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Problem Solving Following Neonatal Exposure to Cocaine, Ethanol, or Cocaine/Ethanol in Combination in Rats

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BARRON, S., L. HANSEN-TRENCH, D. H. KAISER AND T. M. SEGAR. *Problem solving following neonatal exposure to cocaine, ethanol or cocaine/ethanol in combination in rats.* PHARMACOL BIOCHEM BEHAV **53**(1) 197–203, 1996. – This study examined the effects of neonatal drug exposure on performance in a digging maze. Subjects were Sprague-Dawley rats, artificially reared (AR) and fed through a gastrostomy tube from postnatal days (PND) 4–10. The AR groups included a cocaine group (20 mg/kg/day cocaine hydrochloride), an ethanol group (4 g/kg/day ethanol), a cocaine/ethanol group (20 mg/kg/day cocaine and 4 g/kg/day ethanol), and an AR control group. A suckled control raised by its dam was also included. At approximately PND 55, subjects were tested in a digging maze paradigm. The digging maze required subjects to use a species typical behavior (digging) to solve a novel problem (gaining access to water). While neonatal treatment had no effect on acquisition of a simple runway task for water reward, neonatal exposure to cocaine and ethanol in combination resulted in impaired performance on the digging maze task. None of the other neonatal treatment groups showed impairments on this task. These findings suggest that exposure to these doses of cocaine and ethanol during neonatal development may have more serious effects on problem solving tasks in rats than exposure to either drug alone.

Neonatal exposure Prenatal cocaine effects Prenatal alcohol effects Polydrug exposure Problem solving

APPROXIMATELY 12 million people in the U.S. have used alcohol and cocaine concurrently. The greatest proportion of men and women using these drugs were between the ages of 18 and 36 (16). These findings are troublesome because this age range encompasses a large proportion of child-bearing years. Indeed, recent clinical studies have shown that the women that use cocaine during pregnancy rarely use cocaine alone (46). More commonly, these women are polydrug users and alcohol is the second most frequently reported drug (after tobacco) to be used in combination with cocaine.

A considerable literature exists regarding the effects of exposure to alcohol and cocaine during development. Fetal Alcohol Syndrome (FAS) has been well documented (47), and there are a number of studies reporting the more subtle effects that can occur in the absence of a full FAS (27). While there are some discrepancies in the clinical literature regarding the effects of prenatal cocaine exposure (22), there is evidence that cocaine-exposed infants display reductions in birthweight and head circumference (22,23,25) and show abnormal performance on certain neonatal tests such as the Brazelton Neonatal Behavioral Assessment Scale (11,14).

With the increased trend toward polydrug use, researchers are now attempting to differentiate the relative effects of each drug on development (23). This emphasis has shown that polydrug exposed infants appear to be at greater risk for a variety of compromised outcomes (29). However, these studies still have considerable interpretational problems due to the additional variables inherent with these clinical populations (i.e., undernutrition, inadequate prenatal care, other drug use, impoverished postnatal environment, etc.).

Animal models have been useful in trying to discern the effects of prenatal ethanol and cocaine exposure while controlling for many of the factors discussed above. Rodent models have provided a substantial amount of information regarding the behavioral consequences associated with prenatal exposure to these drugs. Prenatal ethanol exposure has been associated with deficits in a variety of behaviors including response inhibition (42), learning (3,28), activity (10), and mo-

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tor and balance coordination (2,26). Behavioral changes associated with prenatal cocaine exposure include learning deficits (20,45), activity (19), and reactivity (9,35,44) changes.

The literature from rodent models on the effects of cocaine and alcohol in combination is extremely limited. To the best of our knowledge, only one laboratory has directly addressed this question. Prenatal cocaine/ethanol exposure resulted in increased maternal toxicity, more pronounced birth weight deficits, increased postnatal mortality and delays in a number of developmental milestones relative to exposure to either drug alone (12,13).

