NAVAL MEDICAL RESEARCH INSTITUTE

Bethesda, Maryland 20889-5055 NMRI 92-44 July 1992

(2)

COLD STRESS AND DELAYED MATCHING-TO-SAMPLE: THE EFFECTS OF TYROSINE

D. Shurtleff
J. R. Thomas
S. T. Ahlers

Naval Medical Research
and Development Command
Bethesda, Maryland 20889-5044

Department of the Navy
Naval Medical Command
Washington, DC 20372-5210

NOTICES

The opinions and assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the naval service at large.

When U. S. Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever, and the fact that the Government may have formulated, furnished or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

Please do not request copies of this report from the Naval Medical Research Institute. Additional copies may be purchased from:

National Technical Information Service
5285 Port Royal Road
Springfield, Virginia 22161

Federal Government agencies and their contractors registered with the Defense Technical Information Center should direct requests for copies of this report to:

Defense Technical Information Center
Cameron Station
Alexandria, Virginia 22304-6145

TECHNICAL REVIEW AND APPROVAL

NMRI 92-44

The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

LARRY W. LAUGHLIN
CAPT, MC, USN
Commanding Officer
Naval Medical Research Institute

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION: UNCL	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; distribution is unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): NMRI 92-44	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: Naval Medical Research Institute; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION: Naval Medical Command
6c. ADDRESS (City, State, and ZIP Code): 8901 Wisconsin Avenue, Bethesda, MD 20889-5055	7b. ADDRESS (City, State, and ZIP Code): Department of the Navy, Washington, DC 20372-5120
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: Naval Medical Research & Development Comman; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code): 8901 Wisconsin Avenue, Bethesda, MD 20889-5044	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
61152N. 62233N.	MR04120 MR03C30	00D-1383 004-1002	DN242603 DN247509

11. TITLE (Include Security Classification)
Cold stress and delayed matching-to-sample: The effects of Tyrosine

12. PERSONAL AUTHOR(S)
David Shurtleff*, John R. Thomas, and Stephen T. Ahlers

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Technical Report	FROM 10/91 TO 09/92	1992 July 21	11

16. SUPPLEMENTARY NOTATION
*This research was conducted while the first author held a National Research Council-NMRI Research Associateship from 02/90 to 02/92.

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
			Tyrosine, Delayed Matching-to-Sample, Rats, & Short-term Memory

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Military personnel can experience memory deficits while working in cold environments. The inability to recall standard operating procedures during cold exposure could jeopardize personal safety and military operations. It is possible that cold-induced memory deficits could, in part, be ameliorated through pharmacological intervention. To test this assumption, a delayed matching-to-sample task was used to assess working memory in rats exposed to 2°C or 22°C following tyrosine (50-200 mg/kg) or saline administration. Overall matching accuracy was lower at 2°C than at 22°C. Tyrosine improved overall accuracy at 2°C relative to saline. The data support the hypothesis that tyrosine attenuates catecholamine depletion during cold exposure, reducing cold stress-induced performance deficits.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION	
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT ☐ DTIC USERS	Unclassified	
22a. NAME OF RESPONSIBLE INDIVIDUAL: Regina E. Hunt, Command Editor	22b. TELEPHONE (Include Area Code): (301) 295-0198	22c. OFFICE SYMBOL: SD/RSD/NMRI

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

TABLE OF CONTENTS

ACKNOWLEDGMENTS

Experiments reported herein were conducted according to the principles set forth in the Guide for the Care and Use of Laboratory Animal Resources, National Research Council, DHHS Publication (NIH) 86-23, (1985). The research was supported by Naval Medical Research and Development Command research and technology work units 61152N.MR04120.00D.1383 and 62233N.MR03C30.004-1002. 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.

INTRODUCTION

Recent research indicates that exposure to acute cold stress results in short-term or working memory deficits in both humans and rats (1, 2). It is hypothesized that acute stress may impair memory by depleting central nervous system (CNS) neurotransmitters in areas responsible for memory, such as the hippocampus, amygdala (3), and prefrontal cortex (4).

