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Maze Exploration in Juvenile Rats Treated with Corticosteroids During Development[1]

MARI S. GOLUB

Behavioral Biology Unit, California Primate Research Center, Davis, CA 95616

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GOLUB, M. *Maze exploration in juvenile rats treated with corticosteroids during development.* PHARMAC. BIOCHEM. BEHAV. **17**(3) 473–479, 1982.—The possibility of permanent damage to brain function after developmental corticosteroid treatment has been raised in connection with therapeutic use of potent synthetic corticosteroids during the period of brain development in the human fetus and infant. In the present study, brain function was evaluated in rats treated during brain development with triamcinolone acetonide (TAC). A subtoxic dose (0.9 mg/kg), which did not retard growth, was used. TAC treatment at two periods of post-embryonic brain development (day 0 and day 10 postnatal) led to deviations from normal exploration strategies in a radial maze. Treatment on day 16 gestation was effective only in males. Neonatal TAC-treatment also affected spontaneous alternation in a T-maze. Measures which reflected arousal-activity levels during behavioral tests, such as time to initiate exploration and time to complete exploration, were not affected by treatment. These results suggest that the development of complex brain function in rats can be altered by subtoxic corticosteroid treatment in the perinatal period.

Corticosteroids Behavior Radial maze T-maze Rats Neonates Brain development Triamcinolone

TREATMENT of rodents with large doses of corticosteroids (cortisol or corticosterone) during the first few days after birth produces a characteristic syndrome including stunting of growth and retardation of motor development [28,29]. Effects of this treatment on the developing brain include a permanent reduction of brain weight and DNA content [7,15] and changes in neuronal morphology [20,31].

Behavioral changes are also seen in rodents as part of the corticosteroid runting syndrome. These include: retarded appearance of simple reflex and motor patterns [30], a transient increase in spontaneous motor behavior in post-weaning period [16], a higher level of responding on operant schedules [15], greater sensitivity to shock in a shock avoidance situation [22], and decreased sexual responsiveness [34].

Little is known, however, about the behavioral consequences of developmental corticosteroid treatment at doses which do not produce the severe general developmental toxicity described above. Such information is of interest in view of the clinical utility of corticosteroid therapy reigmens in pregnancy and early childhood.

In particular, the use of corticosteroids as preventive therapy for neonatal respiratory distress syndrome (RDS) has prompted attempts to anticipate harmful effects of low level prenatal treatment on the brain [3, 25, 33]. Recently, Johnson, *et al.* [17], have reported that prenatal betamethasone treatments which influenced lung maturation in monkeys also reduced the head circumference of the fetus. Frank and Roberts [12] have shown that low level prenatal dexamethasone treatment in rats lowers the brain weight of the near-term fetus. On the other hand, clinical studies of children treated antenatally with betamethasone have not demonstrated cognitive performance deficits [18].

The present experiment examines exploratory behaviors in young rats treated during brain development with subtoxic doses of triamcinolone (TAC). This synthetic corticosteroid was chosen for study because it is the most potent corticosteroid teratogen in rodents [35], and it also exerts a teratogenic action in the CNS in primates [13,14]. Spatial exploration was selected as the measure of behavioral function because it is an important element in the adaptive behavior of rats. It can also be effected by treatments that damage the developing brain [5,27].

EXPERIMENT 1: SUBTOXIC DOSE RANGE

In order to determine an appropriate dose level for the behavioral studies, developmental toxicity of TAC was investigated in rats injected subcutaneously on the day of birth with dosages ranging from 2 μg to 4000 μg per pup. At the higher doses, 200 to 4000 μg, the typical corticosteroid runting syndrome was observed as outlined in Table 1.

At doses between 8 μg and 80 μg per pup, symptoms decreased in severity with dosage and at 2 dose levels under 8 μg per pup (or about 1 mg/kg) no signs of the toxicity syndrome were observed.

