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BRIEF COMMUNICATION

d-Amphetamine Effects on Attention and Memory in the Albino and Hooded Rat[1]

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BECKWITH, B. E., C. A. SANDMAN, W. D. ALEXANDER, M. C. GERALD AND H. GOLDMAN. *d-Amphetamine effects on attention and memory in the albino and hooded rat.* PHARMAC. BIOCHEM. BEHAV. 2(4) 557–561, 1974. – Albino and hooded rats were injected with either d-amp or physiological saline and tested on acquisition, reversal, and recall of a brightness discrimination. Hooded rats acquired and reversed the discrimination more quickly than albino rats. D-amp retarded both acquisition and reversal while enhancing recall. The results indicated that d-amp disrupts attention while enhancing memory. The systems which may mediate this behavioral fractionation are discussed.

d-Amphetamine Attention Memory Visual discrimination Learning difference in Albino and Hooded rats

THE MOST consistent and pronounced behavioral effect of administration of amphetamines has been the appearance of stereotypic behavior [16, 25, 26]. The findings concerning other behavioral effects of amphetamines have been far less consistent. Early work with amphetamines suggested that it retarded performance of a discrimination problem [1], whereas later research demonstrated facilitating effects of amphetamine upon performance of a brightness discrimination problem [24]. Additionally, amphetamines have been found to enhance memory processes in humans [15] and rats [11, 24, 28]. Other studies have reported that amphetamines have no effect on memory [7,10].

There are several possible reasons for such apparent discrepancies in the literature. For instance, the effects of amphetamines have typically been studied using either d-amphetamine, l-amphetamine, dl-amphetamine, or methamphetamine. Conclusions based upon this literature may be inconsistent due to the fact that these compounds have different potencies [3,4].

A second confounding factor is dosage. Cole [9] in a review of the effects of amphetamines indicated that investigators had not taken cognizance of dose response effects. He recommended that increased attention be given to dose-response relations to avoid possible overdose effects resulting from spilling over of drug effects into adjacent behavioral systems.

A third possible reason for the discrepant findings may be due to the paradoxical effect of amphetamines. Amphetamines do not act as a general stimulant for all response categories, but selectively stimulate some responses while

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inhibiting others [27]. This characteristic of amphetamine action allowed Maickel *et al.* [20] to segregate behavioral tasks on the basis of minimum brain levels of amphetamine necessary to cause disturbances in performance on a given task. This point is further underscored by the finding that amphetamines increased operant barpress rates relative to base rates for some rats while decreasing barpress rates for others [6,30].

A fourth confounding variable is possible drug by strain interactions. Sandman *et al.* [29] suggested that certain drugs interact with strain which resulted in superior performance of hooded rats relative to albino rats on a visual discrimination task. Therefore, often neglected strain differences may interact with drug treatment and hence account for some of the discrepancies in the literature.

Finally, very little attention has been directed toward tasks which separate attention from memory. Mackintosh [18,19] has argued for a two-stage attentional model of discrimination learning. Accordingly, Mackintosh argues that a reversal learning task is an appropriate indicator of attentional processes operative in a discrimination learning problem. By combining a reversal task with a memory task, one can independently assess the relative contribution of attentional process to memory on a given discrimination problem.

The present study was designed to investigate several issues which have confounded research on the behavioral effects of amphetamines, while carefully attending to establishment of dosage level. Reversal and memory tasks were used to evaluate the effects of an optimal dose of d-amphetamine (d-amp) upon the performance of hooded and albino rats.

METHOD

Animals

Forty, ninety-day old, male albino rats (Holtzman) and 40, ninety-day old, male hooded rats (Long Evans) were housed individually under indirect constant illumination and maintained by means of ad lib watering and feeding schedules. All animals were allowed 10 days of adaptation to the lighting and were handled 5 days prior to testing.

Apparatus

The test apparatus was a black Plexiglas Thompson-Bryant Box [31] which consisted of a start box, a choice compartment and a goal box. A guillotine door separated the start box from the choice compartment. Black and white discriminanda were inserted into a 9 cm square opening separating the choice chamber from the goal box. A partition, which extended 7 cm into the choice compartment, separated the choice compartment into 2 sections. The floor of the start box and choice compartment consisted of a stainless steel grid, whereas the floor of the goal box was constructed from a solid piece of black Plexiglas. Shock was administered simultaneously to start box and choice compartment by means of a Grason-Stadler power source and shock scrambler.

