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Further Consideration of the Learning Impairment after Aceperone in the Marmoset: Effects of the Drug on Shape and Colour Discrimination and on an Alternation Task

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BAKER, H. F., R. M. RIDLEY, T. A. J. HAYSTEAD AND T. J. CROW. *Further consideration of the learning impairment after aceperone in the marmoset: Effects of the drug on shape and colour discrimination and on an alternation task.* PHARMACOL BIOCHEM BEHAV 18(5) 701–704, 1983.—Ten marmosets *(Callithrix jacchus)* learned to discriminate between pairs of small grey objects differing only in shape or small plain plaques differing only in colour, in a Wisconsin General Test Apparatus. Each day, each animal was presented with three consecutive visual discrimination problems in the order shape-colour-shape or colour-shape-colour. After aceperone, an α-noradrenergic antagonist, animals were impaired at learning the first but not the subsequent tasks of each trio. These results suggest that the previously observed impairment [10] on the first of a pair of object discrimination tasks after aceperone is a consequence of disruption of a mechanism common to both shape and colour discrimination learning. The fact that there is no impairment on task 2 in a dimension differing from task 1 suggests that the deficit is not one of attending to, or switching attention to, the appropriate visual dimension. Three further marmosets were trained to perform an alternation task and tested under aceperone. No impairment in performance was seen, suggesting that a variety of cognitive skills other than stimulus-reward association were intact. We conclude that the impairment following aceperone is a dysfunction of processes involved in association formation, but that it is one which is manifest only when the animal is faced with a type of task which has not recently been performed and that it can be overcome with persistence even when the animal encounters novel stimuli.

Marmoset Learning Discrimination Aceperone Noradrenaline

IN a previous paper [10] we reported that marmosets pretreated with the α-noradrenergic antagonist, aceperone [1, 5–7, 11], were severely impaired at learning the first object discrimination task of a test session and were impaired on reversal learning but that they were unimpaired at learning a second object discrimination task in the same test session or on the performance of a well-learned task. These results were thought to be consistent with a role for noradrenergic transmission in processes involved in association formation, although the failure following α-noradrenergic receptor blockade appeared to be one which could be reversed by "priming" or recent experience of that type of task. In the present experiment we demonstrate that, after aceperone, marmosets are impaired at learning either a shape or a colour discrimination given as the first task of a test session but are unimpaired at learning a second discrimination in the contrasting dimension. Since a beneficial effect of learning a task in one dimension is carried over to learning another task in a different dimension it appears that the initial learning impairment cannot be explained as a failure of attention to a particular stimulus dimension. On an alternation task there was no impairment after aceperone; this suggests that several cognitive skills other than stimulus-reward associations are intact.

METHOD

Subjects and Apparatus

A total of 13 marmosets (*Callithrix jacchus*, 7% male, 6% female) weighing 250–300 g each were used. Of the 10 animals used in the visual discrimination experiment (Experiment 1), 7 had participated in the study on the effect of aceperone on object discrimination [10]. Three animals which were naive at the beginning of training were first shaped to displace a small object stimulus for food reward, then trained to a criterion of 90 correct responses in 100 consecutive trials (2–3 days training) on a simple object discrimination task ("ballerina" vs "soldier") and, finally, trained on several shape and colour discriminations (see below) until they could reliably perform 3 tasks within one day (usually requiring 5–6 days training).

The 3 animals used for the alternation taks (Experiment 2) were naive at the beginning of training and were trained only on this task.

Reversible α-noradrenergic blockade was achieved by the use of aceperone. When given peripherally to rats this drug produces a significant increase in brain levels of 3-methoxy-4-hydroxy-phenylglycol between 1 and 4 hr (at least) after administration [1]. It also causes an increase in

brain normetanephrine levels but not in 3-methoxy-tyramine [11] suggesting an action on central noradrenergic but not dopaminergic systems. It has also been shown in radioligand binding studies [5,7] that aceperone is 50–100 times less potent than haloperidol as a dopamine blocker.

Discrimination Training (Experiment 1)

All animals were trained in a miniature Wisconsin General Test Apparatus (WGTA) [4]. Small cubes of fresh banana were used as reward. Animals were given their normal diet of bread, egg, fruit and pellet chow sometime after training each day in order to maintain appropriate motivational levels during testing. A variable number of trials was required to complete the learning tasks each day. Each trial commenced when the screen of the WGTA was raised to reveal 2 stimuli covering 2 small food wells, 12 cm apart. The animal could obtain the food reward, which was consistently placed under one stimulus, by displacing that stimulus. Touching the other stimulus was scored as incorrect. The left/right position of the rewarded stimulus was varied according to a pseudorandom Gellermann schedule [3]. The screen was replaced after a response was made and the stimuli positioned for the next trial. The intertrial interval was <15 sec. Stimuli used for shape discrimination were objects less than 5 cm in greatest dimension (e.g., pen tops, plastic toys) mounted on round plastic discs and painted a uniform dark grey. These objects were spray-painted at regular intervals throughout testing to maintain their uniform appearance. Stimuli used for colour discrimination were opaque perspex samples measuring 50×28×3 mm differing only in colour. Pairs of samples were chosen consisting of one light and one dark colour. Choice of the reward stimulus of each was allocated randomly. Pairs of stimuli were arranged in a sequence for presentation such that each pair was neither grossly similar to, nor clearly the reverse of the previous discrimination. Each animal received a different combination of stimuli at each drug dose such that task difficulty and stimulus-preference were distributed across drug doses. All stimuli were novel at the beginning of testing and were used only once for each animal.