For example, under conditions in which organisms are exposed to stressors such as cold or electric shock, norepinephrine (NE) turnover increases and levels become depleted in the CNS (e.g., 5). Depletion of NE has been related to decreased motor activity in rats (6) and decreased cognitive ability in non-human primates (7, 8).

Research has indicated that the administration of the amino acid tyrosine, a precursor to the neurotransmitters dopamine (DA) and NE, may reverse behavioral and cognitive deficits caused by acute stress exposure (6, 9).

The present experiment examines tyrosine's ability to minimize the effect of cold stress on rats' working memory by use of a delayed matching-to-sample (DMTS) procedure.

METHOD

Procedure: Three male Long-Evans rats served as subjects. Rats were placed into an operant chamber, located in a temperature-controlled environment, 30 min before the session started. The session began with the illumination of the houselight and the sample stimulus light above one of the front wall levers (right

or left). The rat was required to press the lever under the illuminated sample stimulus light, which extinguished the light and initiated a delay interval. Delay intervals were randomly selected and were either 1, 2, 4, 8, or 16 sec in duration. At the end of the delay interval, both lights above the levers were illuminated. The rat was then required to respond to the lever under the light used as the sample stimulus. Each session consisted of 180 trials or 75 min, whichever came first.

Drug Administration and Temperature Manipulations.

L-tyrosine methyl ester hydrochloride was dissolved in 0.9% saline, and saline was used for vehicle injections. All injections were administered intraperitoneally in a volume of 1.0 ml/kg bwt.

On Tuesdays and Fridays rats were administered either 50, 100, or 200 mg/kg of l-tyrosine or saline 15 min prior to being placed in the temperature-controlled chamber set at either 2°C or 22°C. Each rat experienced all eight combinations of drug administration and temperature conditions three times in a mixed order. The remaining days of the week (M, W, TH) served as recovery days during which the chamber was set at 22°C, and no tyrosine or saline was administered.

RESULTS

The mean (± SEM) overall percent correct on the DMTS task as a function of saline and tyrosine dose, during both 2°C and 22°C air exposure for each rat, and the mean of the three rats is shown in Figure 1. Tyrosine administered prior to 22°C air

exposure had no effect on overall matching accuracy. For all rats, cold exposure combined with saline administration resulted in a large reduction in overall matching accuracy. Tyrosine improved matching accuracy in the cold; however, the most effective dose varied among rats. For rat 31, doses of 50, 100, and 200 mg/kg tyrosine were most effective in enhancing performance in the cold relative to saline. For rat 32, 50 mg/kg and possibly 200 mg/kg tyrosine improved performance in the cold relative to the other doses. For rat 33, 100 and 200 mg/kg improved performance in the cold relative to saline and 50 mg/kg tyrosine.

Figures 2 through 4 present the percent change in matching accuracy, relative to the 22°C saline control condition as a function of saline and tyrosine doses, at each delay interval, for rats 31, 32, and 33. For rat 31 (Fig. 2), the greatest deficit in matching accuracy occurred at the 2-, 4-, 8-, and 16-sec delay intervals during the 2°C air exposure following saline administration. Tyrosine, regardless of dose, improved performance at these delay intervals during 2°C air exposure. Tyrosine administered during 22°C air exposure did not impair performance at any delay interval and, in fact, 100 mg/kg and 200 mg/kg tyrosine actually improved matching accuracy at the 16-sec delay interval.

For rat 32 (Fig. 3), 2°C air exposure caused the greatest deficit in matching accuracy at the 8- and 16-sec delay intervals and a slight deficit in matching accuracy at the 1- and 2-sec

delay intervals. All doses of tyrosine attenuated the deficit in accuracy during 2°C air exposure at the 1- and 2-sec delay. The 50 mg/kg tyrosine dose attenuated the matching accuracy deficit at the 8- and 16-sec delays, while 200 mg/kg tyrosine attenuated the matching accuracy deficit at the 16-sec delay during 2°C air exposure. With the possible exception of 100 and 200 mg/kg tyrosine at the 8- and 16-sec delay intervals, tyrosine, regardless of dose, did not affect performance during 22°C air exposure.

