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Ontogenetic Differences in Response to d-Amphetamine: Two-Way Avoidance, Intertrial Responses, and Locomotor Activity

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BAUER, R. H. *Ontogenetic differences in response to d-amphetamine: Two-way avoidance, intertrial responses, and locomotor activity.* PHARMAC. BIOCHEM. BEHAV. 16(2) 217–223, 1982.—In Experiment 1, 15-, 17-, 21-, 36-, and 90-day-old rats were injected with either physiological saline, 0.5-, 1.0-, 4.0-, 8.0-, or 16.0-mg/kg of d-amphetamine sulfate and 20-min later they were allowed to explore a two-way avoidance apparatus for 8 min. Immediately following adaptation, they were given a single session of 100 two-way avoidance trials. In general, in all ages, there was a dose related increase in avoidance on the first block of trials. However, across trials avoidance of the two youngest ages decreased, avoidance responding by 21-day-old animals remained relatively constant, and avoidance of the two oldest ages increased. In the three youngest ages, avoidance and intertrial responses had a similar pattern, but in older ages there was little relationship between avoidance and intertrial responses. Shuttle crossings during adaptation were increased more by higher doses in younger rats than adults. In Experiment 2, para-hydroxyamphetamine (1.0, 4.0, or 16.0 mg/kg) did not alter two-way avoidance, intertrial responses, or crossings during adaptation in 15-, 17-, 21-, 36-, or 90-day-old rats. The age-dependent behavioral effects of d-amphetamine may be due to maturation of central nervous system catecholaminergic neurons.

Amphetamine Development Aging Motor activity Avoidance Rats Catecholamines

THE catecholamines, norepinephrine and dopamine, are thought to be synaptic transmitters in the central nervous system [8,10] and to play an important role in acquisition and performance of learning tasks, motor activity, and arousal [12,13]. A variety of histochemical and biochemical evidence indicates that at birth catecholamine-containing neurons in altricial species, such as the rat, are not fully developed. In the rat, catecholamine-containing cell bodies in the lower brain stem appear to be nearly mature at birth, but the axons from these neurons are not yet fully grown. As the animal matures, axons from these cell bodies grow in a rostral direction, such that successively higher brain structures are innervated. In the rat, innervation of the cerebral cortex occurs at about 45 days of age (for reviews see [15,19]). Thus development of catecholaminergic neurons may play an important role in the behavioral changes during development.

Since catecholaminergic neurons grow during development, it has been suggested that the behavioral effects of catecholaminergic drugs, such as amphetamines, would differ as a function of development [3,4]. In support of this suggestion, d-, l-, and dl-amphetamine have differential effects on locomotor activity and wall climbing in immature and mature rats [3, 4, 6, 7, 16]. Locomotor activity has usually been examined in developmental psychopharmacological studies; perhaps, because there are large changes in locomotor activity during the normal course of development [2, 4, 6, 7]. However, since catecholaminergic neurons change with development and in adults these neurons are thought to be important for acquisition and performance of both positively and negatively reinforced tasks, catecholaminergic drugs would also be expected to produce differential effects on acquisition and performance in immature and mature animals. The finding that d-amphetamine (2.0 and 8.0 mg/kg) has an insignificant effect on one-way avoidance in 30-day-old rats but intermediate doses increase acquisition in adults [4] supports this suggestion. In addition, methylphenidate (1.5 mg/kg), which appears to alter behavior by releasing catecholamines, impairs two-way avoidance of 47-day-old rats but produces little change in avoidance of adults [11]. The effects of catecholaminergic drugs on acquisition of rats younger than 30 days of age and adults have apparently not yet been compared. However, due to the

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large maturational changes in catecholamine-containing neurons from birth to 30 days of age, catecholaminergic drugs would be expected to have quiet different effects on avoidance in rats younger than 30 days of age and adults.

The major purpose of the present experiments was to compare the effects of d-amphetamine on two-way avoidance by immature and mature rats. d-Amphetamine was used, because of its well known action on catecholamines, i.e., increased release and reduced reuptake [5, 8, 12, 14]. Two-way avoidance was examined, because catecholamines are known to be important for performance of this task [1, 9, 18] and because two-way avoidance increases during the normal course of development [2].