Procedure

The dosage of d-amphetamine was determined in a separate pilot study which used 4 dosage levels: 1 mg/kg, 2 mg/kg, 3 mg/kg, and 4 mg/kg. The appropriate dosage level was set at 2 mg/kg since this dosage did not produce marked stereotypic behavior.

The albino and hooded rats were each divided into four groups and administered a 2 mg/kg i.p. injection of either d-amp or physiological saline solution 30 min before each acqusition, reversal or recall session. The experimental design and sequence of injections are illustrated in Table 1.

TABLE 1

EXPERIMENTAL DESIGN AND ORDER OF INJECTION FOR EACH GROUP

Group	Original Learning and Reversal	Recall
A-A	d-amphetamine	d-amphetamine
A-S	d-amphetamine	saline
S-A	saline	d-amphetamine
S-S	saline	saline

Pretraining. Each animal was permitted to explore the apparatus (without doors) for 15 min on the first day. Day 2 pretraining consisted of two stages. First, a vertically and a horizontally striped door were placed at the end of the goal box while the animals were trained to avoid shock by running into the goal compartment immediately upon the opening of the guillotine door. Second, the doors were moved into a position which partially obscured the openings into the goal box and on successive runs moved into a position which completely blocked the goal box entries. The goal of this second stage was to train the animals to avoid shock by dislodging doors which allowed entry into the goal box. Both pretraining sequences were done with criterion set at 5 consecutive entries into the goal box without the animal's having received a shock. Shocks of 0.5-sec duration each were administered successively for either a 5-sec hesitation in the start box or a 5-sec hesitation in the choice compartment and were terminated when the animal either left the start box or approached the goal box. Shock intensity was maintained at 0.5 mA throughout the experiment.

Original learning. The discrimination task required that the animal avoid shock by running to a solid white door, displace it and enter the goal box. A solid black door remained locked at one of the goal box entries during this phase of the experiment. Door positions were altered according to a Gellerman series [13]. Animals were run in squads of six and were given 25 trials per day. Trials were spaced so all animals were given Trial 1, then all animals were given Trial 2 and so on until all trials were run. Each session of 25 trials was broken into 3 approximately equal segments with intersession blocks separated by approximately 5 min. Acquisition of the discrimination task was defined as 9 of 10 correct responses. An error was scored if an animal approached within 7 cm of the negative stimulus door or failed to approach either door within 15 sec after leaving the start box.

Reversal. Identical procedures were used for the reversal shift except that the black door allowed shock avoidance whereas the white door was locked.

