MATERNAL OR PATERNAL EXPOSURE TO CANNABINOIDS AFFECTS CENTRAL NEUROTRANSMITTER LEVELS AND REPRODUCTIVE FUNCTION IN MALE OFFSPRING

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I. INTRODUCTION

Marijuana, and its main psychoactive component delta-9-tetrahydrocannabinol (THC), have been reported to exert a wide range of effects on reproductive performance (1). Association of chronic marijuana use by men with decreased plasma testosterone levels, reduced sperm counts and impotence has been reported (2,3). In adult male mice acute exposure to THC or chronic treatment with CBN, a relatively non-psychoactive cannabinoid, can decrease plasma testosterone, prolactin and gonadotropin levels. While the suppression of prolactin secretion may involve alterations in serotonergic and dopaminergic activity (7), the central mechanisms by which THC alters gonadotropin release are not clear, although direct effects of THC on the hypothalamic-pituitary axis have been suggested (8,9).

In general, the reports on the effects of THC on central nervous system (CNS) neurotransmitters are conflicting, with investigators presenting evidence of increased or decreased levels of norepinephrine (NE) and serotonin (5-HT) after THC treatment (10-13). Recently, low concentrations of THC have been shown to stimulate dopamine (DA) and NE uptake by hypothalamic and striatal synaptosomes whereas higher concentrations inhibited DA and NE uptake (13). In the mouse, THC has been shown to increase synaptosomal DA synthesis in striatum at low doses, but decrease DA synthesis at higher doses (14).

In addition to these effects of cannabinoids on the CNS it is apparent that these compounds can directly affect the steroidogenic and spermatogenic functions of the testes in several species of laboratory animals (1,4,15). Although the mechanisms responsible for cannabinoid-induced alterations in testicular function remain to be elucidate, available evidence suggests that interference with gonadotropic stimulation (15), reduction in testicular synthesis of proteins, lipids, and nucleic acids (17), and prostaglandins (18,19), glucose utilization (20) or activity of cholesterol esterase (21,22) may be involved in the reduction of testicular steroidogenesis.

The testicular hormonal milieu is critical for normal spermatogenesis and at present it cannot be determined whether cannabinoid-induced suppression of spermatogenesis in mice (23), or in humans (24) is secondary to a reduction in testosterone production or due to a direct action on the germinal epithelium. Cannabinoids have been reported to influence acrosomal morphogenesis and condensation of chromatin in sperm heads as well as inhibit sperm maturation (25).

On the basis of these findings it can be concluded that cannabinoids affect adult male reproductive functions. However, the possible implications for male fetal development have been given less attention. We have previously reported that exposure of female mice to either THC or CBN on the last day of gestation and for the first six days post-partum resulted in long term alterations in body weight regulation and reproductive functions in their male offspring (5,6). Effects of perinatal exposure to cannabinoids on the male reproductive system did not become evident until after weaning (21 days of age). During and after sexual maturation male mice exposed to THC had reduced testes weights and elevated levels of plasma luteinizing hormone (LH). In contrast, CBN-exposed males had reduced concentrations of these hormones after sexual maturation. Copulatory behavior was also reduced in adult males exposed to either THC or CBN during the perinatal period of sexual differentiation (5,6). Biochemical changes, including alterations in brain RNA synthesis, in neonatal rats have been induced by THC administration during pregnancy (26) and effects of prenatal cannabinoid exposure on development and learning have been reported (27,28).

The present experiments were designed to further characterize the consequences of perinatal exposure of male mice to THC or CBN, or to the non-psychoactive component cannabidiol (CBD). In particular, we have examined the concentrations of brain amines in adult male mice prenatally exposed to these compounds.

We have previously reported that treatment of adult male mice with THC, CBN or CBD reduced fertility and resulted in chromosomal abnormalities (15). In the present study we have

examined the consequences of paternal exposure to cannabinoids on the subsequent fertility of their male offspring.

II. METHODS

Primiparous female mice obtained from our colony of randomly bred animals received a single oral administration of THC, CBN, or CBD at a dose of 50 mg per kg body weight on one of the last four days of gestation. On the first day postpartum litters were culled to five or six male pups; the offspring were weaned at 21 days of age and housed in groups of three until adulthood (60-80 days).

Half of the animals in each treatment group were castrated in connection with ongoing studies on the effects of prenatal cannabinoid exposure on androgen receptor levels in seminal vesicles. Castrations were performed under ether anesthesia and the testes were removed, weighed, homogenized in distilled water (9:1 w/v) and stored frozen for the radioimmunoassay determination of testosterone as described previously (29,30). Two days post-castration the males were sacrificed by cervical dislocation and the brain was quickly removed and stored frozen for measurement of amine concentrations.

