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Neurobehavioral Effects of Perinatal AZT Exposure in Sprague–Dawley Weaning Rats

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BUSIDAN, Y. AND D. L. DOW-EDWARDS. *Neurobehavioral effects of perinatal AZT exposure in Sprague–Dawley weaning rats.* PHARMACOL BIOCHEM BEHAV **64**(3) 479–485, 1999.—Because AZT (azidothymidine, zidovudine, ZDV) has become the standard of care for preventing HIV transmission during pregnancy, we conducted a study to assess the possible neurobehavioral effects of this drug, using a rat model. Each litter was randomly assigned to a treatment group: vehicle, AZT 50, 100, or 150 mg/kg, or no treatment. Treatments were administered once daily via gastric intubation, prenatally from gestation day (G) 19–22 and then postnatally from postnatal day (PND) 2–20, except the nontreated group, which was only weighed every 4 days. On PND21 each rat was given a single dose of amphetamine (0.25, 0.50, 0.75, or 1.0 mg/kg) or saline and placed in the Accuscan activity chamber for 1 h of data collection and video taping. Results show that all of the behaviors analyzed produced statistically significant main effects of perinatal treatment, challenge drug, and time block. For distance traveled, there was a significant three-way interaction between treatment, sex, and time block, an effect that was independent of the effects of handling and injecting the rats. That is, within the males, the AZT 150 group displayed the greatest amount of locomotion, while among the females, the AZT 50 group was the most active. Furthermore, the AZT 50 group showed significantly less margin time (wall hugging) and more grooming than the nontreated control group. However, handling contributed to these differences because they were not observed when the vehicle-intubated group was used as the control. Across all treatment groups, amphetamine increased locomotion, the duration of rearing, and sniffing, while it decreased wall hugging, grooming, and time spent quiet. Complex interactions between amphetamine dose and time block were also seen for each behavior. In summary, these data indicate that amphetamine, at the doses used in the current study, alters behavior in the rat at 21 days of age, and that perinatal AZT exposure alters behavior in a single domain, locomotion with the threshold for this effect depending on genders. © 1999 Elsevier Science Inc.

AZT Zidovudine Amphetamine Distance traveled Margin time Neurobehavior

AN estimated 7000 infants are born to HIV-positive mothers each year in the United States, with 100,000 such births anticipated worldwide by the end of the decade. In February 1994, the AIDS Clinical Trial Group (ACTG) study 076 found that AZT (3′-azido-3′-deoxythymidine, zidovudine, ZDV) treatment in pregnancy and the newborn period prevented approximately 67% of the perinatal HIV infections, reducing the transmission rate from 26.6 to 8.3% (4). Due to this overwhelming evidence, the study was halted by a safety monitoring board, and shortly thereafter AZT administration during pregnancy became the standard of care in the United States.

Although there has been a limited amount of data published about the long-term neurobehavioral effects of prenatal AZT, another study using rats and rabbits found no overwhelming evidence to suggest that AZT alters open-field behavior (6). However, most studies failed to use the human-appropriate exposure period for the drug. AZT is administered to HIV-positive women beginning gestation week 14 and continuing to the peripartum period, and then the infant receives the treatment for the first 6 weeks of life. Although the exact timing of developmental events relative to birth is not completely known, the state of maturation of the human brain at 20 weeks gestation is relatively equivalent with the state of maturation of the rat brain on the day of birth (2). Therefore, we modeled the human exposure period by administering AZT during both the pre- and postnatal periods in the rat, and determined whether this treatment altered behavioral responses to an amphetamine challenge. Because the direct effects of AZT in the CNS are not well established, amphetamine, a stimulant that interacts with multiple neu-

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TABLE 1
CHARACTERISTICS OF RATS TREATED WITH AZT DURING THE PERINATAL PERIOD (MEAN ± SEM)

Treatment	Dam's Weight (g) G1	Dam's Weight (g) G22	Litter Size	% Male	% Female	Number of Pup Deaths
No treatment*	265.4 ± 6.5	423.0 ± 15.3	12.1 ± 0.8	51.1%	48.9%	0.067 ± 0.1
Vehicle†	260.7 ± 7.3	402.9 ± 12.1	13.0 ± 0.5	51.0%	49.0%	0.357 ± 0.1
AZT50†	265.2 ± 7.0	411.6 ± 10.7	13.2 ± 0.8	56.2%	43.8%	0.083 ± 0.1
AZT100†	259.2 ± 4.7	407.8 ± 8.5	13.0 ± 0.7	47.1%	52.9%	0.08 ± 0.1
AZT150†	256.5 ± 6.2	413.7 ± 12.0	13.7 ± 0.9	56.6%	43.4%	0.67 ± 0.3‡

n = 65 dams.
*No treatment group was only weighed every 4 days.
†Vehicle and AZT groups were intubated daily from G19-22 and then from PND2-20.
‡Statistically significant, Dunnett test.

rotransmitter systems (11), was selected as a challenge drug to examine the functional response of multiple CNS circuits. In a previous study for our lab, female Sprague–Dawley rats that were exposed to AZT throughout pregnancy displayed increased locomotor responses and decreased wall hugging to an amphetamine challenge at 21 days of age (1). Therefore, we hypothesized that we would observe behavioral differences in 21-day-old rats that received AZT during a clinically relevant period of development.