The present study examined the effects of neonatal cocaine and/or ethanol exposure on a problem-solving task, the digging maze. The neonatal model used by our laboratory allows us to examine the effects of drug exposure during a developmental period that is equivalent, in terms of CNS development, to the last portion of the second trimester and the third trimester of human pregnancy (4). This period is characterized by rapid neuronal growth and proliferation and, thus, may be a particularly sensitive period for the behavioral teratogenic effects of cocaine and/or alcohol. While the pattern of CNS development is relatively similar across species, when birth occurs relative to CNS development differs. In rats, this developmental period extends into the first weeks after birth (15). Therefore, cocaine and ethanol administration to neonatal rats was used as a model to focus primarily on "third trimester" drug exposure.

There have been a number of studies assessing the behavioral effects of neonatal drug exposure in rodents. Neonatal exposure to ethanol in rats can result in a variety of behavioral alterations including overactivity (24), learning impairments (8,17), and motor deficits (32,33). There is only a limited literature on the effects of neonatal cocaine exposure. Still, neonatal cocaine exposure has been associated with impairments in balance (6) and some forms of learning (41). The literature on activity is mixed with hyperactivity and no effects on activity reported (5,6,21). To the best of our knowledge, there are no published studies on the effects of neonatal cocaine and alcohol exposure in combination.

The digging maze task that was used in this experiment required the subject to transfer a species-typical behavior (digging) to a novel detour problem (gaining access to water by digging through a maze filled with wood chips). This learning task has been considered to be a relatively complex problem-solving task because lesion studies to various cortical regions, the basal ganglia or the limbic-hypothalamic system, impairs performance of this task (49,50).

METHOD

Mating Procedure

Parent animals were Sprague–Dawley rats obtained from Harlan Laboratories. Pregnant rats were individually placed in plastic breeding cages with ad lib chow and water and maintained in a temperature controlled nursery with a 14 L : 10 D cycle. Twenty-four hours after parturition, litters were culled to 10 pups, maintaining 5 males and 5 females whenever possible.

ARTIFICIAL REARING

Neonatal Surgery

On postnatal day (PND) 4, pups from each litter were weighed and randomly assigned to one of five treatment groups; an artificially reared (AR) cocaine group (20 mg/kg/day cocaine), an AR ethanol group (4 g/kg/day ethanol), an AR cocaine/ethanol group (20 mg/kg/day cocaine and 4 g/kg/day ethanol), an AR control group that received a stock milk formula, or a sham surgery group that remained with their dam as a suckled control. Within each litter, one male and one female pup were assigned to each of the five treatment groups. This ensured that only one subject per sex from each litter represented each of the neonatal treatment groups (1).

The surgical procedure used for the artificial rearing technique has been described in detail in previous reports [see (43) for additional details]. Briefly, on PND 4 each pup was lightly anesthetized with a 50% halothane/50% compressed air mixture and implanted with an intragastric cannula (Clay Adams PE-10 polyethylene tubing). The sham surgery group was also anesthetized and received a sham surgery with no cannula implanted. After recovery from anesthesia, the sham controls were returned to their home cages and raised with their dam and the AR pups were placed in the AR apparatus.

Artificial Rearing and Maintenance

The AR pups were individually housed in covered styrofoam cups that contained wood chips and a piece of artificial fur. This fur was attached to the side of the cup and served to help compensate for any behavioral depression associated with maternal deprivation (48). Each cup was placed in a second styrofoam cup that was partly filled with sand that acted as ballast and floated in a stainless steel tank of aerated water. The water temperature was set at 48°C for PND 4–5 and then reduced 2° every 2 days thereafter, resulting in a final temperature of 42°C on PND 10–11.

The AR pups were fed for 20 min every 2 h, resulting in 12 daily feeds. Milk was infused by a multisyringe infusion pump (Harvard Apparatus #2265) and a timer. The milk formula was a variation of the Messer diet used as a substitute for rat milk (51). Drugs were added directly to the milk each day. Drug exposure was concentrated during the four daily feeds that occurred between 1000 and 1600 h, to mimic a binge model of drug use. For the remaining eight daily feeds, all AR pups received a stock milk formula.