Prior to the amine assay, the brains were partially thawed and the hypothalamus was dissected free. The hypothalamus consisted of a tissue block 2.0 mm deep extending from the rostral margin of the mammillary body to the rostral border of the optic chiasm and laterally to the hypothalamic sulci. The hypothalamic block and the remaining brain tissue were weighed and sonicated in 0.1 N $HClO_4$ containing 3-methoxy-4-hydroxyphenethanol (MOPET) as a standard for the indole amine assay, dihydroxybenzylamine (DHBA) as an internal standard for the catecholamine assay and 1.0 mM sodium metabisulfite.

Indolamines were separated by high performance liquid chromatography (HPLC) and quantitated by electrochemistry (29). Standards were run concurrently, and 5-HT and 5-HIAA were calculated by comparison of peak heights with those of the standards. Values were corrected for recovery of the internal standard which averaged 97.3 +/- 1.2%. The intra-assay coefficient of variation was 5.6% for 5-HT, and 7.2% for 5-HIAA.

Catecholamines were prepared for chromatography as previously described (29,30). Norepinephrine, DA and DHBA were separated by HPLC and quantitated by electochemistry. The recovery of DHBA averaged 82.3 +/- 1.1% and the intra-assay coefficient of variation was 6.1% for NE and 6.7% for DA.

For groups and parameters in which no significant differences were found due to the time of prenatal treatment,

results from animals exposed to cannabinoids on the different days of gestation were combined for further statistical analysis and presentation.

In studies concerning the effects of paternal exposure to cannabinoids on the subsequent fertility of their male offspring, adult male mice were treated with THC, CBN, or CBD (50 mg/kg) three times a week for five weeks, using 18 males per group as described previously (15). The males were individually housed with a different adult female each during the third, fourth and fifth week of treatment and during the first and fourth post-treatment weeks. In each treatment group half of the pregnant females were allowed to deliver and raise their pups. The surviving F_1 male offspring were weaned at 21 days of age, and housed in groups of four until adulthood (60-80 days). Each F_1 male was given the opportunity (duringa one week cohabitation period) to mate with at least three different females. Females were sacrificed between days 15 and 19 of gestation for determination of the number of corpora lutea, resorptions, dead fetuses, live and still births, and postnatal deaths. The overall percentage of females impregnated was also recorded. Female mice who failed to become pregnant were remated to known fertile males to verify their fertility.

III. RESULTS

A. Maternal Exposure

At two days post-castration the concentrations of NE in hypothalamus and NE and DA in the remaining brain were slightly reduced in CBN- and CBD-exposed animals in comparison to castrate controls. In contrast, levels of 5-HT and 5-HIAA were significantly elevated in both the hypothalamus and the remaining brain in these mice (Tables I and II). Exposure to THC during the latter part of gestation did not significantly affect brain amine concentrations. There were no significant differences in the weights of the brain or hypothalamic tissue blocks or in body weight among the animals in the different treatment groups.

Testicular testosterone concentrations were reduced in adult male mice exposed to CBN, although testes weights were not affected. The weights of the seminal vesicles were increased by CBD exposure, but were significantly reduced by CBN exposure (Table III). Exposure to THC did not influence these parameters.

TABLE I. Brain Amine Concentrations[a]

	NE	DA	5-HT	5-HIAA
Oil	398 +/- 12 (12)	1288 +/- 81 (12)	579 +/- 21 (11)	181 +/- 6 (11)
THC	398 +/- 12 (18)	1345 +/- 39 (18)	583 +/- 46 (18)	194 +/- 6 (11)
CBN	254 +/- 29[b] (14)	793 +/- 97[b] (14)	1024 +/- 60[b] (14)	267 +/- 9[b] (14)
CBD	247 +/- 20[b] (14)	748 +/- 60[b] (14)	1010 +/- 28[b] (14)	249 +/- 4[b] (14)

[a]Units are in ng/g (N).

[b]Significantly different from controls ($p < 0.05$) by analysis of variance and Duncan's test.

N.B. All animals were castrated 2 days prior to sacrifice. In addition, the brain consisted of the remaining tissue after the removal of the hypothalamic block.