For rat 33 (Fig. 4), the greatest deficit in matching accuracy occurred at the longer delay intervals under the 2°C condition following saline administration. Tyrosine improved matching accuracy, at these longer delay intervals, in a dose-dependent manner, during 2°C air exposure. During 22°C air exposure, 200 mg/kg tyrosine improved matching accuracy at the 16-sec delay interval. Otherwise, tyrosine had little effect on matching accuracy at any delay interval at this temperature.

DISCUSSION

These results are consistent with the hypothesis that exposure to acute cold stress causes a reduction in NE levels in the CNS (5), leading to impaired memory. These results also suggest that the administration of the catecholamine precursor tyrosine partially restores depleted levels of NE, and possibly DA, resulting in improved performance on a DMTS task.

REFERENCES

1. Thomas, J. R., Ahlers, S. T., House, J. F., & Schrot J. (1989). Repeated exposure to moderate cold impairs matching-to-sample performance. *Aviation Space & Environmental Medicine,* **60**, 1063-1067.

2. Thomas, J. R., Ahlers, S. T., & Schrot, J. (1991). Cold-induced impairment of delayed matching in rats. *Behavioral and Neural Biology,* **55**, 19-30.

3. Mishkin, M. (1978). Memory in monkeys is severely impaired by combined but not separate removal of amygdala and hippocampus. *Nature,* **273**, 297-298.

4. Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficits caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science,* **205**, 929-931.

5. Gibson, C. J., & Wurtman, R. J. (1978). Physiological control of brain norepinephrine synthesis by brain tyrosine concentration. *Life Sciences,* **22**, 1399-1406.

6. Reinstein, D. K., Lehnert, H., Scott, N. A., & Wurtman, R. J. (1984). Tyrosine prevents behavioral and neurochemical correlates of an acute stress in rats. *Life Sciences,* **34**, 2225-2231.

7. Arnsten, A. F. & Goldman-Rakic, P. S. (1985). Alpha-2 mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science,* **230**, 1273-1276.

8. Arnsten, A. F., Cai, J. X., & Goldman-Rakic, P. S. (1988). The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: Evidence for alpha-2 receptor subtypes. *The Journal of Neuroscience*, **8**, 4287-4298.

9. Banderet, L. E., & Lieberman, H. K. (1989). Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. *Brain Research Bulletin*, **22**, 759-762.

FIGURE CAPTIONS

Figure 1. Overall percent correct on the delayed matching-to-sample task for each rat and the mean of all three rats, during 2°C and 22°C exposure, as a function of saline and tyrosine doses.

Figure 2. The percent change in matching accuracy, relative to the 22°C saline control condition, for rat 31 at each delay interval, during 2°C and 22°C air exposure, following saline or tyrosine administration.

Figure 3. The percent change in matching accuracy, relative to the 22°C saline control condition, for rat 32 at each delay interval, during 2°C and 22°C air exposure, following saline or tyrosine administration.

Figure 4. The percent change in matching accuracy, relative to the 22°C saline control condition, for rat 33 at each delay interval, during 2°C and 22°C air exposure, following saline or tyrosine administration.