The amount of milk formula infused each day was 30% of the pups' average daily body weight. Pups were maintained under these conditions from PND 4–9. On PND 10, all AR animals were given the stock milk formula to allow the subjects to recover from any potential acute effects of the drugs or withdrawal from the drugs.

From PND 4–9, the sham controls were also weighed daily. During the AR period, the shams were maintained with a dam and surrogate pups. Litters were kept at 10 pups/litter during this time to maintain lactational performance of the dam until the AR pups were returned to their litter.

On PND 11, the cannulas of the AR subjects were cut close to the abdominal wall. Both AR pups and shams were earmarked for later identification, bathed in a slurry of maternal feces and warm water, and returned to the dam. With this procedure, there was virtually no pup mortality. Subjects were weaned at 21 days of age and housed in groups of two to three same-sex subjects.

Behavioral Testing

The digging maze apparatus was originally designed by Thompson and colleagues (50). The maze consists of a simple runway with a start box and a goal box. The start box (22.5 × 18 × 20 cm), goal box (30 × 24 × 20 cm), and floor of the runway were made of wood coated with polyurethane, and

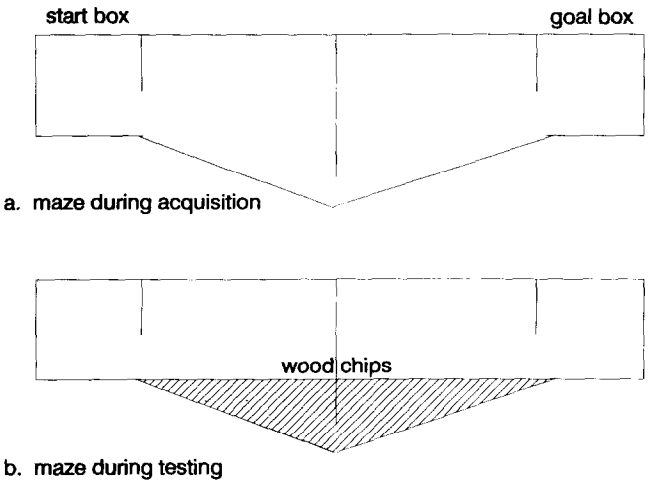

FIG. 1. A depiction of the digging maze set up for acquisition training (a) and the test day (b).

the sides of the runway were made of Plexiglas. The runway was 60 cm in length and sloped downward from both the start and goal boxes. The runway was divided into two sections by a vertical wood compartment that extended from the top of the maze to within 5.8 cm of the floor (see Fig. 1).

At PND 45-50, subjects were individually housed in clear plastic breeding cages (45 × 24 × 20 cm) with fresh wood chips to a height of 6.3 cm. For approximately 1 week, cages were checked daily for the displacement of wood chips as evidence of digging behavior in the home cage.

Two days prior to testing, subjects were weighed and placed on a water-deprivation schedule in which subjects received water access for 10 min daily. Digging maze testing began on PND 52-58 and was conducted over 3 days; an habituation day (day 1), an acquisition day (day 2) and a test day (day 3). All subjects were tested between the hours of 1000 and 1400 h.

During habituation, each subject was given 10 min to explore the digging maze. Water and sweetened wet mash (Noyes Formula P Purified Rodent Diet Pellets dissolved in water) were available in the goal box. The latency for their head and forepaws to enter the goal box was recorded.

During acquisition, subjects were given 10 acquisition trials with an ITI of 90-180 s. Each trial consisted of placing the rat in the start box and raising the start box door. In most instances, the rat would readily leave the start box, traverse the runway, enter the goal box, and ingest the water or mash. After the subject consumed water or mash for 5 s, the subject was returned to its home cage. On the tenth trial, subjects were allowed to ingest the water or mash for 200 s. On each trial, the latency to reach the goal box was recorded. During both habituation and acquisition phases of this experiment, wood chips were scattered on the floor of the runway.

On the test day, the runway was filled with wood chips to the level of the start and goal boxes (see Fig. 1). The subject was placed in the start box and allowed to enter the runway. To gain access to the mash and water, the subject was required to dig through the wood chips to reach the goal box. The subject was given 180 s to initiate digging. If the subject failed to begin digging by 180 s, it was returned to its cage and then given a second trial after approximately a 180 s ITI.