When comparing behavior of immature and mature animals, it is usually necessary to equate the size of the animal with the size of the apparatus, because failure to do so may confound the results [3]. For example, in the present experiments, since 15-day-old rats are approximately one-half the size of adults, 15-day-old rats would require approximately twice as many steps to make a shuttle crossing as adults. This could reduce the acquisition rate of the younger animals, if both ages were tested in the same size apparatus. In addition, if the number of shuttle crossings is used to measure locomotor activity, younger animals might well appear to be less active than adults when tested in the same size apparatus. For these reasons, in the present experiments, the animals' size and the apparatus size were equated.

EXPERIMENT 1

METHOD

Subjects

The subjects were 15, 17, 21–22, 36–37, and 90–100-day-old experimentally naive, male, Sprague-Dawley rats (Rattus norvegicus. There were 10 rats in each age and each dose group.). For brevity, each group will be referred to hereafter by its youngest age. They were offspring of breeding stock obtained from Simonsen Laboratories, Gilroy CA. Light onset and light offset in the colony room were at 6:00 a.m. and 8:00 p.m., respectively. The colony and experimental rooms were maintained at 23±1°C. Throughout the experiment, the rats had free access to Purina Rat Pellets and water.

Apparatus

The apparatus has been described in greater detail previously [2]. Briefly, the apparatus dimensions varied according to the approximate spine length of each age [20]. The oldest rats were trained in a 72×14×17-cm shuttle box with 0.9 cm in diameter stainless steel bars placed 2.5 cm apart. The 36-day-old animals were trained in a 51×10×13-cm box with a floor of 0.7 cm in diameter bars placed 1.7 cm apart. The 21-day-old groups were trained in the same shuttle box as the 36-day-olds, but the dimensions were reduced by 15% by inserting aluminum inner liners. The two youngest ages were tested in a 26×6×7-cm box with a grid floor composed of 0.4 cm in diameter bars placed 1 cm apart.

The walls of each box were covered with aluminum sheets and the top covered with a Plexiglas lid. The floors were separate from the walls and pivoted at the center as the animal's weight tilted the floor. A microswitch opened or closed when the rat crossed the center. Illumination was provided by a 15 W bulb mounted above the box. A speaker, mounted above the shuttle box, provided a 75-dB (SPL) white noise CS (8 dB above background). A 1.5 mA shock could be delivered to the floor and aluminum walls. The occurrence of the CS, US, and shuttle crossings were recorded on a 3-channel event recorder.

Procedure

The procedure has been described in greater detail elsewhere [3]. Briefly, the litters were first reduced to 8 pups. Until 21 days of age, they were housed with their mothers and litter mates in standard cages. Rats tested at the three youngest ages were randomly assigned to each age and each dose group immediately prior to testing. At weaning, rats in the three oldest groups were randomly assigned to group cages and immediately before testing all animals in a cage were randomly selected for training at a particular age. Animals in selected cages were then randomly assigned to dose groups.

The rats were weighed and then given an intraperitoneal injection of either physiological saline, 0.5-, 1.0-, 4.0-, 8.0-, or 16.0-mg/kg of d-amphetamine sulfate (salt). Because preliminary experiments indicated that adults could not tolerate the highest dose, the adult 16.0 mg/kg group was not included. The drug solutions were mixed such that 0.01 cc/g of body weight was injected. The bottles containing the solutions were coded, so the experimenter did not know the dose being injected until the end of the experiment. After the injection, the rats were returned to their home cages. Twenty min later the rats were adapted to the shuttle box for 8 min, and they were then given a single session of 100 two-way avoidance trials. The intertrial interval was variable with a mean of 60 sec. The CS was presented for 10 sec and was followed by the US if no avoidance response occurred within the CS-US interval. The CS and US remained on until an escape response or for a maximum of 20 sec. The CS and US terminated simultaneously with the escape response.

