Pharmacology Biochemistry & Behavior, Vol. 11, pp. 453–456. Printed in the U.S.A.

Memory Storage Impairment or Retrieval Failure: Pharmacologically Distinguishable Processes

THOMAS J. WALSH AND TIBOR PALFAI[1,2]

Department of Psychology, Syracuse University, Syracuse, NY 13210

Received 31 July 1979

WALSH, T. J. AND T. PALFAI. *Memory storage impairment or retrieval failure: Pharmacologically distinguishable processes.* PHARMAC. BIOCHEM. BEHAV. 11(4)453–456, 1979.—The effects of reserpine and syrosingopine on retention of a passive avoidance task in mice were investigated. Following repeated exposure to the training apparatus, the amnesia induced with syrosingopine could be reversed, the amnesia induced with reserpine could not. The amnesia produced by these agents was still evident 35 days following training. The results were discussed in terms of the effects of these drugs on memory consolidation and/or retrieval.

Amnesia Memory Retrieval Rauwolfia alkaloids Consolidation

A NUMBER of drugs that interfere with the synthesis, storage or metabolism of the catecholamines, dopamine and norepinephrine, have been reported to impair memory processes [1, 6, 7, 8, 14, 19, 20]. The consensus seems to be that, regardless of the agents used, decreased levels of catecholamines during or shortly following training result in amnesia. This finding has prompted several investigators to suggest that these biogenic amines play a critical role in memory consolidation [6, 8, 14, 20].

Recently it was suggested that the anti-adrenergic drugs produce their amnesic effects by impairing memory retrieval (i.e., expression of memory) rather than interfering with memory storage. Botwinick and her colleagues [3, 4, 17] reported spontaneous recovery of memory following amnesic doses of the dopamine-beta-hydroxylase inhibitors, DDC and FLA-63. These investigators found that mice were amnesic for a passive avoidance or spatial discrimination task 24 hr following administration of DDC or FLA-63. If, however, the retention test was postponed until 48 hr following training, the animals exhibited good retention. It was thus concluded that these inhibitors of catecholamine synthesis produced their retention impairments by temporarily disrupting a noradrenergic memory retrieval system. The suggestion was further supported by the finding that amnesic animals treated with the monoamine-oxidase inhibitor, pargyline, recovered from the amnesia induced by DDC or FLA-63 [3,4]. Finally, Rainbow and Flexner [18] suggested that the amnesia produced by 6-hydroxydopamine for a discriminated avoidance task was dependent upon the transient impairment of norepinephrine-dependent memory retrieval processes.

Among its many pharmacological effects, reserpine depletes biogenic amines in the brain and periphery [2, 5, 22, 23] and has been shown to produce amnesia for a number of learning tasks [1, 10, 21, 24]. Syrosingopine, a structural analogue of reserpine, has also been reported to deplete catecholamines [11, 13, 16] albeit primarily peripherally and we recently reported that it also produces time-dependent retention impairments for a passive avoidance task [15]. The effects of these two drugs on memory were attributed to an impairment of memory consolidation resulting from the depletion of peripheral, and perhaps central, catecholamines. However, to test the hypothesis that anti-adrenergic agents affect memory retrieval rather than memory consolidation, we investigated whether the reserpine and syrosingopine-induced amnesias were permanent. If, in fact, the drugs impair biogenic amine-dependent memory retrieval processes, time and repeated exposure to the training apparatus should optimize the recovery of memory of a passive avoidance task [12,25].

METHOD

Adult (70–90 day old) male albino mice bred from CD-1 stock in our animal colony were used. The animals were housed in groups of four in standard Econo plastic cages in temperature (70–72°F) and humidity (50–70%) controlled environment. Food and water were available ad lib and a 12-hr light/dark cycle was in effect.