Dose levels for the behavioral experiments were thus set slightly below 1 mg/kg at 0.9 mg/kg. Records of mortality and

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TABLE 1

RELATIONSHIP BETWEEN NEONATAL TAC DOSAGE AND OCCURRENCE OF CORTICOSTEROID RUNTING SYNDROME

Dose	Animals*	Mean 5 Day Weight Change	Mean Survival Time (Days)	
4 mg	M+F	−13%	4.7	Corticosteroid Runting Syndrome:
2 mg	M+F	−14%	4.5	
1 mg	M+F	−12%	4.5	
400 μg	M+F	−12%	4.5	stunted growth
200 μg	M+F	−11%	5.3	shortened snout
80 μg	M+F	−13%	8.0	sparse hair
50 μg	F	−01%	8.0	thin skin
	M	−12%	9.0	lack of subcutaneous fat
20 μg	F	−01%	14.0+	weakness and tremor
	M	−15%	9.0	delayed milestones
8 μg	F	−01%	14.0+	
	M	−12%	9.0	
4 μg	F	+15%	14.0+	
	M	+11%	14.0+	No Runting Observed
2 μg	F	+16%	14.0+	
	M	+12%	14.0+	

*M=male; F=female; N, 2–4/group.

weight gain obtained during the behavioral studies and of organ weights obtained at necropsy showed no drug effects on these parameters.

EXPERIMENT 2: EFFECT OF NEONATAL TAC-TREATMENT ON SPATIAL EXPLORATION

The effect of neonatal TAC-treatment on spatial exploration was studied using the radial maze and the T-maze (Fig. 1). The T-maze and the radial maze have been used to study spatial exploration in adult rats after hippocampal lesions [9,21], or after developmental brain damage [5,27]. Those treatments lead to characteristically rigid exploration patterns. In the T-maze, the animals explore one of the two choices rather than alternating choices as a normal rat does. In the radial maze, the animal uses a repetitious pattern in moving from central area into successive choice arms. Maze behaviors were tested between 20 and 30 days of age because spontaneous alternation in the T-maze has been reported to develop during this time period in the rat [4, 10, 11].

METHOD

Design

A littermate control design was used in which each TAC-treated animal was matched to a vehicle-treated littermate of the same sex and birthweight. Experiments in the T-maze and radial maze were each conducted in two replicates of four litters, half of each litter being assigned to the TAC-treatment group and half serving as controls.

Procedures

Pregnant albino female rats, 60–90 days old, were received from the supplier (Simonson Laboratories, Gilroy, California) on 17–19 days of gestation and were maintained on 12–12 light cycle (dark cycle 10 p.m. to 10 a.m.) with food and water available continually.

On postnatal day 0, pups were removed from nest for neonatal drug or vehicle injection. On postnatal days 5, 10 and 15, pups were weighed and bedding was changed without disturbing the nest area. On postnatal day 21, litters were weighed and weaned by transferring pups in groups of five, balanced for sex and treatment group, to separate plastic cages.

For neonatal injections, mother was removed from the breeding cage within 12 hours after birth. Litters were then removed with as little disturbance of nest area as possible, and each pup was placed in one compartment of an egg carton and warmed to 27°C with a heat lamp; they were then weighed, sexed and marked by injecting ink under the dorsal skin of the foot pad area [1]. Pups were matched in pairs for weight and sex, and one pup in each pair was assigned to the drug treatment group. Litters were culled to ten by eliminating animals without weight-sex matches.

Injections

Triamcinolone acetonide suspension (Kenalog-40, Squibb) was diluted with vehicle to a concentration of 0.4 mg/ml just prior to injection. All injections were delivered subcutaneously in neck region to hand-restrained animal at a dose of 0.9 mg/kg, using a 100 μ liter syringe and 27 gauge needle. Like-volume injections of vehicle served as control injections.

Behavioral Testing—T-Maze

A floorless T-maze constructed of plywood painted black was used for testing. Paper towels were placed under the maze and formed the floor. The towels were changed after testing of each animal. Three maze arms, 4.5×14×16 cm, could be assembled to be used interchangeably as start arm and right and left goal arm. Guillotine doors were inserted in each arm to form a start compartment and to confine the