RESULTS

Avoidance

The percentage of avoidance responses per block of 10 avoidance trials was determined for each animal. The mean percentage avoidance in 10 trial blocks is presented in the left panels of Fig. 1 as a function of age and dose. Because of heterogeneity of variance, the percentage scores were subjected to a square-root arc-sin transformation. Due to the fact that the adult 16.0 mg/kg group could not be included in the experiment, the transformed data were analyzed in a number of ways. In the first analysis, the 16.0 mg/kg groups were excluded and a 5 (age) × 5 (dose) × 10 (blocks of trials) mixed analysis of variance computed on the remaining data. This analysis showed that the main effects for age, $F(4,225)=37.58$, $p<0.001$, dose, $F(4,255)=22.92$, $p<0.001$, and trial blocks, $F(9,2025)=7.26$, $p<0.001$, were significant. (The criterion for significance was $p<0.05$ for all statistics reported.) A significant dose × age interaction, $F(16,225)=2.57$, $p<0.001$ and inspection of the upper panel of Fig. 2 suggests that d-amphetamine increased avoidance more in older ages than in younger ages. A significant dose × trials interaction, $F(36,2025)=9.40$, $p<0.001$, appears to be due to the greater change across trials produced by higher doses. A significant age × trials interaction, $F(36,2025)=16.02$, $p<0.001$, appears to be due to a decrease