METHOD

Subjects

SUNY Institutional Animal Care and Use Committee approved all procedures. Adult virgin female Sprague–Dawley rats (VAF strain, Charles River, Wilmington, ME) were mated in our AAALAC-approved vivarium (20–22°C controlled humidity; 12-h light–dark cycle, lights turned on at 0700 h) with males of the same strain. Upon detection of a sperm-positive smear on the following morning, referred to as gestation day 1 (G1), the females were weighed, housed individually, and left undisturbed until gestation day 19 in 44 × 24 × 20-cm plastic cages containing wood chip bedding with ad lib food and water.

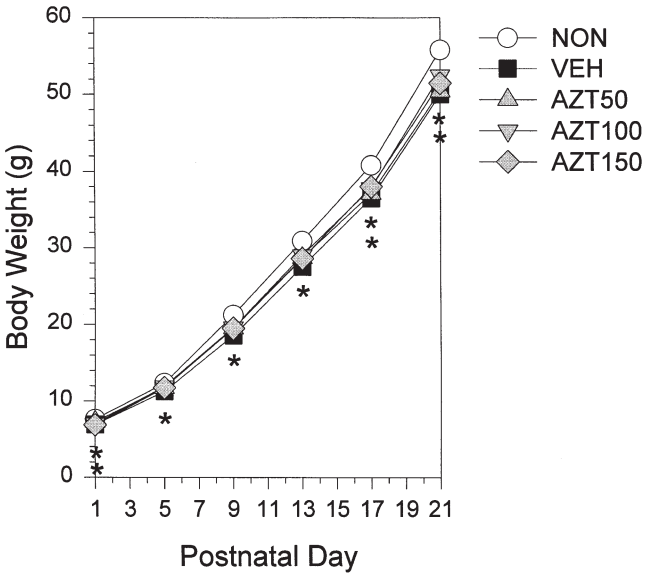

FIG. 1. Individual pups were weighed every 4 days from PND1–PND21. Litter means were plotted against postnatal age. Each line represents a treatment group: nontreated (NON), vehicle (VEH), or AZT 50, 100, or 150 mg/kg, that was administered from G19-PND20. The * indicates a significant difference from the nontreated group by post hoc comparison. n = 12–15 litters/treatment group.

Prenatal Dosing

Females were randomly assigned to one of the five treatment groups—AZT (50, 100, or 150 mg/kg), vehicle (sterile water, 7.5 ml/kg body weight), or no treatment. Between G19–22, the dams were weighed and gastrically intubated once daily using a 16-gauge straight-feeding needle. The nontreated control group was not intubated, but weighed on G19 and G22. On the day of birth (PND1), all litters were culled to 10, maintaining equal sex representation, if possible, and the pups were toe-clipped for identification.

Postnatal Dosing

Individual pups received daily gastric intubations of the same treatment (AZT or vehicle) from PND2-20. Intubations were conducted using 1″ PE 10 tubing between PND2–6, followed by PE 50 tubing that was gradually increased in length to 2″ for the 16–20-day-old rats. Pups in the nontreated group were only weighed every 4 days.

Behavioral Measures

On PND21, the pups were subjected to a behavioral study, the data of which will be the subject of the current report. In the morning, between 1000–1400 h, each rat was removed from its home cage, weighed, injected IP with a randomly assigned dose of amphetamine (0.25, 0.50, 0.75, or 1.0 mg/kg) or saline (1.0 mg/kg body weight), and immediately placed in the open Plexiglas box (42 × 42 × 30 cm; with no wood chip bedding), of the Digiscan Activity Monitor [model RXYZCM (16), Accuscan, Columbus, OH], for 60 min of behavioral recording. The Digiscan monitor has 32 infrared sensor pairs, with 16 along each side spaced 2.5 cm apart and 2.3 cm from the floor of the Plexiglas box. The sensors for vertical activity were not used in this study. The Plexiglas box and Digiscan monitor were within a white laminate chamber measuring 60 ×