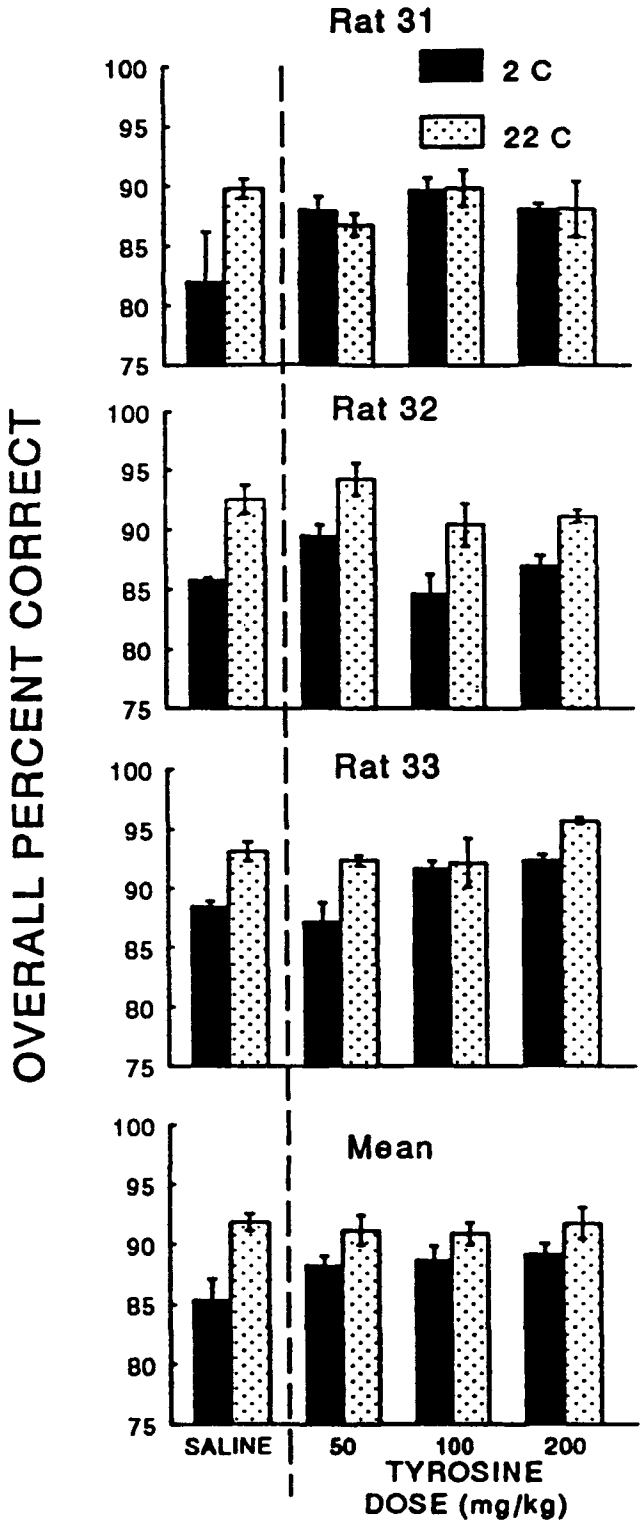
Rat 31
2 C
22 C
Rat 32
Rat 33
Mean
OVERALL PERCENT CORRECT
100
95
90
85
80
75
SALINE
50
100
200
TYROSINE
DOSE (mg/kg)