If a subject failed to reach the goal box after two trials, it was manually placed in the goal box and allowed to ingest water and wet mash for 5 s. The subject was then returned to its home cage for a 180 s ITI. This was followed by a training trial in which the sawdust was partially displaced from the center of the runway, allowing the subject to traverse the runway without having to dig through the wood chips. When the subject reached the goal box, it was given free access to the water and mash for 10 s before being returned to its cage. After another ITI, the subject was given a final test trial with the wood chips once again added to the maze to the level of the start and goal box. Experimenters were blind to treatment condition throughout all phases of the experiment. The number of subjects ranged from 9-12 per sex and neonatal treatment group.

The dependent variables were recorded using a real-time event recorder (NEC #PC-8300) and included latency to begin digging, trial latency (latency from the start of the trial to reaching the goal box), digging time (the amount of time from the start of digging to reaching the goal box), and the number of trials necessary to solve the task. If subjects did not dig on the first trial, they were assigned a 180 s ceiling for the latency to begin digging. Subjects that did not reach the goal box in a trial were assigned a 300 s ceiling for both trial latency and digging time. This 300 s ceiling was chosen because subjects that were successful in completing the task did so in 250-290 s range; therefore, 300 s appeared to be a ceiling for successful completion of the task.

RESULTS

The data were examined using analysis of variance (ANOVA) with planned comparisons and repeated measures where necessary. The accepted probability value was $p < 0.05$ unless otherwise stated. All subjects showed evidence of digging in their home cage. There were no differences across

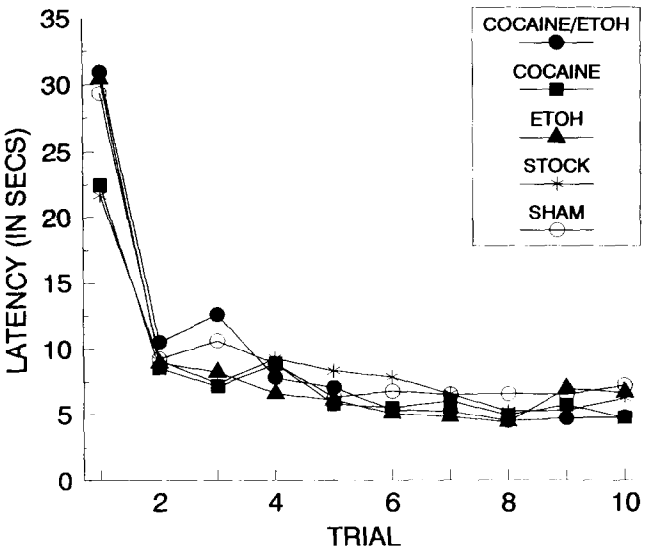

FIG. 2. Acquisition latencies (in s) across the ten trials as a function of neonatal treatment (20 mg/kg cocaine hydrochloride + 4 g/kg ethanol, 20 mg/kg cocaine hydrochloride, 4 g/kg ethanol, AR stock group, and sham control, for the cocetoh, cocaine, ethanol, stock, and sham groups, respectively).