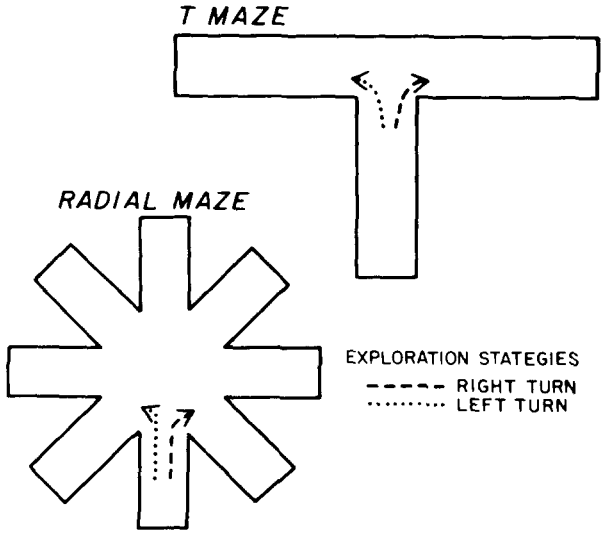

FIG. 1. Schematic of spatial mazes. In the T-maze, the animal is released from the start compartment, and can choose a right or left turn exploration strategy at the choice point. In the radial maze, the animal chooses a right or left turn strategy as it exits from one arm and moves to another.

animal after a goal arm was chosen. The maze was located in the home cage room.

Prior to testing, animals were adapted to the maze by placing each weanling cage group (5 pups) in the maze for a 5-min period on day 17 of age.

Animals received two daily test sessions of two trials each between 21 and 30 days of age with at least four hours intervening between the two daily sessions. Order of testing of each weanling cage group, and each animal within the cage group, was determined with a random schedule.

At the beginning of each session, the animal was placed in the start compartment for 3 sec, the door was removed and a timer was activated to record choice latency. If the animal failed to leave the start box within one minute, it was replaced in the home cage and tested again after its cagemates. Once the animal entered a goal arm with all four paws, it was confined there for 30 sec and then returned to the start compartment for the second trial after which it was returned to its home cage. All tests were scored by a trained observer who was unaware of the treatment group of animals.

Behavioral Testing—Radial Maze

The maze was a floorless octagonal maze constructed of masonite. Each alley was 7.5×15.0×11.2 cm and opened into the central area. The threshold of each alley consisted of a 0.3 cm masonite barrier. The maze was placed on the floor of the animal room on white bench paper, which was changed as needed if animals defecated or urinated.

On day 18 of age, animals were adapted to the maze by placing each cage group as a whole in the maze for a 5 min period. Maze testing was carried out on days 22, 25 and 28.

At the beginning of each testing session, the animal was placed in the central area of the maze facing an arm, released, and allowed 5 minutes to explore the maze. Alleys were recorded in the order entered along with the time of entry and exit from the alley. Any animal not completing five alley choices in 5 min was returned to the maze for another trial after cagemates completed testing.

Behavioral Measures

Measures of exploration strategy were based on how often the animal used a "right turn" or "left turn" strategy in chosing a maze arm (see Fig. 1). In the T-maze, a 2-trial test session was scored as "repeating" if the animal chose the same arm on the second trial that it had chosen on the first trial. In the radial maze, a 5 min test was classified as "repeating" if the strategy chosen most often ("left turn" or "right turn") in exploring successive maze arms was used more frequently than would be expected on the basis of chance (0.50 probability, binomial test). Because of the dichotomous scoring strategies used, all group differences in strategy measures were evaluated with a nonparametric statistic (χ^2).

In addition to the strategy measures, latencies were recorded during each session to assess possible differences in arousal-activity levels in TAC-treated and control animals. In the T-maze, the average choice latency per animal on 4 trials of a given day was the latency score. For the radial maze, a latency measure (seconds per arm) was obtained by dividing the number of seconds in the test period by the number of arms chosen during the test period. Latency measures were converted with a log transformation and analyzed in a 3 factor (Sex, Treatment, Age) repeated measures analysis of variance (ANOVAR).

RESULTS AND DISCUSSION

Analysis of strategy scores demonstrated significantly more rigid exploration patterns in TAC-treated animals than in nontreated animals in both mazes. By the end of the ten day test period (see Fig. 2). Because the rigid exploration patterns developed in both maze situations between 25 and 28 days of age, it is possible to suggest that neonatal TAC treatment affects a behavior regulating system which matures during this period in the rat.

The TAC treatment effect on strategy measures was found when male and female data were pooled for analysis, and when treated females were compared separately to same-sex controls. However, treated and nontreated males did not differ significantly on any test day.

Analysis of latency measures demonstrated no effect of TAC-treatment, or interaction of treatment with sex or age.

The information on choice latencies is useful in considering possible indirect effects of TAC on choice strategy mediated by changes in activity-arousal level. Maturation of a major arousal-regulating system in the rat at about 28 days of age has been demonstrated by Campbell, Lytle and Fibiger [6], Moorcroft [19] and Blozovski and Bachevalier [2]. Increase in choice latencies in the present study at 27–28 days of age may also reflect the maturation of this system. However, since TAC treatment did not influence choice latencies, it seems unlikely that the TAC effect on exploration strategies was mediated by changes in activity-arousal.

