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Monoamine Roles in Retention and Reversal of Delayed Response in Cats[1,2]

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ROBERGE, A. G., C. BOISVERT AND J. EVERETT. *Monoamine roles in retention and reversal of delayed response in cats.* PHARMAC. BIOCHEM. BEHAV. 12(2) 229–234, 1980.—Two experiments were performed to study the effects of manipulation of central monoamines upon behavior in a delayed response (DR) situation. In the first study, serotonin (5-HT) levels were increased by administration of 5-hydroxy-L-tryptophan (5-HTP) and RO4-4602, a decarboxylase inhibitor, to cats that had overlearned the DR. This intervention had no significant effect upon performance in the 0 sec delay condition, but significantly increase error and non-response scores during delay trials; the effect is specific to an "information holding" demand upon the animal and according to the neurochemical analysis appears to be due to a central effect of 5-HT. In a second experiment, dopamine levels were raised by L-DOPA administration during a reversal of the original DR situation, and the effect of L-DOPA on the evolution of response strategies was observed. All animals developed a position habit that proved impossible to correct but L-DOPA animals developed a significant position habit more quickly than controls, thus suggesting a possible relationship between the neostriatal dopamine accumulation and behavioral plasticity.

Serotonin (5-HT) 5-Hydroxy-L-tryptophan (5-HTP) Dihydroxy-L-phenylalanine (L-DOPA)
Delayed responses

THE studies reported here are part of an ongoing research program centered on the roles of central nervous system neurotransmitters in learning and more specifically to explore the association formed between learning in the delayed response (DR) situation and the biochemical equilibrium between dopamine (DA) and serotonin (5-HT) in mesolimbic neurons [21]. These data emphasize the inhibitory control of the serotoninergic system involving the neurons of raphe nuclei as also suggested by other authors [7, 25, 26], and the hyperactivity of the mesolimbic system related to a high DA content corresponding to the expression of a high performance in regard to vigilance, motivation and perception as a consequence of an experimental reduction of 5-HT [2, 4, 9, 14, 15, 17, 21]. L-DOPA was described as an ineffective drug if administered during the acquisition of the DR task [21] whereas the performance of partially trained cats and "poor-learning" cats trained on DR was improved.

The effect of an intervention on a subject's behavior in a learning situation cannot be properly interpreted unless: (1) a clear distinction is made between performance (response capacity, latency, etc.) and learning and the effect of the intervention on each of these processes can be assessed and, (2) the process of learning is further analysed into component processes such as attention, information, retention, strategy formation etc.

In the first experiment to be reported here, the effect of an elevation of 5-HT following the administration of L-5HTP and RO4-4602, a decarboxylase inhibitor, on an overlearned appetitive discrimination is assessed in order to specifically test the effect of such an intervention upon performance as opposed to learning. In a second experiment the effect of an elevation of DA on reversal learning is tested in order to specifically examine the impact of such an intervention upon the evolution of response strategies.

METHOD

EXPERIMENT 1

Thirty-two adult cats of both sexes, weighing 2.5 ± 0.3 kg, were kept in individual cages and maintained on a stable diet of cat food with water ad lib. Animals were fed at least

[1]Preliminary report of this research was presented at the first International Meeting for Drugs as Discriminative Stimulus July 1978, Beerse, Belgium.

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18 hr before the training period or the administration of the drug. A limited additional amount of meat was given during the testing session in order to maintain a constant body weight. Of the 32 cats used, 6 cats were considered as non-learning cats and 8 as learning cats (delayed response cats) and received concomitantly a single dose of L-5HTP (25 mg/kg, per os) and RO4-4602 (50 mg/kg, per os) at the retention period. Six untrained cats received L-5HTP (25 mg/kg, per os) and 6 cats, L-5HTP and RO4-4602 (25 and 50 mg/kg, per os respectively). These cats were sacrificed with 6 normal and untreated cats, 3 hr after the administration of the drug and served as control animals.

Delayed Response Task (DR)

The apparatus and the various phases of the training used were the modified testing situation of Wikmark and Divac [27] described in detail by Roberge *et al.* [21]. DR trials involved an interpolated delay between the termination of the stimulus and the release of the animal. The correct feeder was signaled for only 3 sec and the delays (0, 9, 27 and 54 sec) interpolated between the termination of the stimulus and the release of the animal were presented in a selected irregular sequence according to Gellerman Series [10]. Cats were tested daily until they reached the criterion fixed at 90% of correct responses. Trials were performed in blocks of 24, 6 trials on each of the four delays during a mean of 12 days. The obtained criterion was followed by a 5 days consolidation period. Five days later cats were tested six times for retention at an interval of five days, the last time being 24 hr before receiving the drug. Afterwards, they were tested during the effects of the drug (3 hr after the administration) and retested 24 hr after.

