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EFFECT OF CHRONIC ORAL ADMINISTRATION OF CANNABIS (BHANGO) ON BRAIN BIOGENIC AMINES AND SEXUAL BEHAVIOUR OF MALE RATS

Mekkawy, H.A.*; Dawlat, A. Salamah and I. El-Wardany*****

* *The National Center for Social and Criminological Res., Physiology Branch, Zamalek, Cairo, Egypt.*
** *Biochemistry Department, Faculty of Agriculture, Ain Shams University, Cairo, Egypt.*
*** *Poultry Production Depart., Physiology Branch, Faculty of Agric., Ain Shams Univ., Cairo, Egypt.*

ABSTRACT

Crude Cannabis resin extracted with methanol was orally administered to male rats (*Ruttus norvegicus*) at the dose level of 5 mg/100g body weight to study the effect of chronic administration cannabinoid on sexual behavior, some related blood parameters and biogenic amines in the whole brain tissues. The treatment was continued daily for 15, 30 and 45 days. Control rats received Saline-Tween 80 through the same route. Samples of homogenate brain tissue and blood were subjected to determination of biogenic amines, some enzymes in brain and blood, besides blood glucose and testosterone at different periods. The obtained results showed that *Cannabis sativa* methanol extract caused an increase in the level of dopamine (DA), noradrenaline (NE), and serotonin (5-HT) in brain, however, both 5-hydroxyindole acetic acid (5-HIAA) concentration and acetylcholinesterase (AChE) activity in the brain tissues were significantly decreased. These changes were associated with the extension of treatment time. Hence, brain contents of DA and 5-HT were higher at 45 days post-treatment, and NE increases were concomitant with 5-HIAA and AChE decreases along the whole experimental period. A significant increase in blood glucose was also recorded in treated rats. The results revealed that the marker enzyme for testicular activity i.e. Gamma-glutamyl transpeptidase, (G-GT) was significantly increased by cannabis methanol extract indicating

suppression in the spermatogenic activity of male rats, which in turn suppress testosterone secretion from Leydig cell of the testis. Daily oral administration of cannabis methanol extract for 30 days to male rats resulted in significant decrease in the level of serum testosterone. However, the lowest value was recorded after 45 days. A significant reduction in the general behavior activities of treated rats was observed. Sexual activity of male rats, including libido, mounting and courtship behavioral responses, was significantly decreased. Also, the non- sexual activities, i.e. feeding, drinking, walking, etc. were dramatically decreased, hence the quiescence time increased. Based on the abovementioned, it could be concluded that chronic oral administration of methanol extract of cannabis could modulate biogenic amines in the brain tissues, along with some enzymes, which may disrupt the physiological homeostasis of male rats by suppressing their sexual activity and reducing the concentration of the principal male sex hormone that may resulted in lowering their fertilizing capacity.

Key words: Cannabis - Biogenic amines – Acetylcholinesterase – Glucose - Gamma-glutamyl transpeptidase - 5-hydroxyindole acetic acid – Testosterone - Sexual behavior - Rat.

INTRODUCTION

Cannabis is one of the most commonly used illegal drugs in many countries including Egypt. Its use is prevalent regardless of age, ethnicity and sex (Cami and Farre, 2003). *Cannabis sativa* contains more than 60 active compounds, the most active of which is Δ-9-tetrahydrocannabinol (Δ- 9–THC) (Ramos *et al.*, 2005). It has different street names i.e. Hashish, Marijuana, Bhango, Magon, etc. (Mekkawy and others, 2000).

Cannabis extract or THC can be taken orally in fat-containing food or dissolved in a suitable pharmaceutical oil, but absorption is delayed and variable (Iversen, 2003). The compound is acting as agonist at the CB_1 cannabinoid receptor in the brain, which is the only one known to be expressed in the brain (Matsuda *et al.*, 1990). The second cannabiniod receptor, CB_2, is known to be expressed only in peripheral tissues, principally in the immune system (Felder and Glass, 1998 and Russo *et al.*, 2005).

There are several reports (Sumnall *et al.*, 2006 and Suris *et al.*, 2007) indicating that long-term use of cannabinoids induce euphoria and enhance both biogenic amines activity and sexual behavior, though controversial results are also reported (Kreek *et al.*, 2002). Recent studies have demonstrated that cannabinoid drugs exert their role on sexual behavior via the hypothalamic-pituitary axis, which considered the main neuroendocrine regulator of reproductive behavior in different mammalian species including human being (Jackson and Murphy, 1997).

It was suggested that acute and chronic doses of THC cause significant depression of the principal male hormone (testosterone) synthesis in rat testis by causing reduction of gonadotropin releasing hormones from the hypothalamus (Park *et al.*, 2004). This effect may explain the behavioral studies demonstrating that THC reduced copulatory behavior in male rats (Merari *et al.*, 1973). Since the reproductive behavior is controlled by the anterior pituitary hormones, and since cannabinoids are neuroactive drugs, it seems reasonable to assume that the hypothalamic pituitary axis was the active site of action for reproductive functions (Park *et al.*, 2004 and Howlett *et al.*, 2004) through different biogenic amines which modulate this process (Tasker, 2004).