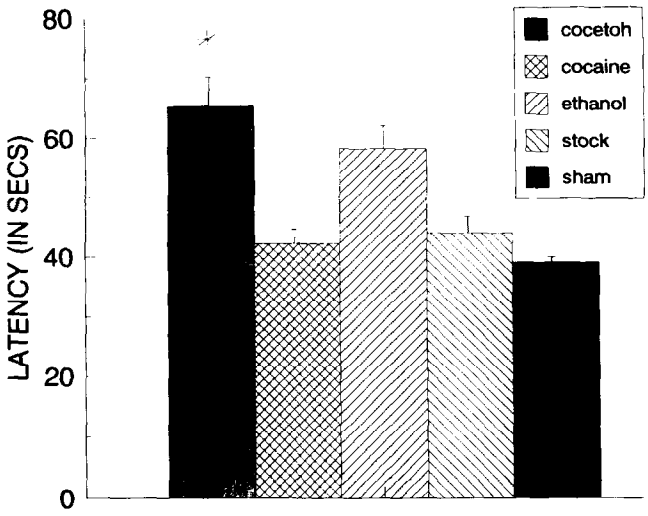

FIG. 3. Latency (in s) to begin digging on the test day (180 s ceiling) as a function of neonatal treatment (20 mg/kg cocaine hydrochloride + 4 g/kg ethanol, 20 mg/kg cocaine hydrochloride, 4 g/kg ethanol, AR stock group, and sham control, for the cocetoh, cocaine, ethanol, stock, and sham groups, respectively). The asterisk signifies the group significantly differs from the two controls ($p < 0.05$).

neonatal treatment groups in the latency to enter the goal box during habituation (data not shown). In addition, all subjects showed evidence of acquisition in the simple runway task and there were no differences across neonatal treatment groups on this measure ($ps > 0.25$) (see Fig. 2).

The latency to begin digging on the test day is presented in Fig. 3. The ANOVA revealed that exposure to the cocaine/ethanol combination resulted in a delay in the latency to begin digging relative to the two control groups, $F(1, 98) = 4.92$, which did not differ from each other. Subjects exposed to either drug dose alone did not differ from controls. While visual observation suggested a trend for the ethanol exposed group to differ from controls, this was nonsignificant, $p > 0.10$. Cocaine/ethanol exposed subjects also took marginally longer than controls to complete the trial, $F(1, 98) = 3.80$, $p = 0.052$ (data not shown). There were no differences across neonatal treatment groups in the digging time measure suggesting that all groups performed similarly once they began to dig (data not shown). There were also no differences across neonatal treatment groups in the number of trials to successfully complete the task (see Table 1). Two subjects never learned the task; one of these was a female in the cocaine/ethanol-exposed group and the other was a male in the 20 mg/kg cocaine-exposed group.

Two additional analyses were conducted on the above data. In the first series of analyses, the data were examined including only those subjects that successfully completed the task in a single trial. This resulted in a reduction in total n from 103 to 92. The number of subjects that were eliminated from each neonatal treatment group are presented in Table 2.

The analyses of the subset of data excluding these 11 subjects suggested that among subjects that solved the task in a single trial, there were no neonatal treatment effects on the latency to begin digging ($ps > 0.20$). However, the cocaine/ethanol subjects that solved the task in one trial exhibited significantly longer latencies to complete the trial relative to controls, $F(1, 87) = 4.33$ (see Fig. 4). In addition, the 20 mg/kg cocaine-exposed offspring that learned the task in one trial displayed faster digging time than controls, $F(1, 87) = 3.99$ (data not shown).

TABLE 1

THE AVERAGE NUMBER OF TRIALS (±SEM) TO SUCCEED ON THE DIGGING MAZE TASK

Neonatal Treatment Group	Number of Trials
Cocaine/ethanol	1.2 ± 0.10
20 mg/kg cocaine	1.1 ± 0.07
4 g/kg ethanol	1.1 ± 0.14
Stock	1.2 ± 0.14
Sham	1.2 ± 0.10

The second set of additional analyses examined the latency scores for each subject on the trial in which they successfully completed the digging maze task. All subjects were included in this analysis with the exception of the two subjects that never successfully performed the digging maze task. There were no differences across neonatal treatment groups in the latency to begin digging or in digging time when the data was examined on the successful trial. However, the cocaine/ethanol group still displayed longer trial latencies than either control group, $F(1, 96) = 4.63$. Because the trial latency measure represented the latency to begin digging and the digging time, it is likely that the cocaine/ethanol group exhibited nonsignificant delays in the two dependent variables, which when summed together resulted in a statistically significant effect.

Body weights are presented in Table 3. There was a significant main effect of neonatal treatment, $F(4, 93) = 2.47$, $p = 0.05$ and a main effect of sex, $F(1, 93) = 403.19$, $p < 0.001$. Males weighed more than females, and the post hoc Duncan's tests revealed a drug effect. All neonatal drug-exposed groups weighed less than the sham control group, $ps < 0.05$. The stock controls did not differ from either the AR drug-treated groups or the sham control group.