Biochemical Assays

The treated learning animals were saved for Experiment 2; treated and nontreated controls were sacrificed 3 hr after the administration of a single dose of L-5HTP with or without RO4-4602, a decarboxylase inhibitor. All cats were decapitated without anesthesia using a guillotine. Immediately afterwards, both neostriatum and piriform lobe (amygdala), the frontal cortex, thalamus, hypothalamus, septum, tuberculum olfactorium, raphe nuclei of the mesencephalon, pons and medulla respectively, mesencephalon, pons and medulla without raphe nuclei were individually dissected out on ice and kept frozen at −20°C until assays were performed. DA, NA and 5-HT were determined by the method of Early and Leonard [6] using ion exchange resin Sephadex G-10. All estimates were corrected for losses. Recoveries were 78 ± 5, 98 ± 2 and 83 ± 4 percent for DA, NA and 5-HT, respectively.

Statistical Analysis

Results are expressed in μg of amines per g of fresh tissue. Standard deviation, standard error of the mean and Student's t test were calculated according to Lison [16]. The nonparametric measures (Friedman analysis of variances, Wilcoxon test) were used for all behavioral statistical analyses [22].

EXPERIMENT 2

Following the two months period without training, the 8 experimental animals were retrained to a 90% correct criterion on the original learning situation. Only two delays were used, 0 and 27 sec, at this time. The retraining was terminated after 4 days, all cats reaching criterion. The animals were divided into two groups counterbalanced with respect to trials to criterion on re-learning. One group [4] received L-DOPA (30 mg/kg per os) 3 hr before testing and the second group [4] received only empty capsules.

The animals were trained three days a week on the reversal learning task, a situation identical in all respects to the original learning situation, except that a response was now rewarded only when directed toward the food dish opposite to the auditory stimulus. Cats received L-DOPA each day during learning and were tested 3 hr after the administration of the drug.

RESULTS

EXPERIMENT 1

Animals were tested in the situation under either non-delay (delay = 0 sec) or delay (9, 27, 54 sec) conditions. A Friedman analysis of variance across delays showed no significant effect of delay duration. Consequently, these data were grouped for further analysis (Fig. 1). In this figure, the proportion of errors and of non-response (response latency greater than 15 sec) is represented during each phase of the experiment: two phases of acquisition, consolidation, retention, 5-HTP and RO4-4602 and post-test. The effect of the 5-HTP and RO4-4602 intervention was evaluated by comparing baseline performance on the last two days of the retention period, the 5-HTP and RO4-4602 and the post-test trials.

On non-delay trials, performance is virtually perfect throughout the experiment. During the 5-HTP and RO4-4602 trials there is a relative increase in the proportion of non-responses that narrowly misses significance (Friedman $\chi^2=4.5$, n.s.). However, the accuracy of response at delay 0 is not affected (Friedman $\chi^2=0.2$, n.s.).

For the delay trials, a quite different picture emerges. First, there is a clear reduction of errors during the two phases of acquisition, the acquisition trials of Days 7 to 12 showing significantly fewer errors (Wilcoxon $T=0$, $p<0.01$). After acquisition, performance accuracy statilizes, as shown by the equivalent error scores during consolidation compared with retention trials; there is no difference between these phases (Wilcoxon $T=8$, n.s.). The effect of 5-HTP and RO4-4602 on error scores during delay trials was significant (Friedman $\chi^2=9.4$, $p<0.05$). After 5-HTP and RO4-4602 treatment, error scores return to the normal range (retention versus post-test Wilcoxon $T=5.5$, n.s.). Finally, the increase of non-responses during delay trials under 5-HTP and RO4-4602 is significant at $p<0.001$ (Friedman $\chi^2=18.9$).

In Fig. 2, the striking effect of 5-HTP and RO4-4602 treatment on response latencies is shown. At each delay the mean latency is at least twice as high as in pretreatment levels. A comparison of Day 6 retention latencies with 5-HTP and RO4-4602 latencies shows that for each delay, the latter are longer ($p<0.001$). Latencies return to pretreatment range 24 hr after the treatment.