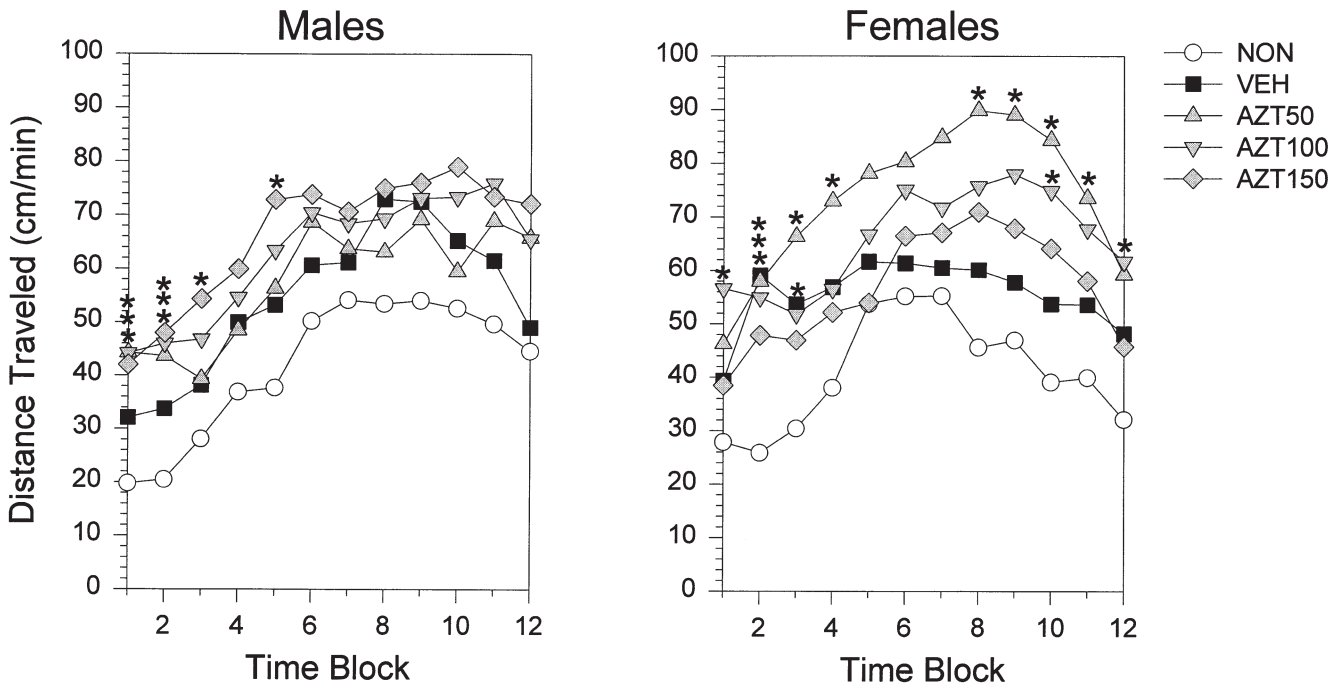

FIG. 2. Distance traveled produced a significant interaction between treatment group, gender, and time block. Plotted here are the weighted means (cm/min) for each treatment/gender group collapsed across challenge drug. Each line represents one of the perinatal treatment groups: nontreated (NON), vehicle (VEH), or AZT 50, 100, and 150 mg/kg. The * indicates a statistically significant Dunnett test using the nontreated group as the control (shown by the white circles). n = 54–63 male pups/treatment group, 46–54 female pups/treatment group. Error bars were eliminated for clarity. However, the standard error of the means ranged from 5.3 to 9.6 for the AZT 50 males, 5.4 to 9.8 for the AZT 100 males, 5.3 to 9.6 for the AZT 150 males, 5.0 to 9.1 for the vehicle-intubated males and the same for the nontreated controls. For females, the errors were somewhat greater, ranging from 6.1 to 9.6 for the AZT 50 group, from 6.0 to 9.4 for the AZT 100 group, 6.4 to 10.0 for the AZT 150 group, 6.1 to 9.5 for the vehicle group, and 5.9 to 9.2 for the nontreated group.

60 × 37 cm inside and containing two 6-watt light bulbs and a fan (model 30 CFM). Although the Accuscan Monitor collects information in 21 behavioral categories, we analyzed only distance traveled and margin time. (Margin time was defined as the time spent within 2.5 cm of a box wall, and will be referred to as wall hugging.) Behaviors were collected in minute intervals and then subsequently collapsed into 12 5-min blocks to simplify the analysis. The behavioral sessions were also video taped using a Panasonic video camera through a one-way window measuring 30 × 30 cm, and centered on the top of the laminate chamber. Following the session, each rat was ear clipped for identification, the rat was returned to its home cage, and the activity boxes were washed with soap and thoroughly rinsed. The videotapes were later analyzed using the Observer software (Noldus, The Netherlands) by an individual unaware of the gender, perinatal treatment, or challenge drug status. The videotaped behaviors, which were scored in seconds for 1 out of 10 min, starting at minute 9, included: total sniffing (sniffing on all fours—stationary or walking ± 1 s), rearing (subject is standing on hind legs with forelegs free in the air or in contact with a wall of the box ⩾1 s), and quiet (subject not engaged in any behavior—may be asleep or awake ⩾2 s). To determine the reliability of the observer, a sample of tapes was assessed both before and after all the video tapes were evaluated, and the data compared using the F-test. The results indicated that there were no signifi-