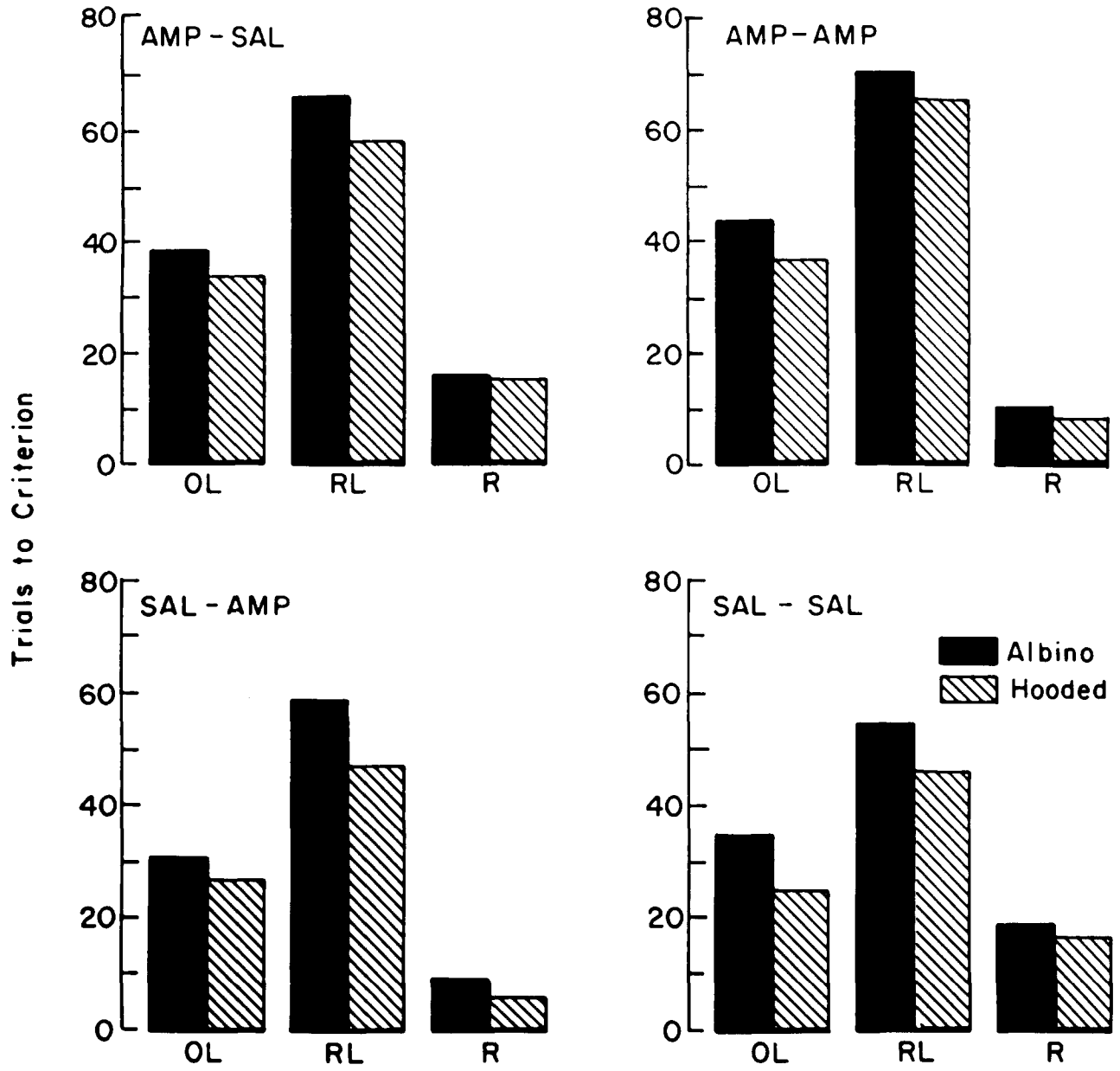

FIG. 1. Mean trials to criterion for hooded and albino rats given identical injection sequences on original learning, reversal learning, and memory.

Recall. After reaching criterion on the reversal task each animal was given 14 undisturbed days in his home cage. At the end of the 14 days the animals were again run to a 9 of 10 criterion with the black door positive. The procedure was identical to that used on the reversal task.

RESULTS

The data were analyzed according to a mixed design analysis of variance, with strain and drug treatments serving as the between subjects variables and task serving as the within subjects variable. The results of this general analysis demonstrated clear-cut main effects due to strain, $F(1,72) = 17.63$, $p<0.01$, drug condition, $F(3,72) = 11.39$, $p<0.01$, and task $F(2,144) = 494.65$, $p<0.01$, with a significant interaction between drug and task, $F(6,144) = 7.27$, $p<0.01$.

Scheffe's multiple comparison method was used for detailed analysis of simple effects. Rather than using the traditional error rate per comparison set at 0.05, the following analyses were carried out with a conservative error rate experiment-wise set at 0.10 in accordance with logic developed in Myers [23].

Reference to Fig. 1 reveals the superiority of hooded rats relative to albino rats on both original learning, $F(1,72) = 8.75$, $p<0.05$, and reversal, $F(1,72) = 12.34$, $p<0.01$, of

the visual discrimination. However, analysis of performance on the recall or memory task showed no significance differences between albino and hooded rats, $F(1,72) = 0.83$.