FIGURE 1

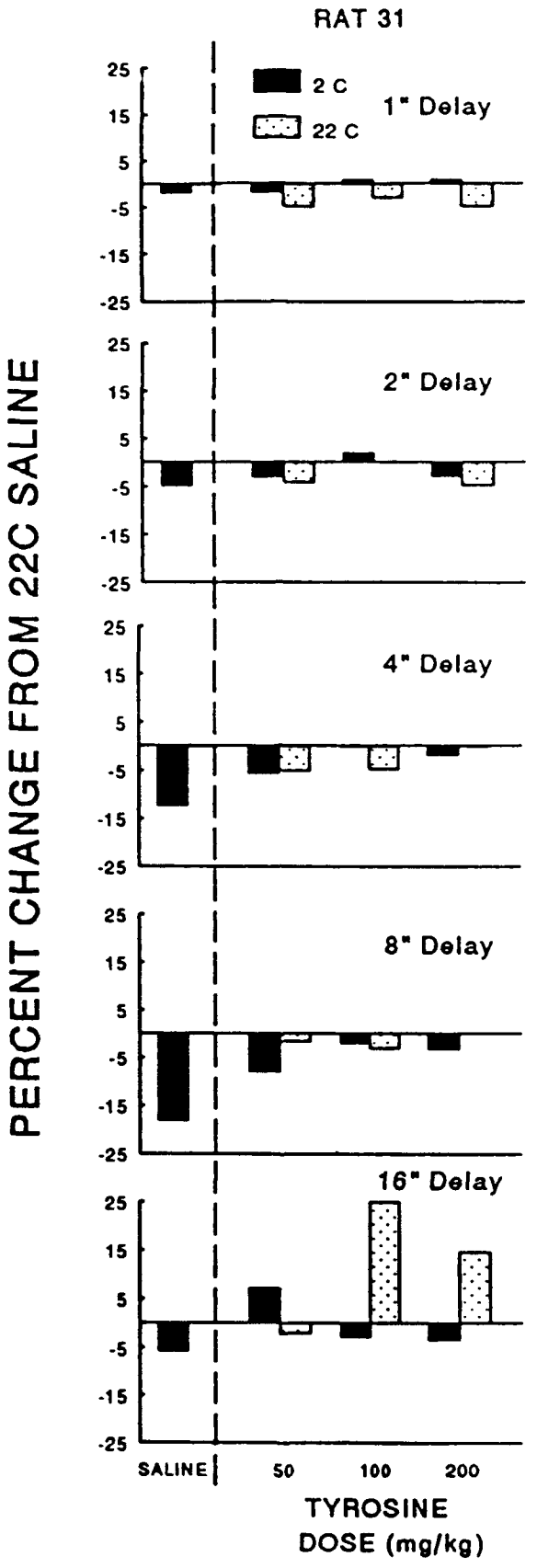
RAT 31
2 C
22 C
1" Delay
2" Delay
4" Delay
8" Delay
16" Delay
25
15
5
-5
-15
-25
PERCENT CHANGE FROM 22C SALINE
SALINE
50
100
200
TYROSINE
DOSE (mg/kg)

FIGURE 2

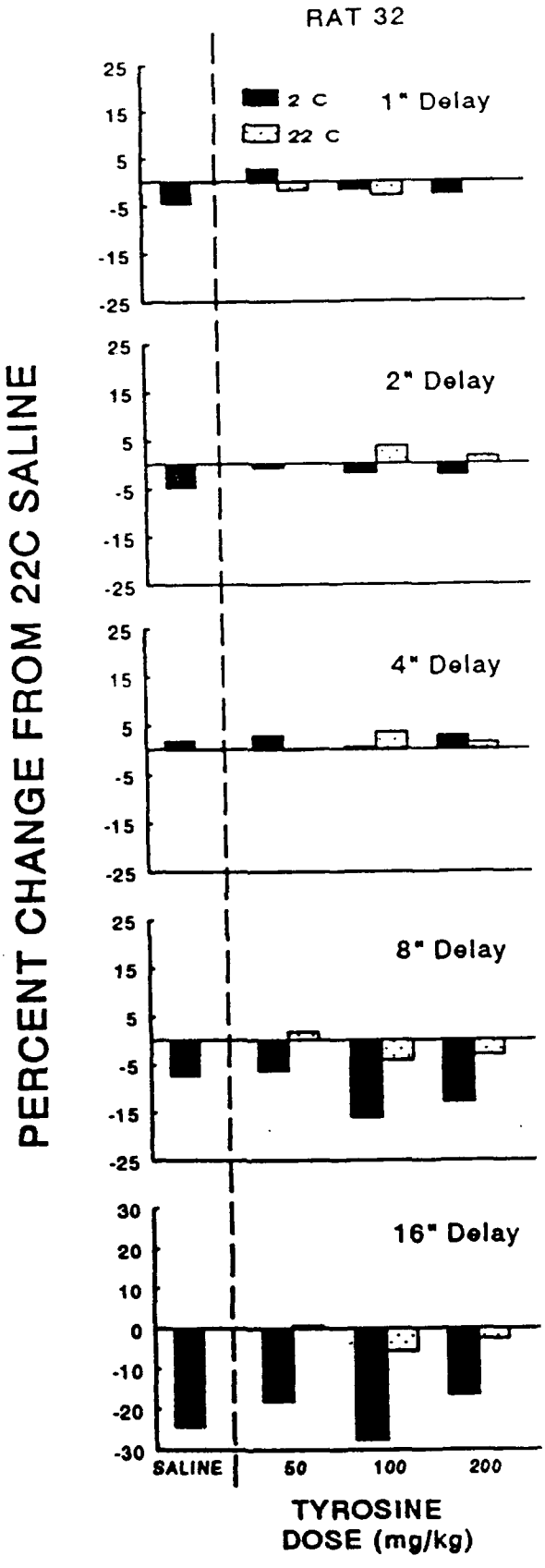
RAT 32
2 C
22 C
1" Delay
2" Delay
4" Delay
8" Delay
16" Delay
PERCENT CHANGE FROM 22C SALINE
SALINE
50
100
200
TYROSINE
DOSE (mg/kg)