TABLE 2
EFFECTS OF AMPHETAMINE ON BEHAVIOR

	Amphetamine Dose (mg/kg)				
Behavior	Saline	0.25	0.5	0.75	1.0
Distance (cm/min)	12.4 ± 3.8	30.1 ± 3.8*	52.6 ± 3.8*	88.3 ± 3.8*	105.4 ± 3.8*
Margin (s)	58.6 ± 0.7	57.5 ± 0.6	55.4 ± 0.7*	52.7 ± 0.7*	49.6 ± 0.7*
Rearing (s)	1.4 ± 0.3	2.6 ± 0.3	4.0 ± 0.3*	5.1 ± 0.3*	6.6 ± 0.3*
Sniffing (s)	25.1 ± 1.0	36.8 ± 1.0*	45.5 ± 1.0*	48.1 ± 1.0*	48.2 ± 1.0*
Grooming (s)	4.1 ± 0.4	5.1 ± 0.4	3.9 ± 0.3	3.2 ± 0.3	2.3 ± 0.4*
Quiet (s)	29.1 ± 1.0	14.6 ± 1.0*	5.4 ± 1.0*	1.3 ± 1.0*	0.2 ± 1.0*

*Statistically significantly different from the saline-injected group $p < 0.05$, Dunnett's.