EXPERIMENT 3: COMPARISON OF THREE TREATMENT PERIODS

The developmental period for producing changes in exploration strategies was explored by administering TAC treatment at 3 postembryonic ages, day 16 gestation, day 0

postnatal and day 10 postnatal, known to be susceptible to brain damage [8,26].

The gestational treatment was administered to mother at same mg/kg dosage as the postnatal treatments were administered to pups. Because littermate controls could not be employed for gestational treatment, additional litters in which all animals received vehicle injections served as controls.

In this experiment, only the radial maze was used, and a quantitative measure of rigidity of exploration strategy was derived for each test session. This is in contrast to the dichotomous scoring system ("repeating" and "non-repeating") used previously to measure exploration strategies. With a quantitative measure, parametric statistics and factorial designs could be utilized more effectively in evaluating the TAC treatment effect.

METHOD

Design

The design of this experiment is outlined in Table 2. For the first two groups (day 0 and day 10 postnatal treatment) injections were administered to individual pups after birth and a littermate control procedure was used, as in Experiment 1. For the third group (day 16 gestation treatment) injections were administered to the pregnant female and a fourth group of animals injected with vehicle at all time points (whole litter control) was added to the experiment to provide controls for the gestational treatment group. Four to six pregnant females were assigned to each of the 4 experimental groups.

Procedures

Virgin female Sprague Dawley rats (Simonson Laboratories, Gilroy, CA) were bred by caging 3–4 with a male on day of estrous as determined from vaginal smears. On day 16 of gestation, subcutaneous injection of either triamcinolone or vehicle was administered to pregnant females. On day 19 of gestation, pregnant females were transferred to plastic tub-type breeding cages with sawdust and paper nesting material and procedures used in the previous experiment were employed for the remainder of pregnancy and the postnatal period.

Behavioral Testing

The radial maze and procedures for testing were described in the previous experiment with the following modification: (1) Duration of the test; animals remained in the maze until 16 arm choices were made, rather than for a 5 minute period. (2) Time of testing; animals were tested early in the dark cycle (6–10 p.m.) rather than during the light cycle. (3) Age of testing; all animals were tested once at 35 days of age. (4) Adaptation; animals were adapted on 3 successive post-weaning days (25, 28, 32 days of age) by placing each animal in one arm of the radial maze with access to the rest of the maze blocked by a masonite door at the threshold of the arm. (5) Arousal measures; grooming, rearing and defecation were recorded cumulatively during each session.

Behavioral Measures

Two quantitative measures of rigidity of exploration strategy were derived from the sequence of maze arms chosen for exploration during each session. Choice sequences for each animal were processed with a computer program which classified each choice of an arm as "right turn," "left turn" or "opposite choice." Thirty-five day old animals sometimes ran across the open area in the center of the maze, a behavior not seen in younger animals; this made it necessary to add the third classification of strategy choice, "opposite choice." From this information, two scores were obtained, a "change strategy" score which was the number of strategy choices that were not the same as the preceding choice, and a "favorite strategy" measure which was the frequency of the strategy chosen most often as a percent of all choices. Because of the different control procedures used, prenatally and postnatally treated animals were evaluated in separate ANOVARS.