The concentrations of serotonin (5-HT) are described in Table 1 following the administration of L-5-HTP (25 mg/kg per os) and a concomitant administration of L-5-HTP and RO4-4602 (25 and 50 mg/kg per os, respectively). A significant increase in 5-HT content ($p<0.05$, <0.01 or <0.001) is observed in the frontal cortex, neostriatum, thalamus, hypothalamus, septum, piriform lobe, pons and medulla

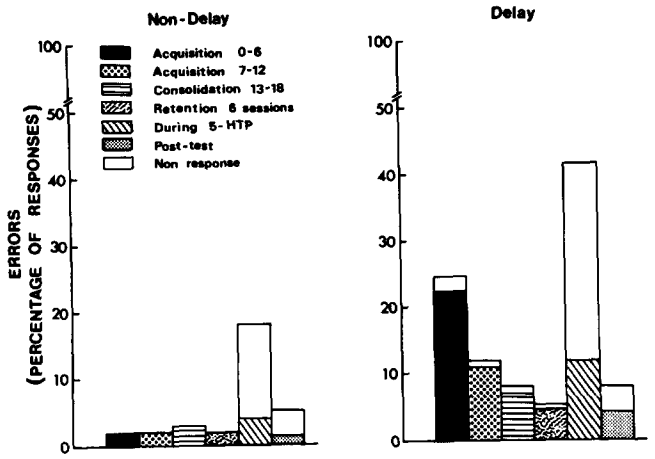

FIG. 1. Effects of acquisition (0–6 and 7–12 days), consolidation (13–18 days) and retention, (6 sessions at an interval of 5 days; 3 hr after the administration of 5-HTP and RO4-4602 and 24 hr after the drugs) on the performance (errors) of a delayed response task in the absence of delay and in the presence of interpolated delays (0, 9, 27 and 54 sec) in cats.

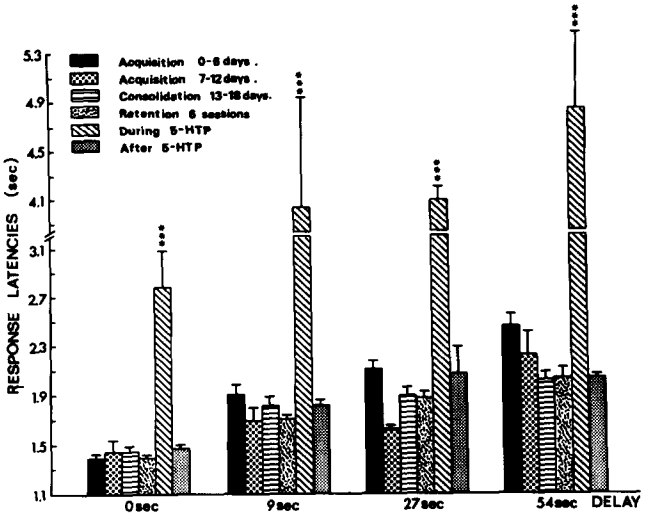

FIG. 2. Effects of acquisition (0–6 and 7–12 days), consolidation (13–18 days) and retention (6 sessions at an interval of 5 days; 3 hr after the administration of 5-HTP and RO4-4602 and 24 hr after the drugs) on response latencies of a delayed response in the absence of delay and in the presence of interpolated delays (0, 9, 27 and 54 sec) in cats.

without raphe nuclei, raphe nuclei of mesencepahlon, pons and medulla and cervical spinal cord following the administration of either L-5-HTP alone or L-5-HTP and RO4-4602. Any significant difference is noticed between the effects of L-5-HTP treatment alone and L-5-HTP plus RO4-4602 administration in the 5-HT content. The concentrations of noradrenaline remain in a normal range in all structures following both treatments (unpublished data).

EXPERIMENT 2

After reversal, all of the cats showed: (1) a tendency to continue responding as before; (2) after a number of trials that varied from animal to animal, a position preference that proved extremely recalcitrant. The L-DOPA administration did not have a significant effect on this overall pattern: experimental animals had a position habit that proved as resistant as that of controls. In Fig. 3, the development of this position preference is illustrated. Means and standard deviations of preference scores for both groups are shown. In each column, the 0 delay and 27 sec delay trials are grouped, as there was no difference in performance at these two delays. A finding of possible importance, however, concerns the relative speed with which the animals abandoned the previously correct strategy to adopt instead their position preference. A binomial test showed that after the first 49 trials, the

TABLE 1

CONCENTRATIONS OF 5-HT 3 HOURS AFTER A SINGLE DOSE OF L-5-HTP (25 mg/kg) AND L-5-HTP PLUS RO4-4602 (25 AND 50 mg/kg) IN DIFFERENT STRUCTURES OF CAT BRAIN