TABLE II. Hypothalamic Amine Concentrations[a]

	NE	DA	5-HT	5-HIAA
Oil	1371 +/- 101 (12)	1244 +/- 189 (12)	1308 +/- 52 (12)	359 +/- 17 (12)
THC	1302 +/- 54 (18)	1161 +/- 83 (18)	1274 +/- 54 (18)	377 +/- 13 (18)
CBN	849 +/- 76[b] (13)	1006 +/- 103 (14)	2247 +/- 206[b] (14)	506 +/- 45[b] (14)
CBD				
Day 2	800 +/- 72[b] (9)	1134 +/- 130 (14)	2191 +/- 144[b] (14)	477 +/- 33[b] (14)
Day 3	1225 +/- 256 (5)			

[a]Units are in ng/g (N).
[b]Significantly different from controls ($p < 0.05$) by analysis of variance and Duncan's test.
N.B. All animals were castrated 2 days prior to sacrifice.

B. Paternal Exposure

The F_1 male offspring of the CBD-treated male mice successfully impregnated all the females with whom they were paired, as did the offspring of the oil-treated control mice. However, the F_1 male offspring of the THC and CBN-treated animals had significantly reduced reproductive performance.

For the analysis of results on F_1 male fertility, offspring from each treatment group were classified into three categories. The first included the males which had successfully impregnated all the females with whom they were paired, with all the resulting litters being normal by the standards of our breeding colony, that is litter size of at least 10 pups and less than 10% pre- or post-natal mortality. The second category consisted of those males in which one out of three matings deviated from these criteria. Finally, the third category consisted of those males whom did not produce a single pregnancy that met our criterion of normalcy.

Among the THC and CBN-exposed offspring, a significant percentage, 36% of the THC and 21% of the CBN-F_1 males, fell into the third category (Fig. 1). In addition, in two litters sired by F_1 males from THC-treated fathers, one contained an exencephalic fetus, while another pup (delivered alive at autopsy on day 19) exhibited exencephaly, spina bifida, and exteriorized intestines (Fig. 2). Testes from the most severely affected group of males were examined cytogenetically and, in testes obtained from two out of eight animals, chromosomal abnormalities (as indicated in a representative sample in Fig. 3) in the form of ring and chain translocations, nondisjunction and aneuploidy were observed, as was a reduction in testicular weights.

TABLE III. Hormone Levels and Organ Weights

	Testicular Testosterone Concentrations (ng/ml)	Testes Weights (mg)	Seminal Vesicles (mg)
Oil	138 +/- 22 (12)	278 +/- 7 (12)	258 +/- 13 (12)
THC	112 +/- 15 (17)	296 +/- 9 (18)	219 +/- 28 (18)
CBN	69 +/- 17* (14)	268 +/- 12 (14)	164 +/- 16* (14)
CBD	126 +/- 21 (14)	310 +/- 8 (14)	308 +/- 12* (14)

*Significantly different from controls ($p < 0.05$) by analysis of variance and Duncan's test. Number of animals = (N).

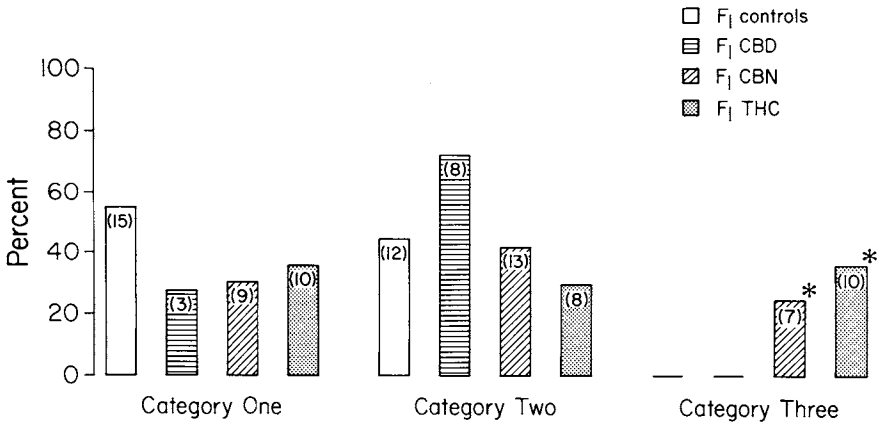

FIGURE 1. Reproductive performance in adult F_1 male offspring of cannabinoid-treated male mice. * = Significantly different from control males in category three; Chi-square = 18.05, df = 3, $p < 0.001$.

IV. DISCUSSION

The present findings indicate that alterations in brain amine levels in adulthood may result from prenatal exposure to cannabinoids. The relatively non-psychoactive CBN and CBD altered brain and hypothalamic concentrations of NE, DA, 5-HT and 5-HIAA as well as testicular testosterone concentrations and seminal vesicles weights, while prenatal THC exposure during late gestation did not appear to influence these parameters. However, we have recently observed that exposure to THC during the mid-portion of gestation did result in altered brain amine levels in adult mice (Dalterio and Steger, unpublished observation). In view of our earlier findings of long-term alterations in other parameters of endocrine and behavioral function in male mice exposed to THC during the perinatal period (5,6) it is possible that critical time periods exist for cannabinoid-induced alterations in developmental processes. We are currently investigating this issue as well as planning experiments to determine effects of perinatal cannabinoid exposure on amine uptake and turnover.