FIGURE 3

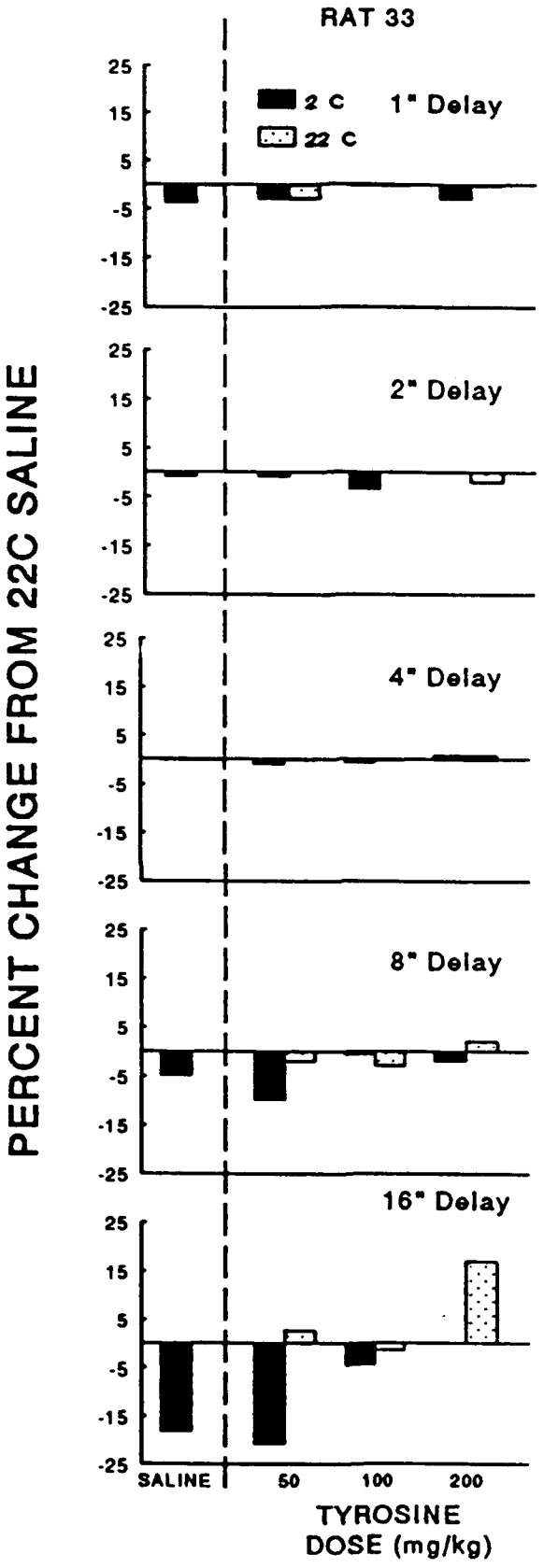
RAT 33
2 C
22 C
1" Delay
2" Delay
4" Delay
8" Delay
16" Delay
25
15
5
-5
-15
-25
PERCENT CHANGE FROM 22C SALINE
SALINE
50
100
200
TYROSINE
DOSE (mg/kg)

FIGURE 4