Structures*	Controls (6)	5-HTP (6)	5-HTP and RO4-4602 (6)
Frontal cortex	0.62 ± 0.14	1.21 ± 0.11§	0.98 ± 0.16‡
Neostriatum	0.97 ± 0.25	5.37 ± 0.52‡	4.76 ± 0.64§
Thalamus	1.15 ± 0.18	2.66 ± 0.30‡	2.34 ± 0.16‡
Hypothalamus	1.74 ± 0.37	3.76 ± 0.48§	3.89 ± 0.5§
Septum	1.42 ± 0.26	3.42 ± 0.48‡	3.89 ± 0.72‡
Piriform lobe	1.47 ± 0.25	2.20 ± 0.25‡	2.17 ± 0.29†
Mesencephalon (without raphe nuclei)	1.38 ± 0.12	2.80 ± 0.26§	2.76 ± 0.11§
Pons and medulla (without raphe nuclei)	1.00 ± 0.17	2.16 ± 0.23‡	1.67 ± 0.15‡
Raphe nuclei	1.45 ± 0.15	2.75 ± 0.21§	2.93 ± 0.25§
Cervical spinal cord	0.57 ± 0.06	—	1.34 ± 0.23‡

*Results are expressed in μg of amines per g of fresh tissues ± SEM. Statistical analysis was done using Student's *t* Test. Number of animals is in parentheses.
†$p<0.05$; ‡$p<0.01$; §$p<0.001$.

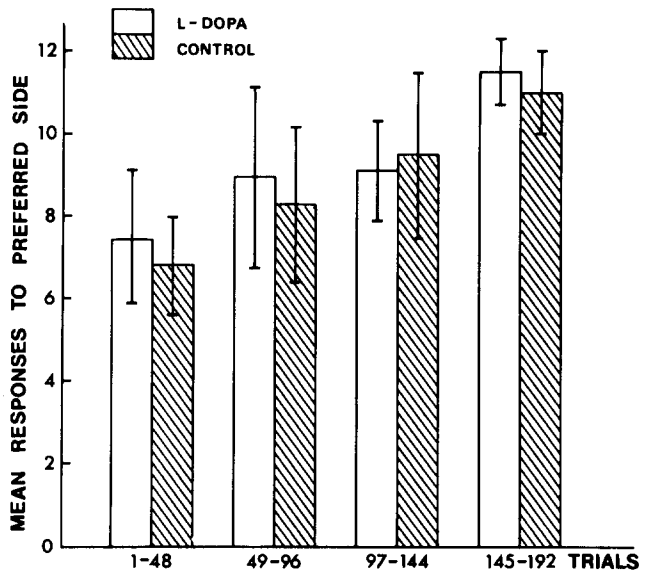

FIG. 3. Effects of reversal learning of a delayed response task on a position habit observed in control cats as well as in L-DOPA treated cats (30 mg/kg, per os) at the 0 and 27 sec delays.

TABLE 2

PREFERENCE FOR L-DOPA OR CONTROL CATS AFTER REVERSAL

Cats	Percentage choices of the preferred side ± SD After 24 trials	After 48 trials
L-DOPA	59.3 ± 13.3*	61 ± 12.5†
Control	53 ± 5.8‡	56 ± 10‡

*Binomial probability<0.05.
†Binomial probability<0.005.
‡Not significant.

L-DOPA animals had a significant position tendency while control animals had not. In fact, the position habit of the experimental animals was already established after only 24 trails (Table 2).

DISCUSSION

EXPERIMENT 1

The results reported in the present study show that cats learn a delayed response task (DR) with a criterion fixed at 90% in 12 days, whatever the length of the interpolated delay. In fact, no significant difference was observed during the acquisition of the DR when learning at delays of 9, 27 and 54 sec was compared.