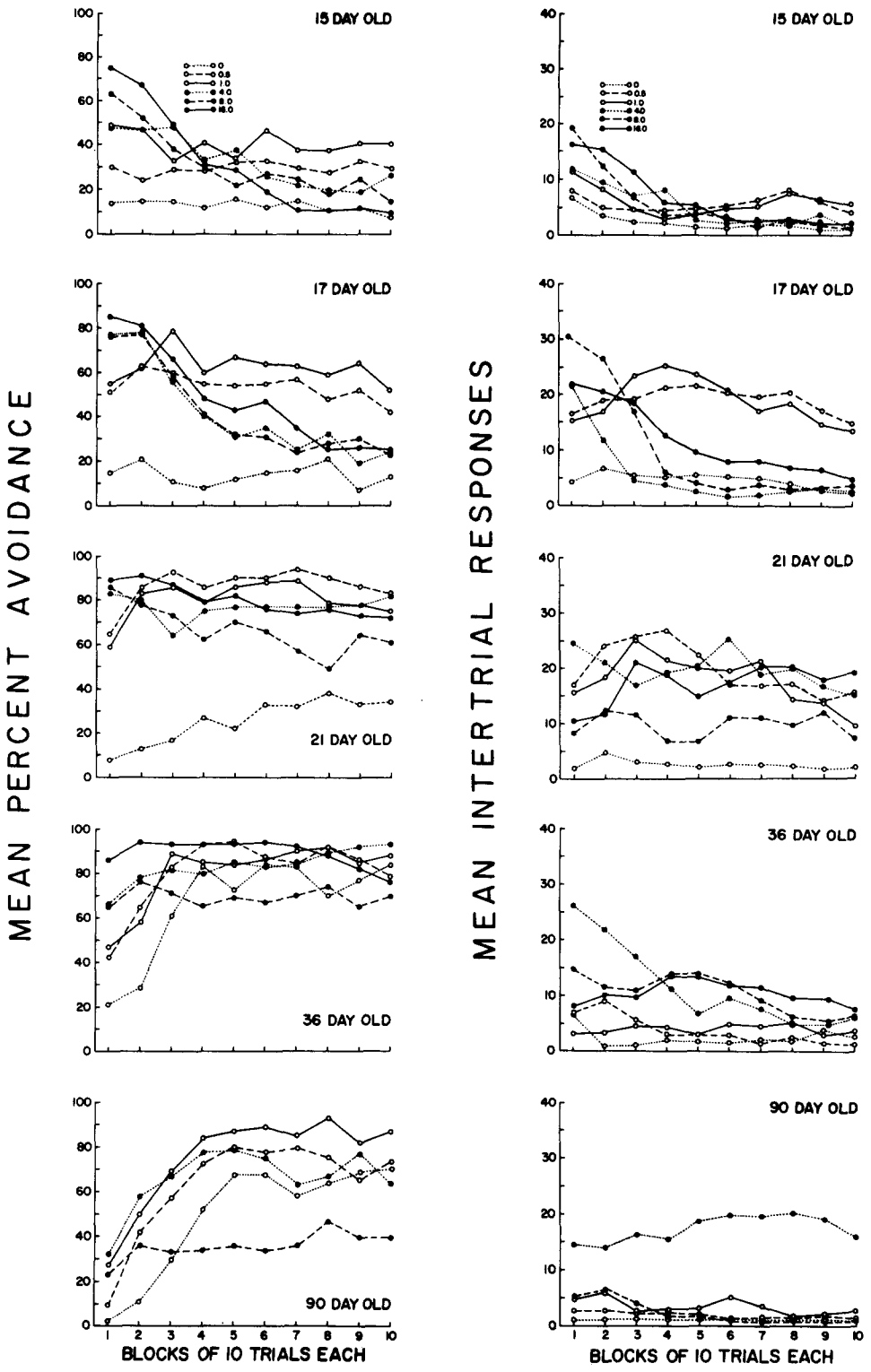

FIG. 1. Mean percentage avoidance per block of 10 avoidance trials (left panels) and the mean number of intertrial responses per block of 10 avoidance trials (right panels) as a function of drug dose for five different ages.

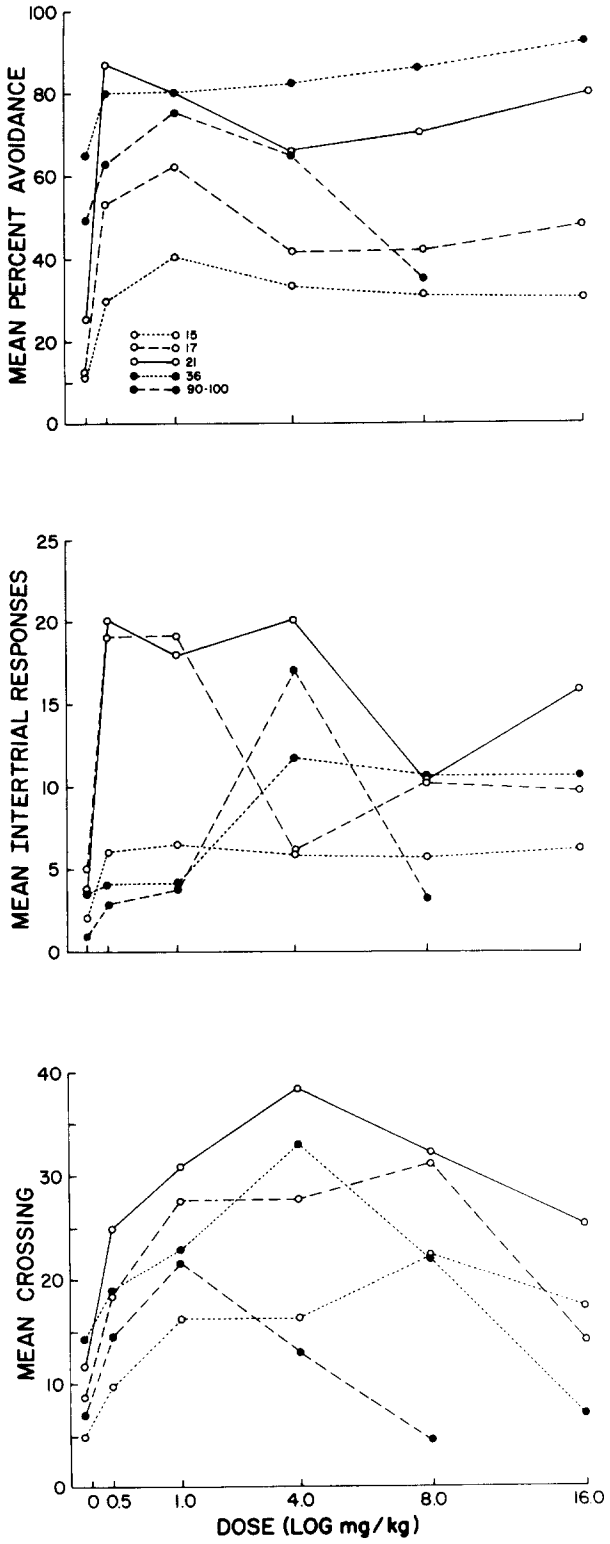

FIG. 2. Mean percentage avoidance for 100 trials (upper panel), the mean number of intertrial responses per block of 10 avoidance trials (middle panel), and the mean crossing during adaptation (lower panel) as a function of age and drug dose.

across trials in the three youngest ages and to an increase across trials in the two oldest ages.