A further analysis was made which compared the performance of albino and hooded rats on a particular task while receiving the same injections (i.e., an analysis of the replication). Due to the lack of significant differences between any of the replications, it was decided that the groups would be combined to observe the effect of d-amp or saline upon each strain for each task. Albino rats treated with d-amp acquired, $F(3,144) = 9.01$, $p<0.05$, and reversed, $F(3,144) = 16.44$, the visual discrimination more slowly than did albino rats given saline injections. Figure 1 also displays the poorer performance of d-amp injected hooded rats on both original learning, $F(3,144) = 11.09$, $p<0.05$, and reversal, $F(3,144) = 27.32$, $p<0.01$, coupled with their better performance on memory, $F(3,144) = 9.22$, $p<0.05$, on the visual discrimination.

It is also evident from Fig. 1 that performance of hooded rats, $F(3,144) = 2.67$, $p>0.10$, and albino rats, $F(3,144) = 1.49$, $p>0.10$, did not differ from the A-S and A-A groups. It is apparent that both hooded rats and albino rats remembered better if reversed with saline injections and tested for memory under the influence of d-amp. This result was significant for albino rats, $F(3,144) = 6.32$, $p<0.05$, but not significant for hooded rats, $F(3,144) = 4.03$, $p>0.10$. A-S animals did not remember significantly better than did A-A animals, $F(3,144) = 4.05$, $p>0.10$, whereas animals in the S-A groups did perform significantly better on the memory task than did animals in the S-S group, $F(3,144) = 6.32$, $p<0.05$.

Finally, an interaction of drug and task variables is clearly present in Fig. 1. It is evident from this figure that d-amp causes significantly slower learning of both the initial visual discrimination, $F(3,144) = 20.04$, $p<0.01$, and its reversal, $F(3,144) = 43.07$, $p<0.01$, while d-amp serves to enhance memory of the reversal visual discrimination, $F(3,144) = 16.11$, $p<0.01$.

DISCUSSION

The results of this study suggested that hooded rats both acquired and reversed a simple brightness discrimination problem more quickly than albino rats. Moreover, all animals treated with d-amp acquired and reversed the brightness discrimination more slowly than did saline injected animals, whereas d-amphetamine enhanced recall performance.

Pigmented animals' ability to perform more efficiently than unpigmented animals on a brightness discrimination task has been related to differences in the visual systems of the two strains [29]. The present paper tends to support the Sandman *et al.* [29] finding that procedural differences accounted for the earlier failure to find strain differences in the performance of a visual discrimination [21]. The present findings also indicated that strain differences do not appear to interact with the effects of d-amp and, therefore, should not be assumed an important source of discrepancies among early studies.

The finding that d-amp retards acquisition and reversal of a brightness discrimination while at the same time enhancing later recall serves to extend the concept of amphetamine induced response differentiation [27], and to establish the present methodology as a means of independently analyzing attention and memory. The opposing effects of amphetamines on different behavioral systems appears to be a very powerful effect which has often been ignored by attempts to interpret the amphetamine literature.

The divergence of these two behavioral processes may reflect the independent actions of d-amp on different neural systems. It is apparent that amphetamines produce their central effects via their interactions with noradrenergic [3, 12, 20], and dopaminergic [6, 8, 14, 25] receptor systems within the brain. Several authors have suggested that the noradrenergic interactions of amphetamines are in part due to stimulation of the ascending reticular activating system [2,3] which produces a state of general arousal or activation in the organism [2,3]. The attentional deficits found in the animals' performance on the reversal training task may be due to the noradrenergic actions producing a high state of arousal which may account for the disruptive effect of d-amp on acquisition and reversal of the brightness discrimination.

Dopaminergic interactions of d-amp may explain the memory enhancement found in this study. Several studies have shown that the dopaminergic effects of amphetamine involve the basal ganglia [6, 8, 14, 25]. Recent evidence has also indicated that L-DOPA potentiates memory [17,22] and that L-DOPA is sufficient to replace amphetamine in facilitating recall [28]. This suggests that the memory effects of amphetamine may be mediated via the dopaminergic system of the basal ganglia Evidence for the behavioral independence of these two systems is provided by the finding that L-DOPA can improve recall without effecting performance of a visual discrimination [17]. Our findings coupled with this evidence lead us to view amphetamine as having a dual action. We believe that noradrenergic mechanisms account for attention whereas dopaminergic mechanisms independently mediate memory. The most logical sequel to the present experiment is to test our hypothesis using specific noradrenergic and dopaminergic agonists and antagonists.

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