DISCUSSION

Neonatal exposure to 20 mg/kg/day cocaine and 4 g/kg/day ethanol in combination resulted in impaired performance in a digging maze detour task. Subjects exposed to this drug combination displayed longer latencies to begin digging and longer trial latencies. In contrast, all drug-exposed groups learned the simple runway task for water reward. These results suggest that while simple learning was not affected, exposure to these doses of cocaine and ethanol in combination had more deleterious effects than exposure to either drug alone on this problem solving task.

A number of factors could have contributed to the impaired performance displayed by the cocaine/ethanol sub-

TABLE 2

NUMBER OF SUBJECTS IN EACH GROUP THAT DID NOT SOLVE THE TEST IN ONE TRIAL

Neonatal Treatment Group	Number of Subjects
Cocaine/ethanol	3
20 mg/kg cocaine	2
4 g/kg ethanol	1
Stock	2
Sham	3

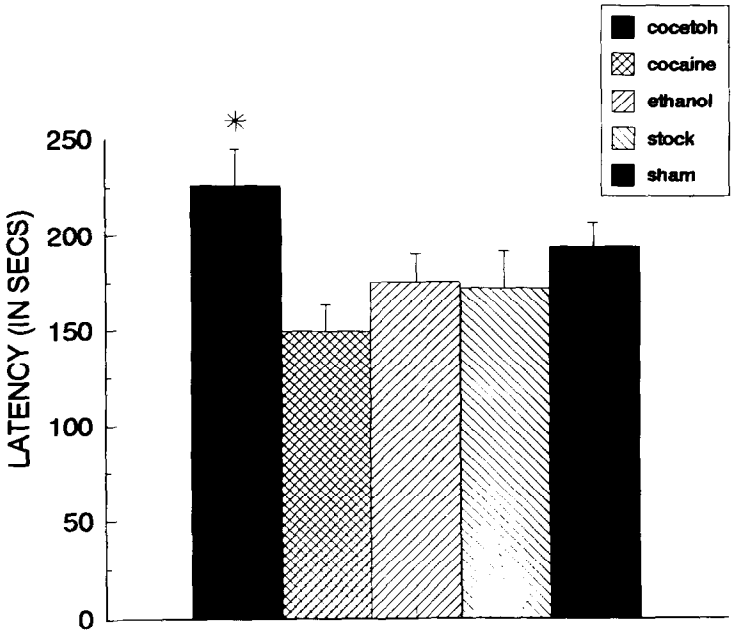

FIG. 4. Trial latency (in s) on the test day including only those subjects that succeeded in the digging maze task in one trial as a function of neonatal treatment (20 mg/kg cocaine hydrochloride + 4 g/kg ethanol, 20 mg/kg cocaine hydrochloride, 4 g/kg ethanol, AR stock group, and sham control, for the cocetoh, cocaine, ethanol, stock, and sham groups, respectively). The asterisk signifies the group significantly differs from controls ($p < 0.05$).

jects. Motivation, visual discrimination, response flexibility, vestibular and proprioceptive integration, and motor performance all play a role in performance of this task. While some of these contributing factors cannot be ruled out, all subjects appeared motivated to gain access to the water reward because acquisition of the straight runway task for water reward was learned relatively quickly and equally well by all neonatal treatment groups.

It is also unlikely that the cocaine/ethanol-exposed animals were so severely motorically impaired that they could not dig. All cocaine/ethanol subjects displayed digging in their home cage. In addition, the cocaine/ethanol group dug through the wood chips to reach the goal box within one to two trials and did not differ from controls in the amount of time spent digging to reach the goal box. Although previous studies have reported that neonatal exposure to either cocaine (7) or ethanol (32) caused deficits in motor coordination and balance, the findings from this study suggest that the motor coordination necessary for digging was unaffected by any of the neonatal drug exposures.