In the second analysis the oldest age was excluded and a 5 (age) × 6 (dose) ×10 (blocks of trials) mixed analysis of variance was computed on the remaining data. This analysis showed that the main effects for age, $F(4,216)=72.68$, $p<0.001$, dose $F(5,216)=19.82$, $p<0.001$, and trials, $F(9,1944)=11.04$, $p<0.001$, were significant. The dose × age interaction, $F(15,216)=2.02$, $p<0.02$, the dose × trials, $F(45,1944)=9.98$, $p<0.001$, and the age ×trials interaction, $F(27,1944)=17.02$, $p<0.001$, were significant.

For the four youngest ages, percentage avoidance was analyzed separately for each age by a 6 (dose) × 10 (trial blocks) mixed analysis of variance. For the oldest age, percentage avoidance was analyzed by a 5 (dose) × 10 (trial blocks) mixed analysis of variance. These analyses showed that the main effect for dose was significant in all ages. The main effect for trials was significant in all ages except 21-day-old rats. However, inspection of the left panels of Fig. 1 clearly shows that avoidance by the two youngest ages decreased across trials, whereas avoidance by the two oldest ages increased across trials. The dose × trials interactions were significant in all ages, but Fig. 1 indicates that the nature of these interactions depended on the animal's age. In all ages, there was generally a dose related increase on the first few trial blocks. However, across trials, the following appears to be the case: (a) In the three youngest ages given lower doses, avoidance remained relatively constant across trials, whereas in these ages given higher doses avoidance decreased across trials. (b) In 36-day-old rats, higher doses resulted in relatively stable performance, whereas lower doses increased acquisition very slightly. (c) In adults, lower doses improved acquisition and asymptotic performance, whereas the highest dose impaired acquisition.

Tukey's test was used to compare the mean percentage of avoidance responses for the total 100 trials in the youngest rats (Tukey's test was used in all individual comparisons).Comparisons among dose groups were made separately for each age. The mean squared error variance for the separate analysis of variance on each age was used as the error term in computing these Tukey's tests. In the youngest age, the only significant difference was the greater percentage avoidance in the 1.0 mg/kg group than the saline controls. In 17 and 21-day-old groups, saline controls made significantly fewer avoidances than all other dose groups. The 36-day-old animals given the highest dose made more avoidances than saline controls. In adults, fewer avoidances were made by saline controls than the 1.0 mg/kg group and the 8.0 mg/kg group made fewer than the 0.5, 1.0, and 4.0 mg/kg groups.

Intertrial Responses

For each animal, the number of intertrial responses per block of 10 avoidance trials was determined. The mean number of intertrial responses per block of 10 avoidance trials is shown in the right panels of Fig. 1 as a function of age and dose. In the first analysis of intertrial responses, the 16.0 mg/kg groups were not included and a 5 (age) × 5 (dose) × 10 (blocks of trials) mixed analysis of variance was computed. This analysis showed that the main effects for age, $F(4,225)=7.59$, $p<0.001$, dose, $F(4.225)=5.87$, $p<0.001$, and trials, $F(9,2025)=16.95$, $p<0.001$, were significant. The dose × age interaction was significant, $F(16,225)=2.35$, $p<0.003$ and appears to be primarily due to the large number of intertrial

TABLE 1

PEARSON-PRODUCT MOMENT CORRELATIONS BETWEEN THE PERCENTAGE AVOIDANCE AND INTERTRIAL RESPONSES FOR EACH BLOCK OF TRIALS AND EACH AGE

	Blocks of Trials									
Age	1	2	3	4	5	6	7	8	9	10
15	.53‡	.56‡	.54‡	.55‡	.52‡	.68‡	.81‡	.76‡	.72‡	.76‡
17	.50‡	.37‡	.50‡	.49‡	.61‡	.49‡	.58‡	.61‡	.63‡	.63‡
21	.42‡	.32†	.40‡	.44‡	.34†	.41‡	.35‡	.40‡	.38†	.28*
36	.40‡	.31†	.18	.07	.09	.10	.12	.16	.01	.02
90	.53†	.36†	.30*	.23	.10	.15	.10	.04	.14	.10

*$p<0.05$.
†$p<0.01$.
‡$p<0.001$.

