent research has shown that administering tyrosine to rats prior to exposure to 2°C air improves cold-induced decrements in DMTS performance (29). Tyrosine has also been shown to reduce behavioral depression in rats, following exposure to 17°C water (24). In humans, tyrosine has been shown to be effective in alleviating some adverse symptoms and moods, and improving some cognitive abilities during exposure to a simulated high-altitude cool environment (4). Although previous research indicates that acute cold exposure impairs working memory in humans (32), the effects of tyrosine on this cold-induced working memory deficit have not been assessed. This experiment, therefore, determined whether tyrosine can (1) reduce a cold stress-induced working memory deficit in humans and (2) whether tyrosine has any effect on working memory under a nonstressful ambient temperature condition.

METHOD

Subjects

Eight healthy male volunteers with a mean ± SEM age of 27.5 ± 1.8 years (range 23–37), a mean weight of 81.7 ± 5.3 kg (60–100), and a mean height of 174.4 ± 3.8 cm (158–188) served as subjects. All subjects received monetary compensation for their participation. Each subject received a physical examination and was informed as to all aspects of the study. The subjects wore shorts, t-shirts, and socks during the experimental sessions.

Apparatus

Testing was conducted inside a temperature-controlled environmental chamber. A microcomputer with a color display monitor was used to present stimuli and record responses. Skin temperatures were measured with thermistors connected to a portable data logger.

Procedure

Delayed Matching-to-Sample Task. Subjects were trained on the DMTS task and then performed the task for 10 separate daily baseline sessions to achieve stable performance. The baseline sessions were conducted in the temperature-controlled chamber at an ambient temperature of 22°C. The DMTS task is derived from the matching-to-sample task as part of the Naval Medical Research Institute Performance Assessment Battery (28). The subject initiated a DMTS trial by pressing the 2 key on the computer keypad to present a 64-cell matrix (8 column × 8 row square) for 4 s on the computer monitor. The sample matrix was composed of 32 red and 32 green squares, randomly distributed. After the sample matrix was removed from the screen, a delay interval of 2, 8, or 16 s was initiated. Following the delay interval, two comparison matrices were presented, one on the left portion of the screen and the other on the right. One matrix was identical to the previously displayed sample matrix and the other differed by two cells: one green and one red. The position of the correct matrix was randomly determined. The subject was required to press either a right matrix key (3 key) or a left matrix key (1 key) to indicate if the right or left comparison matrix matched the original sample matrix. After a choice response the screen went blank and the subject was required to respond to present a new sample matrix for the next trial. A session comprised 90 trials, with 30 occurrences of each delay interval randomly distributed throughout the session. A session took approximately 30 min to complete.

Testing. To ensure uniform absorption of tyrosine and similar initial tyrosine blood levels, subjects were tested in the morning after a night's fast. At the beginning of a test session subjects were weighed. The subject was then seated in a room adjacent to the temperature-controlled chamber, and a catheter was placed in the brachial vein of one arm. Following insertion of the catheter, a blood sample was obtained and blood pressure was recorded. Thermistors were placed on the right triceps, pectoral, quadriceps, and the gastrocnemius muscle for skin temperature recording. Using a double-blind procedure, the subject then ingested a mixture of 42 g applesauce and microcrystalline cellulose (placebo) or 42 g applesauce and L-crystalline tyrosine (Tysons & Assoc., Santa Monica, CA). L-Tyrosine was administered in a dose of 150 mg/kg b.wt. Microcrystalline cellulose was always administered as a 5-g quantity because this amount most resembled the tyrosine mixture in appearance and texture. Subjects had no prior experience with either of these mixtures; therefore, any apparent differences in texture or appearance could not be attributed to a particular mixture. The subject then entered the temperature-controlled chamber, set at either 22°C or 4°C, 90 min following mixture ingestion, sat in the chamber for 30 min, and then began performing the DMTS task for approximately 30 min. In addition to the initial blood sample drawn before tyrosine or placebo ingestion, blood samples were drawn at 30, 60, 90, 120, and 150 min following mixture ingestion. Additional blood pressure measures were recorded 60, 90, 120, and 150 min following ingestion.