A step-through passive avoidance apparatus, similar to that of Jarvik and Kopp [9] was used. Briefly, the apparatus consisted of a V-shaped trough that was divided by a

[1]Supported by Syracuse University Institutional Grant.
[2]We would like to thank Ciba-Geigy for the generous gift of the syrosingopine.

narrow guillotine door into a small, illuminated start box and a larger darkened section. Stainless steel panels formed the walls and floor of the trough and served, in the darkened section, to deliver electric shock from a Grason-Stadler, Model-700 Constant Current Shock Generator to the animals' feet.

Passive avoidance (PA) training consisted of placing the mouse into the illuminated start chamber; 60 sec later, the guillotine door was opened and the latency to step-through into the darkened section was recorded. Immediately following step-through (defined as the passage of the hindlimbs over the threshold), the door was closed and the mouse given a 1 mA footshock for 3 sec. Retention was tested 7 days later, well after all the acute effects of drug treatments had dissipated. Testing consisted of measuring step-through latency for an arbitrary maximum of 300 sec. This latency measure was used as the index of retention. The Kruskal-Wallis Analysis of Variance and the Mann-Whitney U-test were used to analyze the data.

Behavioral Procedure

Mice were given an intraperitoneal injection of 2.5 mg/kg reserpine (Serpasil, Ciba) or 2.5 or 4.0 mg/kg syrosingopine 2 hr before passive avoidance training. We have previously reported that these dosages and pretreatment intervals produced amnesia for this task [24]. To examine the permanence of reserpine and syrosingopine-induced amnesias, retention performance was tested every seven days for a total of five retention tests. Drug-treated control groups were tested for retention only once at either 21 or 35 days following training.

RESULTS AND DISCUSSION

The median step-through latencies (STL) for the five retention tests are shown in Fig. 1. A Kruskal-Wallis nonparametric analysis of variance indicated an overall significant treatment effect on the first retention test (Day 7) $p<0.001$. The saline control group showed retention (STL=300) for the entire 35 days. Apparently no extinction occurs following repeated retention testing for this passive avoidance response. The reserpine group was amnesic throughout the five retention tests ($p<0.01$ compared to saline for retention tests 1–5, Mann-Whitney U). The 2.5 and 4.0 mg/kg syrosingopine groups were amnesic only on the first retention test (Day 7). By the second retention test (Day 14) these groups had median STL's similar to that of the saline controls ($p>0.05$). These groups further improved their performance until the fourth retention test (Day 28) when both syrosingopine groups and the saline group had median STL's of 300 sec. The data suggest that while the amnesia induced with syrosingopine is reversible through repeated testing, that resulting from reserpine is not.

The results of the drug-treated control groups are shown in Table 1. The Kruskal-Wallis Analysis of variance indicated a significant treatment effect ($p<0.001$). Compared with the saline groups, both the reserpine and syrosingopine groups had significantly shorter STLs ($p<0.001$, Mann-Whitney U) suggesting that retention impairments produced by these drugs are evident as much as 21 or 35 days following PA training.

Taken together, the following conclusions seem appropriate: Amnesia produced by syrosingopine can be reversed