responses in 17 and 21-day-old rats given low doses (see the middle panel of Fig. 2). The dose × trials interaction was significant, $F(36,2025)=3.08$, $p<0.001$, and inspection of the right panels of Fig. 1 suggests that, at least for younger ages, higher doses increased intertrial responses on the first block of trials but there was a gradual decline on subsequent trials. A significant age × trials interaction, $F(36,2025)=2.11$, $p<0.001$, appears to be due to a decrease across trials in the two youngest ages and to relatively stable crossings across trials in older ages (see the right panels of Fig. 1). A significant three way interaction, $F(144,2025)=1.88$, $p<0.001$, indicates that drug treatment differentially affects the age-related changes that occur across trials.

In the second analysis, the 90-day-old animals were not included and a 5 (age) × 6 (dose) × 10 (trial blocks) mixed analysis of variance was computed on the remaining data. This analysis showed that the main effects for age, $F(3,216)=8.56$, $p<0.001$, dose, $F(5,216)=3.77$, $p<0.003$, and trials, $F(9,1944)=22.66$, $p<0.001$, were significant. Inspection of the right panels of Fig. 1 suggests that in the two youngest ages intertrial responses decreased across trials, whereas older groups showed little change across trials. This was supported by a significant age × trials interaction, $F(27,1944)=2.99$, $p<0.001$. The dose × trials interaction was significant, $F(45,1944)=3.10$, $p<0.001$. A significant three way interaction, $F(135,1944)=1.95$, $p<0.001$, suggests that drug treatment differentially affects the age-related changes that occur across trials.

For the four youngest ages, the number of intertrial responses for each age was analyzed separately by 6×10 mixed analysis of variance; the oldest age was analyzed by a 5×10 mixed analysis. The main effect for dose was significant in 17-, 21-, and 90-day-old rats. The main effect for trials was significant in the four youngest ages and is apparently due to a decrease across trials. As shown in the right panels of Fig. 1, in 15-, 17-, and 36-day-old animals there was a dose related increase on the first block of trials and then a decrease for rats given higher doses; these ages given lower doses remained relatively constant across trials. This was supported by significant dose × trials interactions in 15-, 17-, and 36-day-old rats.

Individual comparisons of the mean number of intertrial responses for the total session showed that there were no significant differences among dose groups in 15 and 36-day-old rats. (In computing these Tukey's tests, the mean squared error variance for the separate analysis of variance for each age was used as the error term.) In 17-day-old animals, saline controls made significantly fewer intertrial crossings than the 0.5 and 1.0 mg/kg groups. The 21-day-old rats given saline made fewer crossings than their same aged counterparts given 0.5-, 1.0-, and 4.0-mg/kg. The adult 4.0 mg/kg group made significantly more responses than other dose groups of this age.

Correlations Between Avoidance and Intertrial Responses

Inspection of the right and left panels of Fig. 1 and the upper and middle panels of Fig. 2 suggest that avoidance and intertrial activity were related in the three youngest ages. The relationship between avoidance and locomotor activity was examined by computing Pearson-product moment correlations between the percentage avoidance and the number of intertrial responses for each block of 10 avoidance trials. Separate correlations were computed for each age. As shown in Table 1, most of these correltions were significant in the three youngest ages but only a few were significant in the two oldest ages.

To examine the percentage of variance in avoidance that is accounted for by locomotor activity, the mean correlation of each age was computed and the coefficient of determination determined for each of these means. These coefficients showed that 41-, 29-, 14-, 2- and 4% of the variance in avoidance was accounted for by motor activity in 15-, 17-, 21-, 36-, and 90-day-old groups, respectively.

Crossings During Adaptation

The lower panel of Fig. 2 presents the mean number of shuttle crossings during adaptation for each age as a function of drug dose. The number of crossings was analyzed by a 5 (age) × 5 (dose) complete factorial analysis of variance (the highest dose was excluded from this analysis). The main effects for dose, $F(4,225)=15.75$, $p<0.001$ and age, $F(4,225)=14.96$, $p<0.001$, were significant. A significant dose × age interaction, $F(16,225)=2.23$, $p<0.001$ and inspection of the lower panel of Fig. 2 suggest that higher doses increased locomotor activity more in younger rats than in adults.