Subjects were exposed to each temperature condition four times, twice following placebo ingestion and twice following tyrosine ingestion. Each of the four conditions was experienced once before any of the conditions were replicated. Within a four-condition block (placebo at 4°C or 22°C, and L-tyrosine at 4°C or 22°C), subjects experienced the conditions in a random order. Test sessions occurred twice a week with at least 1 day separating each test. Subjects practiced the DMTS task the day before each test session with the chamber set at 22°C.

Blood Sample Analysis

Blood samples were collected in 5-ml tubes containing 143 U heparin and immediately cooled. Plasma samples were pre-

pared and analyzed for tyro[illegible] NE by high pressure liquid chromatography with [illegible]hemical detection as described previously [see (33)].

Data Analysis

Significant differences between measures were assessed using repeated measures analysis of variance (ANOVA). The factors included in the repeated measures ANOVA included tyrosine dose (0 or 150 mg/kg), exposure temperature (4°C or 22°C), and replication. For the dependent measures associated with the DMTS task, delay interval between sample and comparison matrices (2, 8, and 16 s) was also included as a repeated factor. To determine significant changes in NE and tyrosine plasma levels, and changes in blood pressure, time since ingestion of the mixture was used as a repeated factor. The least square means multiple comparison test was used to determine differences among paired comparisons. Differences were determined significant at $p < 0.05$. For all ANOVAs, the replication factor did not significantly affect any of the dependent measures.

RESULTS

Delayed Matching-to-Sample Performance

Figure 1 shows the mean ± SEM percent correct matches across the three delay intervals for each condition. Analysis indicated that matching accuracy changed significantly as a function of delay, $F(2, 14) = 76.12$, $p = 0.0001$. Paired comparison tests indicated that percent correct matches following the 16-s delay interval were significantly less than following the 2-s ($p = 0.0001$) or 8-s ($p = 0.0001$) delay interval. There were no differences in matching accuracy between the 2- and 8-s delay intervals ($p = 0.6897$). ANOVA further revealed there was a significant temperature × dose × delay interaction, $F(2, 14) = 4.76$, $p = 0.0265$. Matching accuracy at the 16-s delay during exposure to cold following placebo ingestion was significantly lower than following tyrosine ($p = 0.0001$) or placebo ($p = 0.0001$) ingestion at 22°C. Matching accuracy at the 16-s delay interval in the cold after tyrosine administration was significantly higher than following placebo ingestion ($p = 0.0001$) in the cold, such that matching accuracy at this delay interval at 4°C was not significantly different from the placebo ($p = 0.2546$) or tyrosine ($p = 0.0802$) conditions at 22°C. At 22°C, tyrosine did not significantly alter matching accuracy at any delay, relative to placebo (all $p > 0.08$).

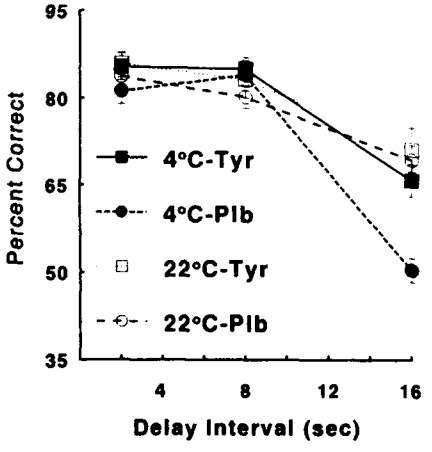

FIG. 1. Mean ± SEM percent correct matches as a function of delay interval for each condition.

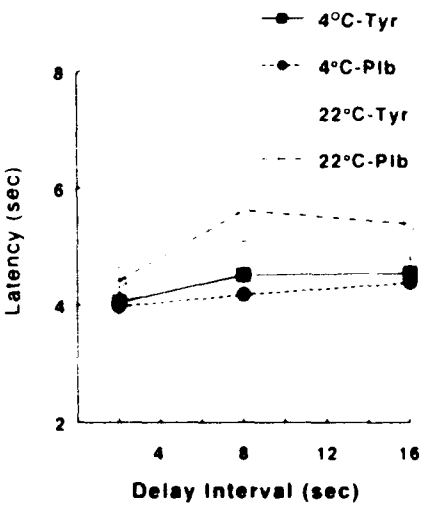

FIG. 2. Mean ± SEM latency to choose a comparison stimulus as a function of delay interval for each condition.