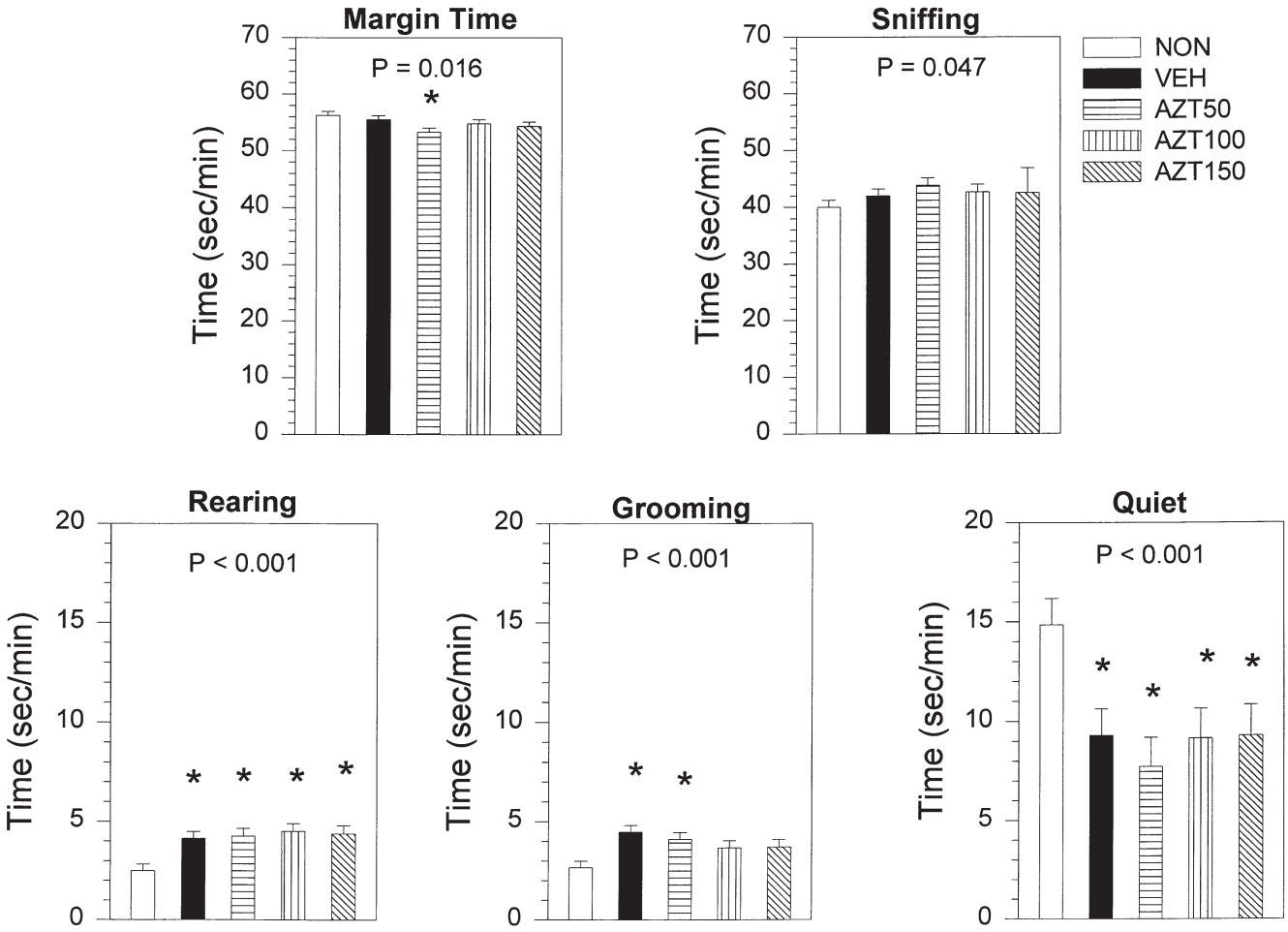

FIG. 3. Other behaviors (s/min) analyzed at 21 days of age in rats exposed to AZT during the perinatal period were collapsed across gender, amphetamine dose, and time block. Each bar represents the weighted average of one of the treatment groups: nontreated (NON), vehicle (VEH), or AZT50, 100 or 150 mg/kg. The *p*-value (ANOVA) for the main effect of treatment for each behavior is indicted in each panel. *Indicates a statistically significant difference from the non-treated controls ($p < 0.05$, Dunnett). $n = 100$–135 pups/treatment group.

cant differences in any of the observed behaviors in the tapes analyzed before the experimental series compared to after the series ($p > 0.80$), suggesting that the criteria used for each behavior and the way in which each behavior was scored were consistent across the time it took to complete the full experiment. Because a single observer examined all tapes, interobserver reliability was not a problem.

Drugs

AZT (3′-azido-3′-deoxythymidine; Sigma Chemical Co., St. Louis, MO) was dissolved in sterile water (Baxter) with sonication and some warming, and administered at 20 mg/ml for maternal doses and 10 mg/ml for pup doses. Amphetamine sulfate (Sigma Chemical Co.) was dissolved in saline (Baxter, 1.0 ml/kg body weight).

Statistics

The dams' body weights on G1 and G22 were analyzed using a two-way ANOVA, with day as the repeat measure. Litter size, sex ratio, and number of pup deaths, were also examined for treatment and gender effects using SYSTAT. Litter means for body weights (males and females nested) were analyzed every 4 days from PND1–21, using the GLM procedure for repeated measures in SAS. Behavioral data were analyzed by a four-way ANOVA with perinatal treatment (50, 100, or 150 mg/kg AZT, vehicle, or nontreated), sex (m or f), and challenge drug (amphetamine doses or saline) as between-subjects variables and the repeated measure, time block, as a within-subjects variable using SYSTAT. Data were expressed as mean ± standard error, and a *p*-value of $\leqslant 0.05$ was considered statistically significant. Post hoc Dunnett's test (two tailed) were used when appropriate.

RESULTS

Seventy-six females were mated which resulted in 65 litters of eight or more pups that could be included in our study: 15 nontreated, 14 vehicle, 12 AZT 50 mg/kg, 12 AZT 100 mg/kg, 12 AZT 150 mg/kg. Seven females (three vehicle, three nontreated, one AZT 50) failed to give birth, and necropsy revealed that there were no implantation sites. Two females (vehicle and AZT 100) delivered small litters of four to five pups, and were eliminated from the study. Only one dam (AZT 50) died due to complications from intubation. Finally, one AZT 150 dam that gave birth to a normal litter, appeared