Testing was carried out on most weekdays. Each day, each animal was trained on three consecutive tasks, either shape-colour-shape (SCS) or colour-shape-colour (CSC), to a criterion of 5 consecutive correct responses on each task. Having reached criterion on a task the animal was immediately presented with the next task in the trio. (Some animals failed to complete the third task; see Fig. 1.) Learning scores for each task were calculated as the number of responses excluding those in criterion. The two day's performance at each drug dose on each trio of tasks (SCS or CSC) were summed for each animal in order to overcome the effects of variation in daily conditions. Each trio of tasks was given on alternate test days.

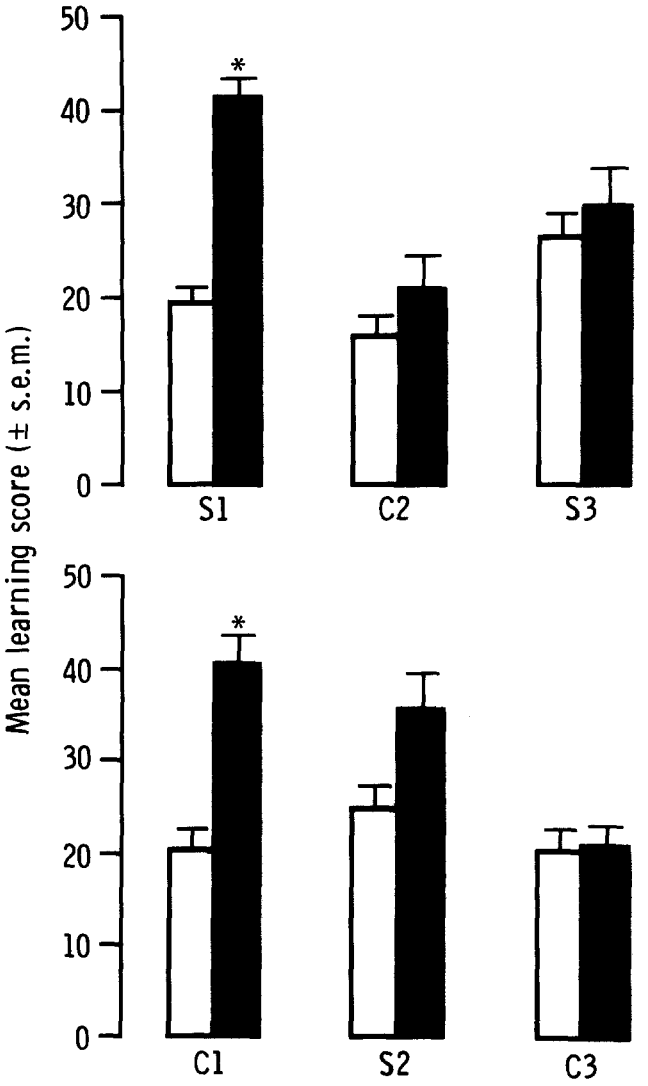

FIG. 1. Effect of 6 mg/kg aceperone on learning consecutively presented discrimination tasks, shape-colour-shape (SCS) or colour-shape-colour (CSC). Ordinate: mean learning score (±SEM) up to but not including 5 consecutive correct responses, summed over two repetitions. □ Vehicle injection; ■ 6 mg/kg aceperone injection 20–30 min before testing. *$p<0.05$ matched pairs t-test comparing aceperone with vehicle for each task. N=10 except S.3 vehicle, C.3 vehicle, S.2 aceperone, where N=9; C.3 aceperone, where N=8; S.3 aceperone, where N=6.

Alternation Training (Experiment 2)

The 3 animals used for alternation were first shaped to displace stimuli for food reward from both food wells. Two object stimuli were used for alternation training, one being placed invariably over the left food well and the other over the right. The banana reward was placed in the food well opposite the side on which the animal had responded on the previous trial. Thus animals are forced to change response position in order to obtain a reward and, if performance was 100% correct, the reward would alternate from side to side. The intertrial interval was 8–12 sec.