Response Latencies

Figure 2 shows the latency to choose a comparison stimulus as a function of delay interval and exposure condition. Latency to choose a comparison stimulus was significantly faster in the cold than at 22°C, $F(1, 7) = 28.63$, $p = 0.0011$. There was also a significant effect of delay interval on latency to choose a comparison stimulus, $F(2, 14) = 12.45$, $p = 0.0008$. Latencies were significantly longer following the 8- and 16-s delays than following the 2-s delay interval (both $p < 0.01$). Latencies to choose comparison stimuli did not differ between the 8- and 16-s delay intervals ($p = 0.706$). ANOVA further indicated a marginally significant temperature × delay interaction, $F(2, 14) = 3.72$, $p = 0.0506$. Latencies to choose comparison stimuli following the 2-s delay at 4°C tended to be faster than latencies following the 2-s delay at 22°C ($p = 0.048$). Latencies to choose a comparison stimulus following the 8- and 16-s delays at 4°C were significantly faster than latencies following these same delays under the 22°C condition (both $p = 0.0001$). Administering tyrosine prior to performing the DMTS task had no significant effect on latencies to choose a comparison stimulus at any delay interval for either temperature condition. Consequently, ANOVA indicated there was no significant effect of dose or significant interactions involving dose for this measure.

Plasma Tyrosine

Figure 3 shows changes in plasma tyrosine levels over the course of the experimental session in which tyrosine or placebo was administered prior to exposure to cold and normothermic temperature conditions. During the first 90 min following tyrosine ingestion, plasma levels increased two-to threefold from an average of 56.3 nmol/ml to approximately 140–168 nmol/ml and stayed at this maximal level for the remainder of the session. Following placebo ingestion, plasma tyrosine levels remained low and constant, at approximately 50 nmol/ml, throughout the experimental session. Conse-

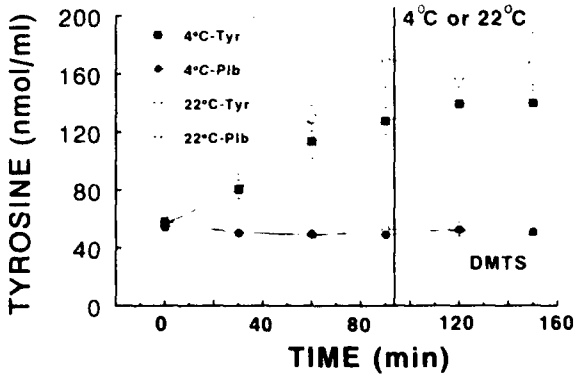

FIG. 3. Mean ± SEM changes in plasma tyrosine levels as a function of time just prior to and since mixture ingestion. The DMTS label indicates when the delayed matching-to-sample task was performed during the experimental session. The vertical line separates the time before entering the chamber with the time spent in the environmental chamber, which was set at either 4°C or 22°C.

quently, ANOVA indicated there was a significant dose × time interaction, $F(5, 35) = 40.42$, $p = 0.0001$. There were no other significant interactions. Paired comparisons indicated that plasma tyrosine levels following tyrosine administration significantly increased successively higher every 30 min for the first 90 min (all $p < 0.0013$). Plasma levels of tyrosine at 90, 120, and 150 min following tyrosine ingestion were not significantly different from each other (all $p > 0.34$). In addition, plasma tyrosine levels following tyrosine administration were significantly higher than those following placebo administration at all time intervals after ingestion (all $p = 0.0001$), but not before ($p > 0.94$).