A 4 (age) ×6 (dose) analysis of variance (the oldest age was excluded in this analysis) showed that the main effects for dose, $F(5,216)=10.76$, $p<0.001$ and age, $F(3,216)=8.67$, $p<0.001$, were significant.

Comparisons among different doses for each age showed that 15-day-old rats given saline and 0.5 mg/kg were less active than the same age given doses of 1.0 mg/kg and greater, and the 8.0 mg/kg group was more active than the 1.0 and 4.0 mg/kg groups. In 17-day-old rats, saline controls were less active than all other dose groups and the 0.5 and 16.0 mg/kg groups were less active than the 1.0-, 4.0-, and 8.0-mg/kg groups. At 21 days of age, saline controls were less active than all other dose groups, the 0.5 mg/kg group was less active than the 1.0-, 4.0-, and 8.0-mg/kg groups, and the 4.0 mg/kg group was more active than all other dose groups. In 36-day-old rats, saline animals were less active than the 1.0-, 4.0-, and 8.0-mg/kg groups, the highest dose group was less active than all other dose groups, and the 4.0 mg/kg group was more active than all other dose groups. In adults, the saline and 8.0 mg/kg groups were less active than other groups and the 1.0 mg/kg group was more active than all other dose groups. In general, these locomotor activity results show that the peak in the dose response curve is at higher doses in young rats than adults. In addition, it appears that the maximum increase from d-amphetamine occurs in 21-day-old rats.

EXPERIMENT 2

METHOD

Development of the central or peripheral nervous system may be responsible for the results of Experiment 1, because d-amphetamine acts on both central and peripheral catecholamine neurons [5,14]. Examining the behavioral changes produced by drugs which act in only the peripheral nervous system is a standard procedure for separating central and peripheral drug effects. Due to the relative inability to cross the blood-brain barrier, the central actions of para-hydroxyamphetamine are minimal, but in the peripheral nervous system para-hydroxyamphetamine and d-amphetamine are equipotent [5,14]. Therefore, if peripheral nervous system development is responsible for the results of Experiment 1, d-amphetamine and para-hydroxyamphetamine would be expected to produce comparable behavioral changes. The purpose of Experiment 2 was to examine the behavioral effects of para-hydroxyamphetamine.

Subjects, Apparatus, and Procedure

The rats were 15-, 17-, 21-, 36-, or 90-days of age, with the same characteristics as described in Experiment 1. They were injected with either saline or 1.0-, 4.0-, or 16.0-mg/kg of para-hydroxyamphetamine ($n=10$ rats for each age and each dose group) 20 min prior to receiving a single session of 100 two-way avoidance trials. The apparatus and other procedures were described in Experiment 1.

RESULTS

For each rat, the number of avoidance responses per block of 10 trials was determined and converted to percentage avoidance. Since the curves of Experiment 2 were very similar to the saline controls in Experiment 1 and those reported previously [2], the curves for Experiment 2 are not presented. These data were transformed by a square-root arc-sine transformation and the transformed data were analyzed by a 5 (age) × 4 (dose) × 10 (trial blocks) mixed analysis of variance. The main effects for age, $F(4,180)=21.32$, $p<0.001$ and trials, $F(9,1620)=61.79$, $p<0.001$, were significant. The age × trials interaction was significant, $F(36,1620)=9.09$, $p<0.001$ and this interaction appears to be due to the more rapid acquisition of older rats. The main effect for drug dose and all interactions involving dose were not significant.

For each rat, the number of intertrial responses per block of 10 avoidance trials was determined and these data were analyzed by a 5×4×10 mixed analysis of variance. This analysis showed that the main effect for age, $F(4,180)=7.07$, $p<0.001$, was the only significant term.

A 5 (age) × 4 (dose) analysis of variance of the number of crossings during the 8-min adaptation period revealed that only the main effect of age was significant, $F(4,180)=12.37$, $p<0.001$.