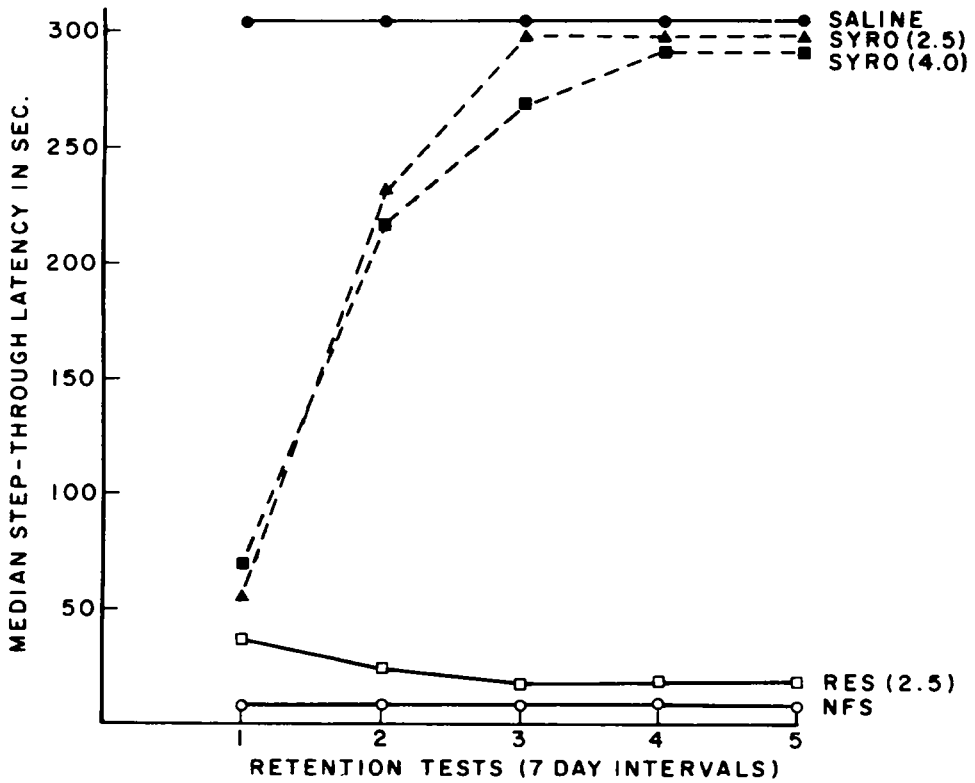

FIG. 1. Group median step-through latencies for retention Tests 1–5. (Saline n=10, SYRO: syrosingopine; 2.5 mg/kg n=21, 4.0 mg/kg n=16, RES=reserpine 2.5 mg/kg n=10, NFS=no footshock n=8.)

TABLE 1

RETENTION PERFORMANCE OF RESERPINE AND SYROSINGOPINE-TREATED ANIMALS TESTED EITHER 21 OR 35 DAYS FOLLOWING PA TRAINING

	(STL)	N
21 days		
Saline	300	12
Res 2.5	21*	11
Syro 2.5	32*	13
Syro 4.0	17*	15
35 days		
Saline	300	11
Res 2.5	18*	11
Syro 2.5	12*	9
Syro 4.0	10*	14

*$p<0.01$ vs saline, Mann-Whitney.

through repeated exposure to the training apparatus; that induced with reserpine cannot. The amnesia produced by both agents is relatively permanent and is apparent for at least 35 days.

An explanation for the difference in the behavioral effects of these drugs might be sought for in the difference of their pharmacodynamics. While reserpine depletes both central and peripheral biogenic amines, syrosingopine, at least in the dosages used here, affects these amines primarily peripherally. Therefore, when the amnesic effect of a drug is mediated peripherally, the reminder procedure might reverse the memory loss. This may not be the case if the drug has central effects as well.