Plasma Norepinephrine

Figure 4 shows changes in plasma norepinephrine levels over the entire session. The NE levels changed significantly as a function of cold exposure. Consequently, ANOVA indicated a significant time × temperature interaction, $F(5, 35) = 22.2$, $p = 0.0001$. However, there were no other significant interactions. Paired comparisons showed that NE levels significantly increased during exposure to cold (120 min following mixture ingestion and following 30 min of cold exposure) relative to the 22°C condition ($p = 0.0001$) and remained elevated immediately after 60 min of cold exposure relative to 22°C exposure ($p = 0.0001$). Relative to NE levels prior to entering the chamber, NE levels were higher under the 22°C condition just before (all $p = 0.0001$) and immediately after (all $p < 0.0003$) performing the DMTS task.

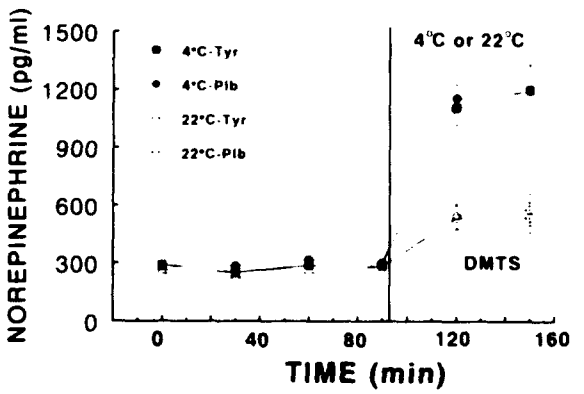

FIG. 4. Mean ± SEM changes in plasma norepinephrine levels as a function of time immediately before and after mixture ingestion. The DMTS label indicates when the delayed matching-to-sample task was performed during the experimental session. The vertical line separates the time before entering the chamber with the time spent in the environmental chamber, which was set at either 4°C or 22°C.

Blood Pressure

The effects of tyrosine administration and cold exposure on systolic and diastolic blood pressure are presented in Fig. 5. Analysis indicated that there was a significant temperature × time interaction, $F(4, 28) = 11.25$, $p = 0.0001$, for systolic blood pressure. There were no other significant interactions. Systolic blood pressure was significantly elevated following 30 min ($p < 0.0007$) and 60 min ($p < 0.015$) of cold exposure relative to the 22°C condition at these same time intervals. Systolic blood pressure also significantly increased after 30 min of exposure to the 22°C condition, just prior to performing the DMTS task, relative to all measures taken prior to entering the chamber (all $p < 0.035$). After 60 min of 22°C exposure, and following completion of the DMTS task, systolic blood pressure declined such that it was not significantly different from blood pressure levels taken before entering the chamber (all $p > 0.10$) except one (60 min following mixture ingestion; $p < 0.02$).

Analysis of diastolic blood pressure also indicated a signifi-

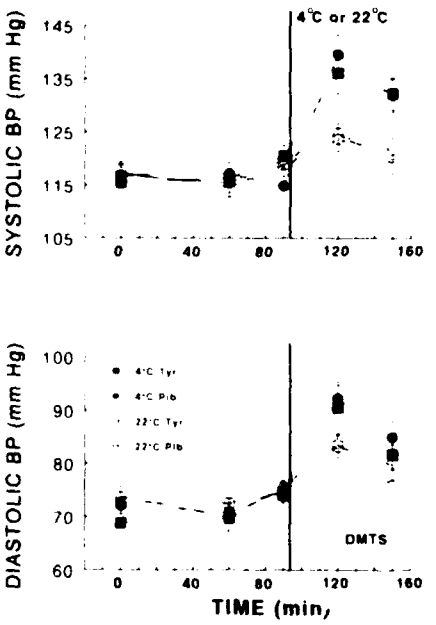

FIG. 5. Mean ± SEM changes in systolic (top) and diastolic (bottom) blood pressure over the experimental session for each condition. The DMTS label indicates when the delayed matching-to-sample task was performed during the experimental session. The vertical line separates the time before entering the chamber with the time spent in the environmental chamber, which was set at either 4°C or 22°C.

cant temperature × time interaction, $F(4, 28) = 4.8$, $p < 0.0045$. There were no other significant interactions. As with systolic blood pressure, diastolic blood pressure was significantly elevated following 30 min ($p < 0.0007$) and 60 min ($p < 0.0157$) of cold exposure relative to these same exposure times during the 22°C condition. Diastolic blood pressure also significantly increased after 30 min of exposure to the 22°C condition, just prior to performing the DMTS task, relative to all previous measures (all $p < 0.0006$). After 60 min of exposure to 22°C, and following completion of the DMTS task, diastolic blood pressure remained elevated such that it was significantly higher than all levels recorded prior to entering the chamber (all $p < 0.04$) except one (90 min following mixture ingestion; $p > 0.20$).