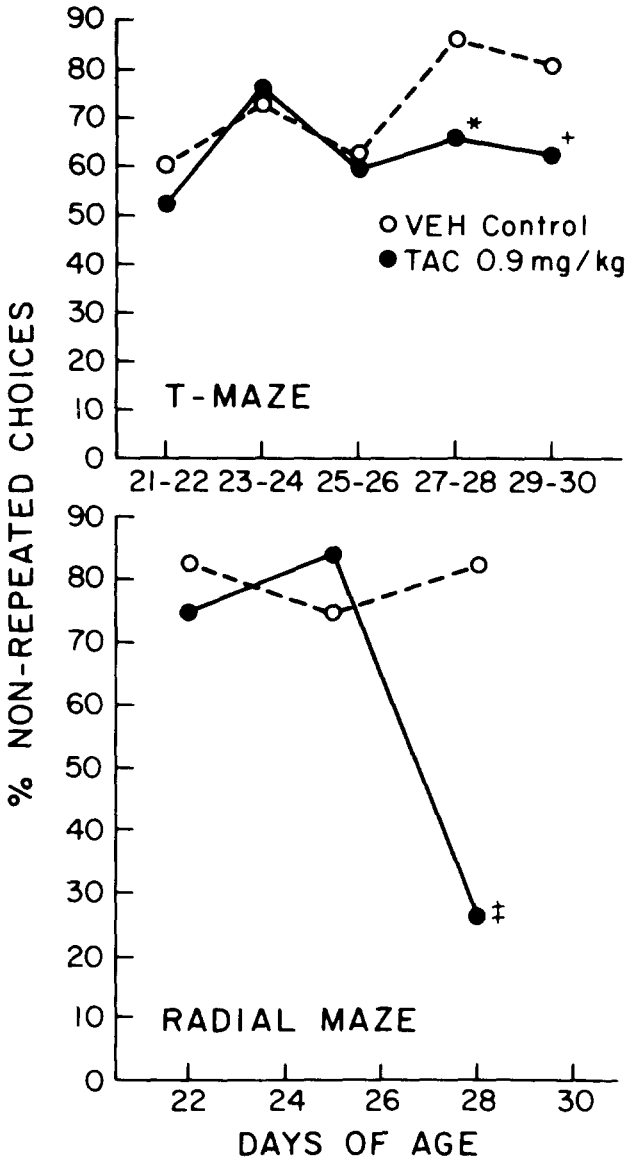

FIG. 2. Frequency of occurrence of repetitive maze exploration patterns in rats treated neonatally with TAC and in vehicle-injected controls. Group differences: $^{*}\chi^2(1)=6.36$, $p<0.025$; $^{+}\chi^2(1)=5.07$, $p<0.025$; $^{\ddagger}\chi^2(1)=5.71$, $p<0.025$.

TABLE 2

INJECTION SCHEDULE FOR EXPERIMENT INVESTIGATING SENSITIVE PERIODS FOR TAC-INDUCED BEHAVIORAL EFFECT

Treatment Group	Injection Time: Day 16 Gestation (Mother Injected)	Day 0 Postnatal (Pups Injected)	Day 10 Postnatal (Pups Injected)
Prenatal treatment	TAC	VEH	VEH
Neonatal treatment	VEH	split litter: VEH	VEH
		split litter: TAC	VEH
Postnatal day 10 treatment	VEH	split litter: VEH	VEH
		split litter: VEH	TAC
Whole litter control	VEH	VEH	VEH

TAC=triamcinolone acetonide 0.9 mg/kg.
VEH=equal volume vehicle injection.

TABLE 3

COMPARISON OF TAC-TREATED RATS AND VEH CONTROLS ON TWO MEASURES OF EXPLORATION STRATEGY AT 35 DAYS OF AGE IN THE RADIAL MAZE

	Strategy Changes (Per 16 Maze Arm Choices)					Favorite Strategy (% of All Strategy Choices)				
	VEH	TAC	*t*	*df*	*p*	VEH	TAC	*t*	*df*	*p*
Females										
Postnatal treatment	9.8	8.1	1.92	24	0.05	45	54	2.48	24	0.01
Prenatal treatment	9.8	10.3	0.38	32	NS	47	47	0.01	32	NS
Males										
Postnatal treatment	8.7	10.6	1.92	22	0.05	54	45	2.32	22	0.02
Prenatal treatment	9.5	10.5	1.38	26	0.10	53	44	3.18	26	0.005

RESULTS AND DISCUSSION

Postnatal TAC treatment influenced both the "change strategy" and the "favorite strategy" measures, with the direction of the effect depending on the sex of the animal. TAC treated females in general made more rigid or repetitive choices, while treated males had less rigid strategies than controls. This was reflected in a significant Sex by Treatment interaction in the 3-factor (Sex, Treatment, Time of Treatment) ANOVAR. For the strategy change measures Sex by Treatment interaction, $F(1,24)=8.56$, $p<0.005$; for the favorite strategy measures Sex by Treatment, $F(1,46)=9.05$, $p=0.004$. Individual group comparisons are presented in Table 3.

Both postnatal treatment ages (day 0 and day 10) had similar effects on behavior. The prenatal treatment (day 16 gestation) produced a behavioral effect similar to that of postnatal treatment in males, but did not alter the behavior of females (see Table 3).