Although we do not know the precise mechanism by which castration differentially affected cannabinoid-exposed animals, it is known that castration stimulates amine turnover in normal animals (31). It is possible that cannabinoid exposure resulted in a differential responsiveness to the surgical stress associated with castration. We have previously reported that adult male mice treated with cannabinoids

exhibit a differential hormonal response to stressful stimuli (32). However, we have also reported that the release of pituitary gonadotropins three weeks post-castration is altered in animals perinatally exposed to THC (33) and it is doubtful that surgical stress could be a factor in these observations. It is possible that alterations in catecholamines, which are known to have a role in the regulation of gonadotropin release (34), may be involved. We have also reported that perinatal, but not pre-pubertal, exposure to THC reduces responsiveness of the vas deferens in vitro to NE and D-Ala^2-Met-enkephalin (35).

It is conceivable that the reported effects of prenatal cannabinoid exposure on development and learning are also related to cannabinoid-induced changes in concentrations of these neurotransmitters (27,28). We have previously reported that adult copulatory behavior was reduced differentially by THC or CBN (5,6). Although the influences of neurotransmitters on sexual behavior are not clear (36), it is conceivable

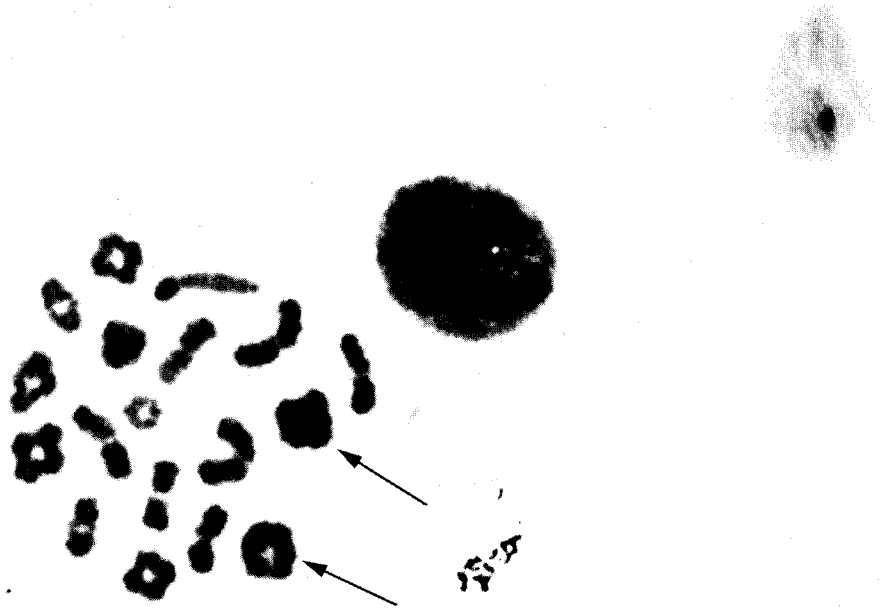

FIGURE 2. Chromasomal abnormalities observed in testes obtained from F_1 offspring of THC-treated adult male mice. N.B. A diakenesis-metaphase 1 plate with 2 ring configurations (indicated by arrows) and 16 bivalents in a spermatocyte from a testis obtained from an F_1 offspring of a THC-treated male.

that changes in behavioral responsivity to stimuli from conspecifics may result from cannabinoid-induced alterations in brain catecholamines during critical periods of sexual differentiation.

Another factor which may be related to the observation that castration brought out an effect of prenatal cannabinoid exposure that was not otherwise observed concerns the presence of gonadal steroids, which can modulate amine levels (37). We have shown that the gonadal steroids modulate the acute hormonal responses to THC administration in adult mice (38). In addition to the possible influences of surgical stress or the presence of gonadal steroids we have also demonstrated that environmental factors such as the presence of female conspecifics can interact with the effects of perinatal cannabinoid exposure. In an earlier study we noted that pre-pubertal cannabinoid-exposed males responded to housing with an immature female as a stressful situation, as suggested by increased adrenal weights and reductions in the weights of the testes and seminal vesicles 95). Thus, although the precise mechanism by which castration appears to reveal effects of prenatal cannabinoid exposure on CNS neurotransmitter levels is at present unclear. However, based on our earlier studies these findings appear to be consistent with cannabinoid-induced alterations in physiological responsivity to events which disturb homeostatic conditions.