Skin Temperature

Following 30 min of cold exposure, and prior to performing the DMTS task, mean skin temperature was 26.2 ± 0.46°C following tyrosine administration and 25.62 ± 0.55°C following placebo administration. Following completion of the task and 60 min after cold exposure, mean skin temperature was 26.44 ± 0.57°C and 26.17 ± 0.71°C for the tyrosine and placebo conditions, respectively. During 22°C exposure, mean skin temperature prior to performing the DMTS task was 30.65 ± 0.18°C and 30.56 ± 0.27°C for the tyrosine and placebo conditions, respectively. At the end of the session, skin temperature was 30.60 ± 0.97°C and 30.56 ± 0.22°C for the tyrosine and placebo conditions, respectively. ANOVA indicated that skin temperature was significantly lower during 4°C exposure than 22°C exposure, $F(1, 7) = 102.3$, $p < 0.0001$. There were no other significant main effects or interactions.

DISCUSSION

These results clearly indicate that exposure to cold stress impairs working memory in humans as assessed by a DMTS task, and this impairment is manifest at the longest delay interval between sample and comparison stimuli of 16 s. These results are consistent with previous studies showing that cold stress induces working memory impairment (1,29,32,34).

Consistent with previous research, subjects chose a comparison stimulus more quickly during exposure to cold (32). However, this decrease in latency to choose a comparison stimulus in the cold was not accompanied by a concomitant decrease in matching accuracy at the two shorter delays, indicating that, for the most part, there was not a speed-accuracy trade-off. The shortened response latencies could be interpreted as a cold stressed-induced increase in arousal levels resulting in faster reaction times, leading to an overall reduction in actual decision making time in the cold (12,13,35). However, it is unclear at present whether this decrease in reaction time is related to cold-induced changes in CNS neurotransmission or other cold-induced changes unrelated to disruption of CNS function, such as peripheral autonomic nervous system activation.

That cold air exposure acted as an environmental stressor in this experiment is evidenced by the significant increase in plasma NE levels and blood pressure and a significant decline in mean skin temperature. Although core temperature was not measured in this experiment, previous research indicated that under similar cold exposure conditions core temperature does not change (33,35). At 22°C there was also a significant, but smaller, increase in plasma NE levels and blood pressure that could be attributed to an increase in cognitive stress in anticipation of performing the DMTS task (15,19,33).

Administration of the catecholamine precursor tyrosine completely protected against the cold-induced memory deficit such that matching accuracy in the cold was the same as matching accuracy at 22°C. However, tyrosine did not increase the latency to choose the comparison stimulus during cold exposure. This is of interest because although matching accuracy improved under the tyrosine-cold stress condition, it occurred in the absence of a concomitant increase in apparent decision time, indicating the lack of a speed-accuracy trade-off. Furthermore, these data suggest that the latency changes induced by cold exposure may be unrelated to tyrosine availability and CNS catecholamine biosynthesis and release.

These results are consistent with the hypothesis that cold exposure disrupts the sustained release of CNS catecholamines needed for optimal working memory, and supplemental tyrosine administration allows for the continued biosynthesis of these neurotransmitters, preventing a cold-induced memory deficit. Administering tyrosine 2 h prior to task performance allows tyrosine plasma levels to become maximal and probably in greater proportion to other large neutral amino acids in the plasma. Because the large neutral amino acids use the same blood-brain transport system, a high relative concentration of tyrosine increases the likelihood of increased transport of tyrosine across the blood-brain barrier and a greater likelihood of catecholamine biosynthesis in those brain regions affected by cold stress [see (37)].