REFERENCES

1. Allen, C., B. S. Allen and A. V. Rake. Pharmacological distinctions between active and passive avoidance memory formation as shown by manipulation of biogenic amine active compounds. *Psychopharmacologia* **34**: 1–10, 1974.
2. Bertler, A., N. A. Hillarp and E. Rosengren. Effect of reserpine on the storage of new-formed catecholamines in the adrenal medulla. *Acta physiol. scand.* **52**: 44–48, 1961.
3. Botwinick, C. Y. and D. Quartermain. Recovery from amnesia induced by pre-test injections of monoamine oxidase inhibitors. *Pharmac. Biochem. Behav.* **2**: 375–379, 1974.
4. Botwinick, C. Y., D. Quartermain, L. S. Freedman and M. F. Hallock. Some characteristics of amnesia induced by FLA-63, an inhibitor of dopamine-beta-hydroxylase. *Pharmac. Biochem. Behav.* **6**: 487–491, 1977.
5. Carlsson, A. Pharmacological depletion of catecholamine stores. *Pharmac. Rev.* **18**: 541–549, 1966.
6. Dismukes, R. K. and A. V. Rake. Involvement of biogenic amines in memory formation. *Psychopharmacologia* **25**: 17–25, 1972.
7. Hall, M. E. and M. A. Mayer. Effects of alpha methyl-para-tyrosine on the recall of a passive avoidance response. *Pharmac. Biochem. Behav.* **3**: 579–582, 1975.
8. Haycock, J. W., R. Van Buskirk and J. L. McGaugh. Effects of catecholaminergic drugs upon memory storage processes in mice. *Behav. Biol.* **20**: 281–310, 1977.
9. Jarvik, M. E. and R. Kopp. An improved one-trial passive avoidance learning situation. *Psychol. Rep.* **21**: 221–224, 1967.
10. Kurtz, P. J. and T. Palfai. Effects of reserpine on retention of escape reversal in mice: absence of state-dependent learning. *J. comp. physiol. Psychol.* **91**: 393–406, 1977.
11. LeRoy, J. G. and A. F. DeSchaepdryver. Catecholamine levels of brain and heart in mice after iproniazid, syrosingopine and 10-methoxydeserpidine. *Archs int. Pharmacodyn.* **103**: 231–233, 1961.
12. Luttges, M. W. and J. L. McGaugh. Permanence of amnesia produced by electroconvulsive shock. *Science* **156**: 408–410, 1967.
13. Orlans, F. B. H., K. F. Finger and B. B. Brodie. Pharmacological consequences of the selective release of peripheral norepinephrine by syrosingopine (SU3118). *J. Pharmac. exp. Ther.* **128**: 131–139, 1960.
14. Palfai, T., T. J. Walsh, B. J. Albala and O. M. Brown. Effects of l-dihydroxyphenylalanine (l-dopa) and d,l,5-hydroxytryptophan (d,l,5-HTP) on reserpine-induced amnesia. *Psychopharmacology* **53**: 269–276, 1977.
15. Palfai, T. and T. J. Walsh. The role of peripheral catecholamines in reserpine-induced amnesia. *Behav. Neural Biol.*, in press.
16. Pham-Huu-Chanh and A. F. DeSchaepdryver. On the pharmacology of syrosingopine and reserpine. *Archs int. Pharmacodyn.* **157**: 207–213, 1965.
17. Quartermain, D. and C. Y. Botwinick. Role of the biogenic amines in the reversal of cycloheximide-induced amnesia. *J. comp. physiol. Psychol.* **88**: 386–401, 1975.
18. Rainbow, T. C. and L. B. Flexner. Studies on memory: spontaneous return of memory in 6-hydroxydopamine-treated mice and its relation to cycloheximide-induced transient amnesia. *Pharmac. Biochem. Behav.* **8**: 1–5, 1978.
19. Rake, A. V. Involvement of biogenic amines in memory formation: the central nervous system indole amine involvement. *Psychopharmacologia* **29**: 91–100, 1973.
20. Randt, C. T., D. Quartermain, M. Goldstein and B. Anagnoste. Norepinephrine biosynthesis inhibition: effects on memory in mice. *Science* **172**: 498–499, 1971.
21. Seiden, L. S. and A. Carlsson. Brain and heart catecholamine levels after l-dopa administration in reserpine-treated mice: correlations with a conditioned avoidance response. *Psychopharmacologia* **5**: 178–181, 1964.

22. Shore, P. A. Reserpine: A survey of its pharmacology. In: *Alterations of Chemical Equilibrium in the Nervous System*, Vol. 1, *Handbook of Neurochemistry*, edited by A. Lajtha. New York: Plenum Press, 1971.
23. Shore, P. A. and A. Giachetti. Reserpine: basic and clinical pharmacology. In: *Handbook of Psychopharmacology*, **10**, edited by L. L. Iversen, S. D. Iversen and S. Snyder. New York: Plenum Press, 1978, pp. 197–219.
24. Walsh, T. J. and T. Palfai. Time-dependent effects of reserpine on retention of passive avoidance. *Pharmac. Biochem. Behav.* **8:** 103–105, 1978.
25. Zinkin, S. and A. J. Miller. Recovery of memory after amnesia induced by electroconvulsive shock. *Science* **155:** 102–104, 1967.