In mice, maternal exposure to cannabinoids appears capable of inducing teratogenesis in male offspring. These effects are observed after a single prenatal exposure or repeated exposure during the perinatal periods of development (5,6). In addition, the effects on the male offspring, including alterations in body weight regulation, pituitary-gonadal function, sexual behavior and central neurotransmitter concentrations, are not inconsistent with results of cannabinoid administration to immature or adult males (1).

Evidence from studies of paternal exposure to cannabinoids indicates that these compounds, in addition to their reported embryocidal or teratogenic potential (1) also may be mutagenic. We have shown that brief or repeated exposure in adulthood to psychoactive or non-psychoactive components of cannabis affects the endocrine system and fertility and that these effects were not rapidly reversible, were associated with chromosomal abnormalities and, in some cases, with reductions in testicular weights and alterations in plasma hormone concentrations (15). Although the mechanisms by which cannabinoids influence the genetic apparatus are unclear, we observed that the F_1 male offspring of cannabinoid-treated male mice exhibited reductions in reproductive performance, as well as cytogenetic abnormalities similar in type and frequency to those observed in their treated sires (15). This

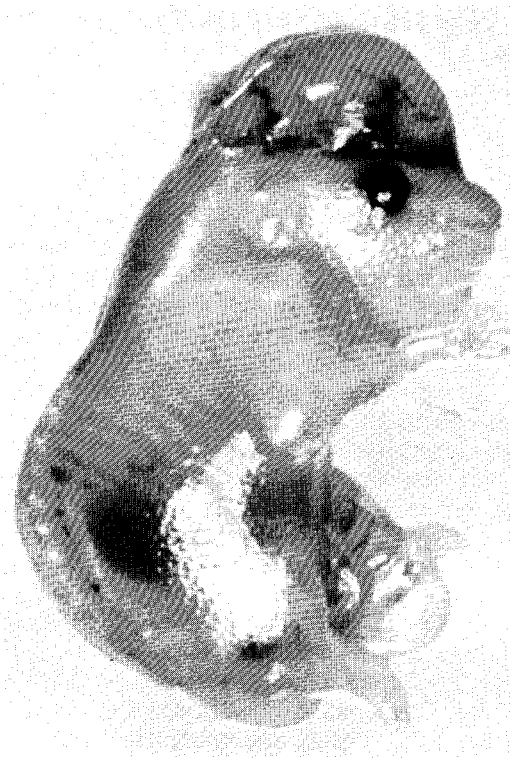

FIGURE 3. Congenital malformations observed in the F_2 generation of THC-treated male mice.

strongly suggests that cannabinoid effects on fertility can be transmitted from one generation to the next. in addition, it must be stressed that these F_1 males were survivors of matings in which indications of subfertility and perinatal loss had been observed, and therefore these animals do not represent the most seriously affected offspring of the cannabinoid-treated males. The observation of severe congenital defects in F_2 offspring of THC-treated males suggests that cannabinoids may affect polygenetic systems involved, not only in reproductive functions, but with a wide range of developmental processes as well.

It is evident that either maternal or paternal exposure to cannabinoids, whether psychoactive or non-psychoactive, are capable of producing long-term alterations in reproductive functions in their male offspring. Furthermore, it is evident that in either situation, that is, pre-gestational orgestational exposure, the effects of cannabinoids may not become apparent until maturational or environmental factors require

physiological responses, particularly those involving the endocrine system.

V. SUMMARY

A single prenatal exposure to cannabinol (CBN) or cannabidiol (CBD) reduced brain norepinephrine (NE) and dopamine (DA) and hypothalamic NE concentrations, but increased brain levels of serotonin (5-HT) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA). In addition, testicular testosterone concentrations and seminal vesicles weights were reduced in animals exposed to CBN. In contrast, seminal vesicles weights were increased in CBD-exposed males. Prenatal exposure to the major psychoactive component of marijuana, delta-9-tetrahydrocannabinol (THC) on one of the last four days of gestation did not affect these parameters.

The F_1 male offspring of male mice treated with CBN, CBD or THC presented evidence of reduced fertility and testicular chromosomal abnormalities. In addition, two of the F_1 male offspring of the THC-treated mice sired litters containing pups with severe congenital malformations.

These findings indicate that maternal or paternal exposure to cannabinoids can influence developmental and reproductive functions in offspring. Thus, cannabinoids appear to be both mutagenic and teratogenic in mice.

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