Tyrosine had no effect on DMTS performance in the absence of exposure to cold, suggesting that if central catecholamine biosynthesis and release increased, this increase had no effect on DMTS performance. However, research suggests that increasing CNS tyrosine levels alone is not sufficient for increased biosynthesis and release of catecholamines; the accelerated firing of catecholaminergic neurons seems to be an important component for tyrosine utilization (30,37). This is an important point, because unlike most pharmacological agents, tyrosine may only be utilized when it is needed, such as under conditions of extreme stress. This form of treatment, therefore, may often times be less efficacious in modifying catecholaminergic neurotransmission than more direct acting catecholaminergic agonists or antagonists. On the other hand, because the biosynthesis of tyrosine may depend on neuronal firing frequency, it may have fewer side effects or adverse effects on behavior under less stressful conditions, allowing neurons to operate in a more normal range, than the more direct-acting catecholaminergic agonists and antagonists.

Although cold stress is known to deplete catecholamine levels and tyrosine is capable of reversing such changes, the exact mechanisms by which these changes affect working memory are not clear at present. Previous research has shown that exposure to acute stress reduces NE (8,14,23,25,36) and DA (8,11,23) concentrations in certain regions of the CNS, and tyrosine has been shown to replete the levels of NE in CNS regions implicated in working memory, such as the hippocampus (25). Furthermore, reduction in either NE or DA in particular brain regions, associated with biochemical lesions, has been related to deficits in working memory (2,9,10). For example, DA and NE terminals in the prefrontal cortex of nonhuman primates have been implicated in working memory, and research has shown that depleting these catecholamines or administering catecholamine antagonists results in impaired working memory, while administering catecholamine agonists has had beneficial effects on working memory. Specifically, administration of the NE agonist clonidine has

been shown to reduce age-related working memory impairment, improve working memory following NE depletion in the prefrontal cortex, and improve working memory in young nonhuman primates, presumably through the stimulation of postsynaptic, alpha-adrenergic receptors (2,3,16). Similarly, the DA agonist apomorphine has also been shown to improve working memory following DA depletion in the prefrontal cortex of nonhuman primates (9), and the DA receptor antagonist haloperidol has been shown to impair radial arm maze performance in rats (7,20). Additional research has indicated that dopamine locally injected into the prefrontal cortex enhances neuronal activity during the delay interval between sample and comparison stimuli on a spatial working memory task (26), and the selective D_1 receptor antagonists SCH23390 and SCH39166 locally injected into the prefrontal cortex of rhesus monkeys increase errors on an oculomotor working memory task (27). On the other hand, the D_2 receptor agonist bromocryptine has been shown to be effective in improving working memory in human subjects (22).

Research further indicates that tyrosine hydroxylase activity corresponds to the distribution of DA in the prefrontal cortex (6), and the rate of DA turnover in the prefrontal cortex is higher than in other brain regions, such as the striatum (5). Following supplemental administration of tyrosine, DA synthesis is enhanced in this area, but DA release does not change (30). Only under conditions of increased activity, such as exposure to environmental stress, does precursor availability become an important factor in determining DA release in this brain region (5,6,30). It appears that DA levels in the prefrontal cortex, therefore, may be uniquely sensitive to tyrosine availability and environmental stress. Thus, changes in DA activity in the prefrontal cortex under conditions of extreme stress or when the availability of tyrosine is diminished could lead to impaired working memory. However, further research is needed to determine in what manner cold stress and tyrosine impact on this and other neurotransmitter systems in the CNS to modulate working memory.

The fact that tyrosine administration prevented a cold-induced memory deficit in humans in the present experiment is consistent with the research of Banderet and Lieberman (4), which showed improvement in mood and other cognitive processes with tyrosine during exposure to environmental stress. Taken together with these results, it appears that cognitive deficits induced by acute exposure to environmental stress, such as exposure to extreme cold, can be ameliorated with the supplemental administration of tyrosine. Given the success of tyrosine in improving cognitive performance, including working memory, and reducing adverse symptoms under environmentally stressful conditions, supplemental administration of this amino acid may be appropriate when acute exposure to extreme environmental stress, such as cold stress, is unavoidable.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Philip Shea and Ms. Munnazza Malik for conducting the biochemical assays for this experiment, and Dr. Mark Thornton and Mr. Joseph Shelton for their expert advice and assistance. The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large. The research was supported by Naval Medical Research and Development Command research and technology work unit 63706N.M0095.004.1008.