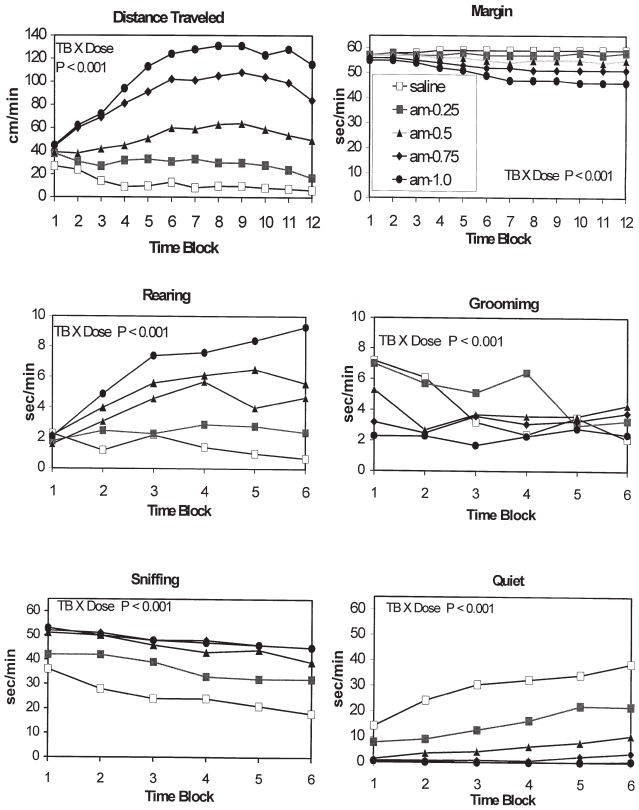

FIG. 4. The interactions between amphetamine dose and time block are shown for each behavior analyzed with the *p*-value (ANOVA) indicated in each panel. Margin time and distance traveled were collected in 12 5-min time blocks, while the remaining behaviors were collected for 1 min/10 resulting in six 1-min time blocks. Each line represents from 106 to 119 cases, and represents the weighted average because the data are collapsed across treatment group and gender. Error bars eliminated for clarity.

to have a paralyzed leg after the delivery, and was subsequently eliminated from the study. In all, there were no systematic, treatment-related differences in lost litters.

Results from the dam's body weight across time produced no significant main effect of treatments or interaction with time. However, there was a significant increase in body weight during pregnancy. There were no significant differences in litter size or sex ratio across treatment groups. However, there was a significant treatment effect for the number of pup deaths, with the AZT 150 mg/kg group having the highest number of occurrences compared to the nontreated group ($p = 0.046$, Dunnett test) (see Table 1). Pups were either found dead in their cage or missing the day after exhibiting weight loss, paleness, or an empty stomach. Two pups died directly from a failed intubation following bleeding from the mouth, and one died the next morning.

The litter means for pup body weight were compared and found to differ by perinatal treatment group, $F(4, 56) = 4.39$, $p = 0.037$, an effect that was primarily due the large weights in the nontreated controls. There was also a treatment × day interaction, $F(20, 280) = 2.62$, $p = 0.0003$, for body weight. Post hoc analysis for each day indicated that the nontreated group was significantly heavier than the vehicle group on each day. The nontreated group was also heavier than the AZT 150 group on day 1, and the AZT 50 group on days 17 and 21 (see Fig. 1).

Behavioral Analyses

For distance traveled, the males and females in the various treatment groups showed different activity patterns over time (Fig. 2). That is, there was a three-way interaction between time, treatment, and gender, $F(44, 5445) = 1.771$, $p = 0.001$. Within males, locomotor activity generally increased across the session, with the nontreated group remaining less active than all the treated groups and, within many time blocks, the AZT 150 group was the most active (significant differences noted in Fig. 2). For females, the AZT 50 group was the most active for all but the middle three time blocks. Because amphetamine dose did not interact with treatment, the data were collapsed across amphetamine doses and the weighted averages were plotted. In addition to the three-way interaction, there was a significant main effect of perinatal treatment, $F(4, 495) = 7.340$, $p < 0.001$, drug, $F(4, 495) = 106.134$, $p < 0.001$, and time block, $F(11, 5445) = 61.799$, $p < 0.001$, and significant two-way interactions between time and sex, $F(11, 5445) = 5.281$, $p < 0.001$, and time and challenge drug, $F(44, 5445) = 26.900$, $p < 0.001$, for distance traveled.

To determine whether the effects of AZT were artifactual due to the handling and intubation of the animals, the ANOVA was rerun without the nontreated group. All of these differences, including the three-way interaction, $F(33, 4268) = 1.943$, $p = 0.001$, remained significant, except for the main effect of treatment, establishing that the treatment-related effects were not solely due to differences between the nontreated control group.

The effects of amphetamine on locomotion were examined by collapsing across treatment and gender groups. All doses of amphetamine increased locomotion (Table 2). The animals receiving saline appeared to show little activity throughout the session, while the animals in the higher amphetamine dose groups exhibited the greater locomotor activity toward the end of the session than in the beginning (Fig. 4).

All of the remaining behaviors (margin time, sniffing, rearing, grooming, and quiet) produced significant main effects of perinatal treatment ($p < 0.05$) when the nontreated group was included in the analysis (Fig. 3). Because treatment did not interact with amphetamine dose, gender, or time block for any of these behaviors, the weighted averages for each treatment group are plotted. Post hoc Dunnett tests using the nontreated group as the control indicated that all treatment groups are different from control for rearing and quiet behaviors ($p < 0.05$, Dunnett test). That is, treatments increased rearing and decreased quiet compared to the nontreated control. For margin time (wall hugging), the AZT 50 group showed a decrease, while for grooming, this group showed an increase compared to the nontreated control. When the nontreated group is removed from the analysis, all of the significant differences are lost, indicating that there were significant effects of the experimental manipulations for all of these behaviors. There were no treatment-related effects for sniffing.