GENERAL DISCUSSION

The results of Experiment 1 clearly show that the effects of d-amphetamine on two-way avoidance, intertrial responses, and locomotor activity during adaptation vary as a function of development. Experiment 2 showed that para-hydroxyamphetamine did not alter these behaviors in any age examined. Since the potency of d-amphetamine and para-hydroxyamphetamine are similar in the peripheral nervous system [5,14], it appears that central nervous system changes are responsible for the behavioral effects of d-amphetamine. d-Amphetamine is thought to induce behavior changes by increasing the amount of catecholamines at postsynaptic receptor sites [5, 8, 12, 14] and catecholamine-containing neurons in the central nervous system of the rat develop from birth to about purberty [15,19]. Therefore, the differential behavioral effects of d-amphetamine in immature and mature rats may be due to development of central nervous system catecholaminergic neurons.

In adult rats, d-amphetamine is thought to alter responses which are important for performance of two-way avoidance. Lower d-amphetamine doses increase two-way avoidance by reducing freezing and increasing locomotor activity whereas higher doses induce a variety of stereotyped behaviors (head bobbing, sniffing, and gnawing) which are incompatible with two-way avoidance and locomotor activity [9, 12, 17]. The present findings with adults are consistent with this interpretation. Furthermore it appears that performance factors are important for two-way avoidance of younger rats. The high levels of avoidance on the first few blocks of trials, the similar pattern of avoidance responses and intertrial responses, and the significant correlations between avoidance and intertrial responses suggest that prior to 36 days of age d-amphetamine alters two-way avoidance by primarily affecting performance. Since d-amphetamine is thought to increase two-way avoidance and locomotor activity by excitation of noradrenergic neurons and to decrease these behaviors by excitation of dopaminergic neurons [9, 12, 14], and development of noradrenergic neurons precedes development of dopaminergic neurons by about 15 days [19], the age-dependent behavioral effects of d-amphetamine may be due to differential excitation of noradrenergic and dopaminergic neurons.

The developmental changes in shuttle crossings during adaptation, two-way avoidance, and intertrial responses

found in saline controls of the present experiments are comparable to previous developmental studies [2]. In normal rats, the CS intensity (75 or 100 dB) and US intensity (0.8 or 1.5 mA) do not alter two-way avoidance in 17-day-olds. In rats 21 days of age and older a more intense CS increases two-way avoidance and in adults both the CS and US intensity alter avoidance [2]. These findings suggest that d-amphetamine does not influence two-way avoidance in 15 and 17-day-old rats by altering sensitivity to foot shock or the CS, but the drug may change avoidance in older rats by altering sensitivity to foot shock and/or the CS. However, inspection of Fig. 1 reveals that avoidance in the youngest ages was highest on the first block of trials, suggesting that sensitivity to the CS and/or US was altered by amphetamine. Thus, no firm conclusions regarding drug induced changes in sensitivity to the CS and US can be reached on the basis of the available evidence.

The effects of amphetamines on locomotor activity in immature and mature rats appear to be inconsistent. d-Amphetamine (2.0 mg/kg) and dl-amphetamine (2.0, 5.0, and 10.0 mg/kg) increased open-field activity during a short test session administered approximately 20 min after treatment to a similar degree in adult and 20-day-old rats but the same doses have little effect in 30-day-olds [4,16]. A variety of d-amphetamine doses are reported to alter stabilimeter cage activity during a 2-hour session in 15-, 20-, 25-, and 100-day-old rats to a comparable degree [6]. The dose response curves of Experiment 1 are different still from these previous reports. Recent studies have shown that the effects of d- and l-amphetamine on photo-cell crossings and open-field activity in immature and mature rats vary as a function of time after drug administration [3,7]. That is, for some doses locomotor activity is highest at the beginning and end of the recording session and lowest in the middle; other doses initially increase locomotor activity and this is followed by a gradual decline. Furthermore, the doses which produce such changes differ as a function of development. Therefore, the time at which locomotor activity is recorded following amphetamines and the duration over which locomotor activity is collapsed may account for some of the apparently discrepant findings. Since d-, l-, and dl-amphetamine have different potencies on locomotor activity of immature and mature rats [3,12], potency of the various amphetamine isomers may also be an important variable in developmental psychopharmacological studies with amphetamines. In addition, during the normal course of development in rats there are different developmental trends in locomotor activity recorded in stabilimeter cages, photo-cell chambers, open fields, and shuttle crossings during adaptation [2, 3, 4, 6, 7, 19], suggesting that apparatus characteristics may be important for developmental findings with amphetamines.

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