REFERENCES

1. Ahlers, S. T.; Thomas, J. R.; Berkey, D. L. Hippocampal and body temperature changes in rats during delayed matching-to-sample performance in a cold environment. Physiol. Behav. 50: 1013-1018; 1991.
2. Arnsten, A. F. T.; Goldman-Rakic, P. S. Alpha2-adrenergic mechanisms in the prefrontal cortex associated with cognitive decline in aged nonhuman primates. Science 230:1273-1276; 1985.
3. Arnsten, A. F. T.; Cai, J. X.; Goldman-Rakic, P. S. The Alpha-2 adrenergic agonist guafacine improves memory in aged monkeys without sedative or hypotensive side effects: Evidence for alpha-2 subtypes. J. Neurosci. 8:4287-4298; 1988.
4. Banderet, L. E.; Lieberman, H. R. Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. Brain Res. Bull. 22:759-762; 1989.
5. Bannon, M. J.; Bunney, E. B.; Roth, R. H. Mesocortical dopamine neurons: Rapid transmitter turnover compared to other brain catecholamine systems. Brain Res. 218:376-382; 1981.
6. Bannon, M. J.; Roth, R. H. Pharmacology of mesocortical dopamine neurons. Pharmacol. Rev. 35:53-68; 1983.
7. Beatty, W. W.; Rush, J. R. Spatial working memory in rats: Effects of monoaminergic antagonists. Pharmacol. Biochem. Behav. 18:7-12; 1983.
8. Brady, K.; Brown, J. W.; Thurmond, J. B. Behavioral and neurochemical effects of dietary tyrosine in young and aged mice following cold-swim stress. Pharmacol. Biochem. Behav. 12:667-674; 1980.
9. Brozoskis, T. J.; Brown, R. M.; Rosvold, H. E.; Goldman-Rakic, P. S. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205: 929-932; 1979.
10. Decker, M. W.; McGaugh, J. L. The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. Synapse 7:151-168; 1991.
11. Dunn, A. J.; File, S. E. Cold restraint alters dopamine metabolism in frontal cortex, nucleus accumbens and neostriatum. Physiol. Behav. 31:511-513; 1983.
12. Ellis, H. D.; Wilcock, S. E.; Zaman, S. A. Cold and performance: The effects of information load, analgesics, and the rate of cooling. Aviat. Space Environ. Med. 56:233-237; 1985.
13. Enander, A. Effects of moderate cold on performance of psychomotor and cognitive tasks. Ergonomics 30:1431-1445; 1987.
14. Gibson, C. J.; Wurtman, R. J. Physiological control of brain norepinephrine synthesis by brain tyrosine concentration. Life Sci. 22:1399-1406; 1978.
15. Halbrugge, T.; Gerhardt, T.; Ludwig, J.; Heidbreder, E.; Graefe, K. H. Assay of catecholamines and dihydroxyphenylethyleneglycol in human plasma and its application in orthostasis and mental stress. Life Sci. 43:19-26; 1988.
16. Jackson, W. J.; Buccafusco, J. J. Clonidine enhances delayed matching-to-sample performance by young and aged monkeys. Pharmacol. Biochem. Behav. 39:79-84; 1991.
17. Keefe, K. A.; Stricker, E. M.; Zigmond, M. J.; Abercrombie, E. D. Environmental stress increases extracellular dopamine in striatum of 6-hydroxydopamine-treated rats: In vivo microdialysis studies. Brain Res. 527:350-353; 1990.
18. Korf, J.; Aghajanian, G. K.; Roth, R. H. Increased turnover of norepinephrine in the rat cerebral cortex during stress: Role of the locus coeruleus. Neuropharmacology 12:933-938; 1973.
19. LeBlanc, J.; Cote, J.; Jobin, M.; Labrie, A. Plasma catecholamines and cardiovascular responses to cold and mental activity. J. Appl. Physiol. Respirat. Environ. Exerc. Physiol. 47:1207-1211; 1979.
20. Levin, E. D. Pharmacological effects in the radial-arm maze. Neurosci. Biobehav. Rev. 12:169-175; 1988.
21. Lovenberg, W.; Ames, M. M.; Lerner, P. Mechanisms of acute regulation of tyrosine hydroxylase. In: Lipton, M. A.; DiMasico,