Amphetamine produced increases in rearing and sniffing and decreases in margin time, grooming, and quiet (Table 2), all with *p*-values <0.001. In addition, amphetamine significantly interacted with time block for each behavior (Fig. 4) such that for distance traveled, margin time, and rearing, the group receiving saline showed a relatively steady amount of the behavior, while those receiving the higher doses of am-

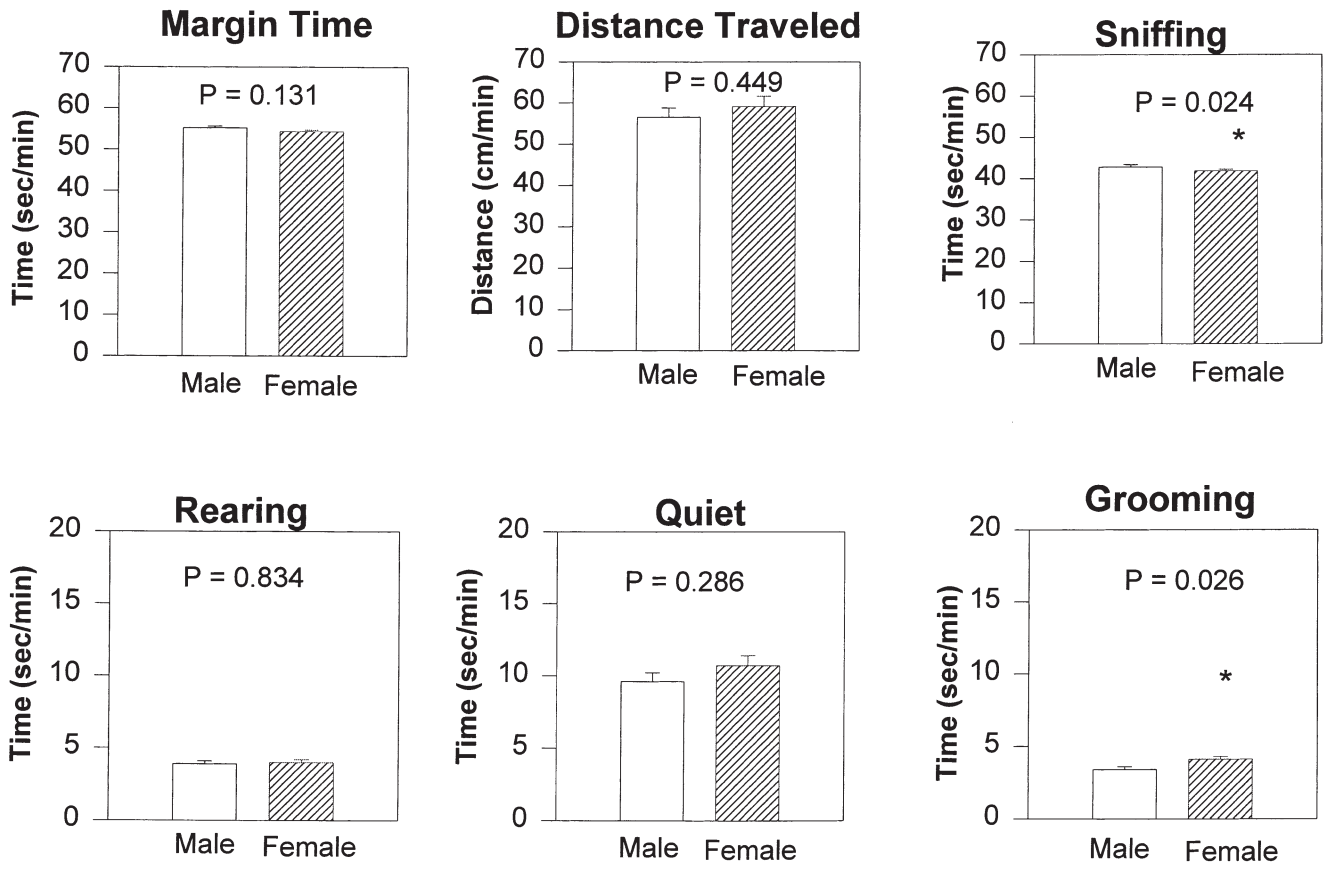

FIG. 5. Effects of gender on behavior at 21 days of age in rats exposed to AZT during the perinatal period. Data were collapsed across perinatal treatment, amphetamine dose, and time block. Each bar represents the weighted average (mean ± SEM) of 311 males or 277 females for each of the behaviors analyzed. The *p*-value (ANOVA) for the main effect of gender for each behavior is indicated in each panel.

phetamine showed great increases or decreases in the behavior. The opposite pattern was seen for grooming and quiet, where the high dose amphetamine group showed a consistent amount of the behavior and the lower amphetamine dose groups showed changes in the amount over time. All amphetamine-injected groups showed decreased sniffing over time, with the lower dose injection groups showing the greatest amount of change.