TABLE 3

BODY WEIGHTS (IN g) ±SEM

Neonatal Treatment Groups	Number of Subjects
Cocaine/ethanol*	197.7 ± 5.1
20 mg/kg cocaine*	199.0 ± 7.3
4 g/kg ethanol*	196.1 ± 5.2
Stock	204.9 ± 6.1
Sham	215.2 ± 7.0

*Significantly differs from sham controls ($p < 0.05$).

The deficit in performance displayed by the cocaine/ethanol group appears most likely to be related to the ability to solve the problem. As stated above, there were no differences across neonatal treatment groups in the length of time required to dig through the maze once the subject began digging, which suggests that once the subject solved the maze problem, subjects from all treatment groups performed similarly. The deficit may lie, then, in response flexibility or applying a species-typical behavior to a novel problem. Alternatively, it is possible that the cocaine/ethanol exposed offspring did not recognize the digging maze filled with wood chips as the same context in which acquisition training occurred. Therefore, the deficit could also be a cue-related memory impairment. Another hypothesis that cannot yet be ruled out is that the cocaine/ethanol exposed offspring may be more reactive to novel stimuli and, thus, were distracted by what appeared to be a novel test chamber.

It was intriguing that the cocaine-exposed offspring showed faster digging time scores than controls when the data analyses included only those subjects that completed the task in a single trial. This effect was not apparent when all subjects were included in the analyses nor when the digging time scores were examined using the latency scores for each subject on the trial in which they successfully completed the digging maze problem. It is unclear whether this indicated a difference in the subpopulation of cocaine-exposed offspring that were able to solve the task in a single trial (i.e., hyperactivity) or whether this effect was simply sampling error. In contrast, regardless of how the data was analyzed, the cocaine/ethanol subjects were impaired on performance of this task.

The ethanol and cocaine doses used in this experiment were

what are typically employed as low doses in our laboratory. It is unknown whether neonatal exposure to higher doses of ethanol could affect digging maze performance; however, subjects exposed to a higher dose of cocaine (40 mg/kg) showed relatively normal behavior on this digging maze task (manuscript in preparation). Additional work using a wider range of doses is clearly needed to gain a better understanding of the interaction between cocaine and ethanol and their effects on development.

The results published by Thompson and colleagues suggested that subcortical lesions and lesions of the parietal cortex including the limbic-hypothalamic system resulted in more severe impairments than other areas, although virtually all lesions in cortical or subcortical areas resulted in impaired performance on this digging maze task (49,50). Their findings may provide some insight regarding the regions of the CNS that should be examined following neonatal exposure to cocaine/ethanol in combination. It should be noted, however, that one important difference between our study and that by Thompson and colleagues was the severity of impairment. In Thompson's original lesion studies, less than 20% of the subjects in the lesioned group successfully performed the task in a single trial (49,50). In contrast, the majority of subjects in our study were able to perform the task in a single trial. These findings were not surprising, however, because we would have predicted that neonatal drug exposure would likely result in more subtle brain damage than that expected by a gross lesion.

These findings also suggest that the digging maze paradigm may be a useful screening tool to assess the behavioral teratogenicity of drugs. It is a relatively easy test to administer yet it can assess what might be considered higher cognitive function (i.e., response flexibility and problem solving).

The use of cocaine and ethanol in combination has increased considerably in recent years. Clinical and animal studies have shown that concurrent use of cocaine and ethanol results in a variety of effects including enhanced and prolonged euphoria (31,37), increased stimulation (30), a potentiation of ethanol-induced loss of righting reflex (34) and ethanol-induced disruption on a rotorod task (39,40), impaired immune function (38), increased hepatotoxicity (36), and increased lethality (18). The findings from our study suggest that concurrent use of cocaine and ethanol at least at the doses employed in this study also results in increased behavioral teratogenicity.

The neonatal drug exposure model used in this study focused on a period of CNS development that encompasses primarily the third trimester of human pregnancy. These findings provide support for the importance of this developmental period in the behavioral teratogenic effects of cocaine and ethanol. It is probable that polydrug use may be contributing to the discrepancies that have been reported in both clinical and preclinical studies on the effects of cocaine on development. Clearly, more work is needed to further understand the consequences associated with multiple drug exposures.

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