A.; Killam, K. F., eds. Psychopharmacology: A generation of progress. New York: Raven Press; 1978:247–259.
22. Luciana, M.; Depue, R. A.; Arbisi, P.; Leon, A. Facilitation of working memory in humans by a D_2 dopamine receptor agonist. J. Cog. Neurosci. 4:58–68; 1992.
23. Palkovits, M. Effect of stress on catecholamine- and neuropeptide-containing neurons in the central nervous system. In: Usdin, E.; Kvetnansky, R.; Axelrod, J., eds. Stress: The role of catecholamines and other neurotransmitters, vol. 1. New York: Gordon and Breach Science Publishers; 1984:75–80.
24. Rauch, M. T.; Lieberman, H. R. Tyrosine pretreatment reverses hypothermia-induced behavioral depression. Brain Res. Bull. 24: 147–150; 1990.
25. Reinstein, D. K.; Lehnert, H.; Scott, N. A.; Wurtman, R. J. Tyrosine prevents behavioral and neurochemical correlates of an acute stress in rats. Life Sci. 34:2225–2231; 1984.
26. Sawaguchi, T.; Matsumura, M.; Kubota, K. Dopamine ennances the neuronal activity of spatial short-term memory task in the primate prefrontal cortex. Neurosci. Res. 5:465–473; 1988.
27. Sawaguchi, T.; Goldman-Rakic, P. S. D_1 dopamine in prefrontal cortex: Involvement in working memory. Science 251:947–950; 1991.
28. Schrot, J.; Thomas, J. R. Naval medical research institute performance assessment battery software. Naval Medical Research Institute, Bethesda, MD, Report 88-6; 1988.
29. Shurtleff, D.; Thomas, J. R.; Ahlers, S. T.; Schrot, J. Tyrosine ameliorates a cold-induced delayed matching-to-sample performance decrement in rats. Psychopharmacology (Berl.) 112:228–232; 1993.
30. Tam, S. Y.; Elsworth, J. D.; Bradberry, C. W.; Roth, R. H. Mesocortical dopamine neurons: High basal firing frequency predicts tyrosine dependence of dopamine synthesis. J. Neural Transm. 81:97–110; 1990.
31. Thierry, A. M.; Tassin, J. P.; Blanc, G.; Glowinski, J. Selective activation of the mesocortical DA system by stress. Nature 263: 242–244; 1976.
32. Thomas, J. R.; Ahlers, S. T.; House, J. F.; Schrot, J. Repeated exposure to moderate cold impairs matching-to-sample performance. Aviat. Space Environ. Med. 60:1063–1067, 1989.
33. Thomas, J. R.; Ahlers, S. T.; House, J. F.; Schrot, J.; Van Orden, K. F.; Winsborough, M. M.; Hesslink, R. L.; Lewis, S. B. Adrenergic response to cognitive activity in a cold environment. J. Appl. Physiol. 68:962–966; 1990.
34. Thomas, J. R.; Ahlers, S. T.; Schrot, J. Cold-induced impairment of delayed matching in rats. Behav. Neural Biol. 55:19–30; 1991.
35. Van Orden, K. F.; Ahlers, S. T.; Thomas, J. R.; House, J. F.; Schrot, J. Moderate cold exposure shortens evoked potential latencies in humans. Aviat. Space Environ. Med. 61:636–639; 1990.
36. Weiss, J. M.; Bailey, W. H.; Pohorecky, L. A.; Korzeniowski, D.; Grillione, G. Stress-induced depression of motor activity correlates with regional changes in brain norepinephrine but not dopamine. Neurochem. Res. 5:9–22; 1980.
37. Wurtman, R. J.; Hefti, F.; Melamed, E. Precursor control of neurotransmitter synthesis. Pharmacol. Rev. 32:315–335; 1981.