Gender differences were only seen for grooming and sniffing ($p = 0.026$ and 0.024, respectively, Fig. 5). Here females showed more grooming than males, while for sniffing, the opposite was seen. Furthermore, margin time and rearing also exhibited statistically significant time block × gender interactions (not shown). For margin time, the males initially showed greater amounts of wall hugging ($p = 0.022$ for the interaction), while the opposite was seen for rearing where the males initially rear less than the females, and later the males rear more ($p = 0.014$ for the interaction).

DISCUSSION

The results show that AZT treatment administered from G19–PND20 produces significant behavioral effects in the offspring that are dose specific and limited to distance traveled. Distance traveled produced a significant interaction between gender, treatment, and time block, such that the females overall showed a more sigmoidal-shaped pattern of locomotion while the males exhibited a simpler pattern across time (Fig. 2). In females, the AZT 50 group showed the greatest locomotion, while in males, the AZT 150 group was the most active. The effects of AZT remained significant when compared to the vehicle-intubated control group, suggesting that the experimental manipulations were not responsible for the effects of AZT on locomotion. Although AZT produced dose-specific neurobehavioral changes, other measures like litter size and maternal and pup weight gains were not affected by the treatment. Therefore, we can conclude that AZT at the doses administered transiently alters neurodevelopmental processes without producing overt toxicity.

Several studies that have examined the neurobehavioral effects of gestational AZT exposure found no changes (3,6,12). On the other hand, Applewhite et al. (1) found that AZT exposure throughout gestation altered locomotor and thigmotactic (wall hugging) responses to amphetamine at 21 days of age. In rodents, mild impairments in passive-avoidance performance have been reported by Calamandrei (personal communication) and Petyko (10), although the latter study did not present data to support their conclusions. Taylor et al. (13) found no effects on passive avoidance in gestationally AZT-exposed pups, yet deficits in negative geotaxis and olfactory discrimination were observed. In addition, using acoustic startle as a behavioral paradigm, we found that perinatal AZT, at 150 mg/kg, increased the amplitude of the acoustic startle response when measured at 75 days of age (unpub-

lished data). Another study that administered AZT acutely to adult females also found an increase in acoustic startle response (9). In macaques, Ha et al. (7) found that AZT exposure throughout pregnancy produced subtle behavioral delays. The AZT-exposed infants also took three times as many sessions as the control infants to meet criterion on a black–white learning test. Therefore, although many studies have found minimal neurobehavioral effects of prenatal or perinatal AZT, at least seven studies have found that AZT does produce at least transitory neurobehavioral effects in exposed offspring.

In the current study, several behaviors were affected by the daily handling and intubation procedures. Generally, the nontreated group was less active and exhibited lower amounts of rearing and grooming and more quiet than all the other groups, including the vehicle-intubated control group. Others, including Meaney et al. (8), have established that handling during the postnatal period produces long-term differences in the development of specific brain regions that regulate the response to stress and drugs such as amphetamine. Because our model necessitates handling of the animals to administer AZT or vehicle, use of a nontreated control group is helpful to determine whether handling effects contribute to the treatment-related behavioral differences. In the current study, only AZT-induced effects on locomotion were independent of the effects of handling.

Gender differences were observed only in two behavioral categories—sniffing and grooming—in the current study, perhaps due to the relative immaturity of the subjects. Although it is well known that amphetamine produces gender-related response differences in adults (5), and the use of amphetamine as a challenge drug might be expected to produce different responses across genders at 21 days of age, gender did not interact with amphetamine dose for any behavioral measure in this study. Other studies of 21-day-old rats receiving amphetamine with no postnatal handling have shown gender effects in response to amphetamine at the same doses (unpublished). Therefore, the extensive handling of the pups during the postnatal period may have masked this gender-related difference in amphetamine response seen at 21 days of age. Gender did play a prominent role in the treatment-related differences in distance traveled in the current study, because, in males, the AZT 150s showed the greatest amount of activity, while in females the lowest AZT dose group was most active. Further study is necessary to determine the neuropharmacological basis for this difference.

In conclusion, AZT exposure during the perinatal period does alter behavior under conditions of an amphetamine challenge study at 21 days of age. Although these behavioral changes do not appear to persist to adulthood (3), abnormal neurobehavioral functioning during critical periods of development may have long-term effects on the development of multiple neurochemical systems. Preliminary studies from our laboratory have determined that the AZT doses used in the current study produced clinically relevant therapeutic blood levels of drug. Therefore, further studies are warranted to determine whether these apparently transient behavioral alterations produced by clinically relevant doses of AZT affect the ontogeny of other behavioral domains.

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