Animals' performance began at slightly less than 50% correct (implying a preference for response repetition) and improved in a gradual but overall linear fashion until it reached ~70% correct in a daily session of 40 trials. This training took ~1100 trials/animal. These animals were then given a further 2500 trials during which certain drug effects were measured (e.g., low doses of haloperidol and amphetamine). Performance on alternation never achieved greater than ~70% correct on average although it became more stable

TABLE 1
SEQUENCE OF TASK AND DRUG DOSES IN EXPERIMENT 1

Day	1	2	3	4	5	6	7	8
Dose (mg/kg)	0	0	6	6	6	6	0	0
Tasks (see text)	SCS	CSC	CSC	SCS	SCS	CSC	CSC	SCS

with training. The animals were drug free and were performing consistently at ~70% correct for several weeks before testing under aceperone. During testing under aceperone, animals were given 40 trials per day and two days training at each dose used. The two days' performance at each drug dose were summed for each animal.

Drug Administration

Aceperone (Janssen) was dissolved in saline acidified with a minimal amount of glacial acetic acid. The pH was adjusted with sodium hydroxide to ~6.8. A vehicle solution of comparable pH was used for control injections. Aceperone was administered in a volume of 0.1–0.2 ml into the thigh muscle, 20–30 min before testing. For Experiment 1, 6.0 mg/kg aceperone, or vehicle, was injected and tasks were presented in the sequence shown in Table 1. For Experiment 2 aceperone was administered in the following order: 0.0, 1.5, 3.0, 6.0, 6.0, 3.0, 1.5, 0.0 mg/kg.

RESULTS AND DISCUSSION

Figure 1 shows that after aceperone animals were impaired at learning either a shape or colour discrimination task presented as the first task of a test session compared to saline treatment. Animals were not significantly impaired after aceperone on colour or shape discrimination in the second task position although the mean performance for shape discrimination in that position demonstrates that some animals had considerable difficulty on this task. Animals were not significantly impaired on either shape or colour discrimination in the third task position. In our previous report [10] we showed that animals were as impaired 3½ hr after injection of aceperone as they were ½ hr after injection on learning a task which was not immediately preceded by another task. Furthermore a mild palpebral ptosis developed within a few minutes of drug administration and lasted several hours. Thus it is unlikely that the different effects of aceperone on learning the first and subsequent tasks of each test session could be attributable to drug elimination. The mean performance on the alternation task was at, or slightly higher than, 70% correct at all doses of aceperone, demonstrating that the drug has no effect on this task. Performance on the first few trials of each session was also not affected.

The lack of impairment on performance of the alternation task implies (1) that orientation is intact, (2) that short-term memory (8–12 sec) is intact, and (3) that long-term memory of a complex habit (alternation) is intact even though the task is of such difficulty that only approximately 70% correct performance can be achieved by protracted training.

Several aspects of our experiments argue against a disturbance of selective attention in animals treated with aceperone. Performance of a well-learned task [10] implies that animals must have been able to attend to the stimuli within the context of the test-box and to direct their responses towards the relevant object. The results of the present experiment suggest that animals are equally capable of attending to shape or colour stimuli in the same task position. Attention to one dimension, e.g., shape, has a beneficial effect on subsequent discrimination in another dimension, e.g., colour, suggesting that animals have no difficulty in switching from one visual dimension to another and that the beneficial effect of learning a task 1 transcends visual dimension. The impairment on reversal learning after aceperone [10] where the same visual dimension was relevant but a new reward association had to be found cannot be easily explained as an inability to attend to the appropriate visual dimension.

Marmosets have been shown to form learning sets, though less efficiently than macaques [9]. The animals used in the present study were experienced in discrimination tasks and thus possessed a partial learning set, i.e., their mean learning scores on novel problems were considerably lower than learning scores on the first ever encountered task but they had not achieved a full learning set (which is defined as criterion performance on the second and subsequent trials of any new task of that set [8]). Animals treated with aceperone may be impaired on task 1 because they fail to make use of a partial learning set rather than because the mechanism of stimulus-reward association is impaired. Learning task 1 may activate this set for solving novel object tasks.

The reasons why the partial learning set is not invariably restored in the task 2 position may be found in an understanding of the interaction between the performance of specific stimulus-related responses and the use of sets (rules of responding which apply to any stimuli used in one type of task). Meyer [8] has shown that a learning set is not invariably used by a monkey which is known to possess such a set. One of the circumstances in which a working learning set is switched off is the presentation of stimuli which are already associated with a response.

Applying Meyer's finding to the effects of aceperone on learning it can be seen that performing a well-learned task (i.e., using stimuli already associated with a response) should not activate a learning set; similarly the use of response-related stimuli in reversal should inhibit the application of the learning set such that reversal is treated as another task 1. An impossible task with identical objects presents the animal with stimuli which are familiar but not response-related and therefore activates the learning set. It would seem from this that it is the lack of response-relatedness (lack of association) rather than the novelty (lack of recognition) of the stimuli which is crucial in activating a learning set.

The ascending noradrenergic pathway, which in the rat may be involved primarily in reinforcement of stimulus-response links [2], may have evolved in more advanced animals to reinforce and maintain learning sets and other sophistications of cognitive processing.

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