These data suggest that there is no "critical period" for producing the TAC effect on exploratory behavior. Dose-effect studies would be necessary to determine with certainty whether some periods are more sensitive than others. However, the lack of time specificity seen here makes it less likely that this behavioral effect of TAC treatment is due to interference with the development of a specific brain structure, and more likely that a nonspecific effect on brain growth is involved.

A striking characteristic of the TAC effect on strategy measures in this experiment was the difference between sexes. Treated females displayed more rigid exploration patterns than controls, an effect that was similar to that recorded in radial and T-mazes in the first experiment. However, treated males in the second experiment had less rigid exploration strategies than like-sex controls. Since sexual maturation is proceeding in the rat at about the age when the animals were tested (35 days), it is possible that the sex-specificity of drug action is produced through interaction with other behavioral changes and does not persist into maturity; however, we have no experimental evidence on this point.

Analysis of weight and activity-arousal measures demonstrated that no TAC treatment group differed from its

appropriate control on these measures, but that animals from litters split for treatment (littermate control procedure) differed from those in which all pups received the same treatment (whole litter control procedure). The animals from split litters were lighter in weight and had shorter emergence times and completion times than animals from homogenously treated litters. When the five treatment groups (3 TAC-treated and 2 control) were compared on measures of emergence time, completion time and weight using a two-factor (Treatment Group, Sex) ANOVAR, a significant effect of treatment group was found on all three measures: weight: Treatment $F(4,10)=9.19$, $p<0.001$; emergence time: Treatment $F(4,110)=9.48$, $p<0.001$; completion time: Treatment $F(4,110)=5.39$, $p<0.001$. Individual group comparisons (Newman-Keuls procedure) indicated that groups made up of animals from litters split for treatment (postnatal TAC groups and split litter controls) differed from groups of animals from homogenously treated litters (prenatal TAC group and whole litter controls).

This information is in agreement with latency measures in the previous experiment and indicates that activity and arousal in the test situation were not apparently affected by developmental TAC treatment.

Examination of defecation, grooming and rearing measures revealed no group differences.

This pattern of results strongly suggests that the split-litter rearing situation in itself produced substantial behavioral changes in offspring. Both control groups received identical injections of vehicle and identical handling, and thus differed only in that split-litter controls were raised with TAC-treatment littermates. Apparently some aspect of this rearing situation produced significant changes in weight and latency measures. The littermate control procedure has been used in the majority of behavioral experiments with neonatal corticosteroid treatment. It is possible that alterations in nontreated littermates due to rearing in litters split for treatment are an important unrecognized factor that should be considered in the interpretation of these experiments.

GENERAL DISCUSSION

These data demonstrate that long-term changes in behavioral functioning can be produced by relatively brief low-level treatment with corticosteroids during the period of brain development in the rat. The behavioral measures affected were concerned with the flexibility of exploratory patterns in spatial mazes. The behavioral techniques do not allow identification of specific cognitive process affected, for example, memory, response inhibition or spatial discrimination. However, there were no group differences in body weights or general activity-arousal levels and no signs of developmental toxicity in the treated animals used in these behavioral studies.

The behavioral effect described in this experiment was sex-dependent; the direction of the deviation from control differed in males and females. Whether this was due to dose level, age of testing or specificity of drug actions is not clear from the information gathered to date. The effect may also be specific to juvenile stage of development, as we have not tested fully mature animals.

Several characteristics of the present study make it particularly relevant to the question of possible impairment of brain function in humans after developmental corticosteroid therapy.

(1) The dose levels used are low. Growth retardation, which is frequently used as an index for adjusting therapeutic levels of corticosteroid, was not seen at the behaviorally effective dose level. In addition, no signs of the well-documented developmental toxicity syndrome for corticosteroids were observed.

(2) The agent used, triamcinolone, is a synthetic corticosteroid with a potency similar to commonly used therapeutic agents.

(3) The drug appeared to be most effective during the period of rapid brain growth in the rat. Corticosteroids administered as prophylaxis for respiratory distress syndrome are administered during the last trimester, a period of rapid brain growth in humans.

(4) The behavior affected involved regulation of relatively complex spontaneous behavior pattern. This type of a deficit might not readily emerge from routine developmental screening tests in infants since it does not necessarily imply a maturational lag; however, this type of deficit may be relevant to syndromes of inadequate regulation of activity and attention in children [32].

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