The effects of 5-HTP and RO4-4602 on the animals' performance as reflected by the increased error scores and increased absences of response on the delay trials are probably due to a central effect of serotonin (5-HT). It is true that central and peripheral mechanisms have been implicated in a variety of behavioral effects produced by 5-HTP [3]. But in the present work, a low dose of benserazide (RO4-4602) which inhibits peripheral but not central L-aromatic aminodecarboxylase [1,19] was used concomitantly with L-5-HTP, in order to implicate more precisely effects on the central nervous system. The increased latencies as well as the disturbed performance (absences of response) might be related to some motivational mechanisms or drowsiness rather than cognitive mechanisms as it is known that 5-HT is involved in sleep and waking states [2, 3, 11, 17]. In fact, as shown by the 0 delay results, the capacity to perform the task is maintained since this group performed correctly on 5-HTP and RO4-4602 treatment in spite of an elevation of latencies. Moreover, if the only effect of 5-HTP and RO-4602 was to change the animals' perception of the situation, and thus their capacity to respond correctly, one would expect an increase in the proportion of errors at delay 0 as well. The fact that this was not observed suggests rather that the effect is specific to a situation in which the animal must retain the pertinent information during a delay period. The interpretation is consistent with the work of Essman [8], whose results suggest that the efficacy of an amnesic intervention is dependent upon an increased forebrain 5-HT. The neurochemical analysis of the effects of a single dose of L-5HTP plus benserazide on 5-HT metabolism confirms a significant increase in the content of this neurotransmitter in all structures within the central nervous system without any change in the concentrations of noradrenaline and thus suggests a correlation between the disturbed performance and the 5-HT content.

The diminished performance resulting from increased 5-HT levels is also consistent with the results of Rake [19], who found that mice with lowered 5-HT levels showed better retention, and this effect could be erased by restoring 5-HT levels to normal. The apparently paradoxical finding of deficient performance following increases of a naturally-occurring monoamine might be explained by a theoretical scheme such as that of Kety [11]: consolidation of significant information would be favored by a noradrenergic activation having an arousing effect. The consolidation and retention of unimportant information would be suppressed by a serotoninergic system, antagonist of the noradrenergic system. This interpretation fits well with the improved performance of cats treated with Metergoline, a specific anti-serotoninergic agent, tested during the acquisition of a DR task [21]. In this study the improved performance might be related to an inhibitory influence of serotoninergic pathways on areas like the mesolimbic system as mentioned by other authors [17,20]

EXPERIMENT 2

L-DOPA has previously been shown to improve learning of a DR task in cats [13], but it is not yet known which aspect of the learning process is affected by the elevated striatal dopamine levels.

One of the crucial steps in the evolution of correct performance is the adoption of an appropriate response strategy, and learning deficits in animals can sometimes be related to a deficient capacity to change an incorrect response strategy [12]. The perseverative tendencies of parkinsonians have long been recognized [23] and more recently, lesions of caudate nucleus, a prime target structure of the dopaminergic system, have been shown to produce difficulties in response modification in cats [18].

Experiment 2 was designed to test the hypothesis that L-DOPA might have its beneficial effect on learning by act-

ing upon the animal's capacity to abandon an incorrect hypothesis. The animals in the DR reversal situation showed a continuation of the original learning situation followed by the adoption of a position strategy, i.e. response directed always to the same side of the apparatus, regardless of the localization of the stimulus. This position habit proved extremely resistant to several attempts at correction, and continued in all animals until the end of the experiment.

The only effect of L-DOPA seemed to be upon the speed with which the original strategy (approach the stimulus), now incorrect, was replaced by the strategy of position, L-DOPA animals abandoning the first strategy relatively quickly. This conclusion was based upon a binomial analysis of the animals' response, showing a significant position preference in the L-DOPA animals appearing after only 24 trials. It should be mentioned that although the L-DOPA animals showed greater position preference than controls after 48 trials, the difference between groups was not significant. It would be necessary to have a number of animals larger than 4 to observe this difference more clearly.

If, as the present results suggest, L-DOPA can have an effect upon strategy modification, how can the ineffectiveness of L-DOPA upon the position strategy be explained? For one thing, animals responding according to a position strategy were rewarded on 50% of the trials, and the relatively high resistance of a partial reinforcement schedule is well-known. Secondly, the position strategy is an extremely frequent strategy, spontaneously adapted by cats in learning situations where two choices are available. It is possible that such a frequent, natural strategy would be more resistant to biochemical interventions.

It would be premature to draw firm conclusions as to the meaning of this difference but further studies could contribute to a better understanding of the role of dopamine in learning. However, some indications of a difference in what "behavioral flexibility" might be involved as a result of L-DOPA treatment and might plausibly be associated with some performances observed in patients treated with L-DOPA.

The present work illustrates an approach that is particularly valuable in the study of the biochemical mechanisms underlying learning, and might be summarised by the following points: (1) the separation of performance from learning and the analysis of an intervention's effect on the one as distinguished from the other; (2) a performance deficit associated with biochemical changes induced by a 5-HTP and RO4-4602 treatment, and related to a diminished capacity to retain information in short-term memory and (3) some subtle changes in the animals' behaviour during learning, interpreted as increased "behavioral flexibility" as a consequence of L-DOPA treatment.

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