In this respect, Schurr and Rigor (1984) reported that cannabinoids interfere with the metabolism of biogenic amines, causing an increase in serotonin, dopamine and catecholamines (Sofia *et al.*, 1971; Cheer *et al.*, 2003 and 2004 and Howlett *et al.*, 2004). Moreover, Ghosh *et al.* (1980) observed a dose-related increase in brain 5-HT and acetylecholine with acetylcholinesterase activity decrease. Also, Paton and Pertwee (1973) indicated that cannabinoids enhance the serotonergic and cholinergic activity of rats brain.

Earlier studies suggest that (Δ-9-THC) plays its role in sexual behavior by reducing gamma-glutamyl transpeptidase (G-GT), a marker protein for spermatogenic activity which is regulated by follicle stimulating hormone (Schwarz *et al.*, 1978 and Caston and Sanborn, 1988). Wilber and Morrison (1955) and Mahfouz *et al.* (1975) reported that the increasing in blood glucose was obtained in the terminal stage of chronic parathion and hashish poisoning.

Hence the present study was conducted to further elucidation of the chronic effect of cannabis oral administration on some sexual and non sexual behavior aspects and on the total brain dopamine (DA),

noradrenaline (NE), serotonin (5-HT), 5-hydroxy indoleacetic acid (5-HIAA) contents and acetylcholinesterase (AChE) activity. Blood glucose and testosterone concentrations and Gamma-glutamyl transpeptidase (G-GT) activity in serum of rats were also investigated.

MATERIAL AND METHODS

1-Material

1-1- Crude cannabis resin was extracted by 95% methanol. The residue was shacked several times using a mixture of petroleum ether and ether (8:2 v/v) and then filtered. The filtrate passed through a silica gel column, the eluted solution was then evaporated under Vacuum (El-Darawy *et al.*, 1978).

1-2- For the preparation of oral doses, the resulting cannabis resin (500 mg) was treated with suitable amounts of Tween 80 for uniform suspension, and completed to volume 200 ml with physiological saline (0.9% NaCl).

1-3- Male adult rats (*Rattus norvegicus*) of body weight from 100–120g were used. They were divided into 4 groups (10 rats/each). Animals placed as 5 rats per cage, and maintained on a standard diet. Food and water were allowed ad libitum.

2- Methods

2-1- Experimental Design

The control rats (group-1) received an equivalent dose of the saline Tween-80 vehicle via oral intubation, while the treated groups received their doses of cannabis extract (5 mg/100 g body weight) for 15 days (group-2); 30 days (groug-3) and 45 days (group-4) as reported by Mekkawy, (1976). Body weights of rats were weekly recorded to adjust the treatment dose.

At the end of every treatment period animals were killed by rapid decapitation, 6 hours after treatment and quickly dissected. At autopsy, the whole brain tissues were carefully removed, wiped dry with filter paper and weighed. Brain tissues were wrapped in plastic films, preceded with aluminum paper and immediately stored frozen in dry ice (-30°C) until analysis were performed. Blood samples were also collected from the experimental rats, via heart puncture and then centrifuged (4000, rpm) for 15 minutes, serum samples were decanted and stored frozen (-20°C) until analysis.

2-2- Biochemical Assays

- **Brain tissues** were homogenized and extracted with acetone according to Fleming and Clark (1965). The determination of dopamine (DA); noradrenaline (NE); serotonin (5-HT) and 5-hydroxyindol acetic acid (5-HIAA) were done according to the method Welch and Welch (1969). The fluorescence was measured in Corning–EEI 244 Fluorometere (Evans Electroselenium Ltd, holstead, Essex).
- **Acetylcholinesterase enzyme** [EC 3.1.1.7] activity was also determined in brain extract using the method of Ellman *et al.* (1961).
- **Gamma-glutamyle transpeptidase** [EC 2.3.2.2] was measured in serum samples by using available Boehinger Mannheim Diagnostic test kits (Mannheim, Germany).
- **Serum concentrations of testosterone** were measured by utilizing a solid phase ^{125}I radioimmunoassay (RIA) technique (Diagnostic Products Corporation, Los Angles.USA) according the method of Cumming (1985).
- **Serum glucose level** was measured as described by Smogyi (1945).

2-3- Tests of General Activity

The objective of this test was to determine the time consumed by a male rat caged with an estrus female in general activities including feeling, drinking, walking around Zig-Zag activity and sexual activity (Minnick *et al.*, 1964). A total of one hour observation time over the 45 days experimental period was recorded. In other word, the time of sexual and non sexual activities and time of quiescence, per hour, of a male caged with an estrus female was recorded for each of 10 control and 10 treated rats as reported by Mekkawy (1976).

2-4- Statistical analysis

Data are present as means (± S.E) and the statistical analyses were performed using Student's t-Test (Snedecor, 1971). The levels of significance were 5% and 1% as shown by the *and **symbols, respectively.

RESULTS AND DISCUSSION

A- Brain Parameters

As shown in (Table 1) oral administration of cannabis extract (5 mg/100 g BW) induced significant increases in the total brain DA, NE, 5-HT and a dramatic decrease in 5-HIAA content of rats.

However DA content of treated rats was not significantly affected after 15 and 30 days of experiment.The increase in DA content was highly significant after 45 days. It is clear from the present results that the brain biogenic amines (NE and 5-HT) were significantly increased with the higher values recorded for NE during the whole experimental periods, but the greatest value for 5-HT was obtained after 45 days.

Results show that the brain content of 5-HIAA was significantly ($P \leq 0.01$) decreased after 15, 30 and 45 days of treatment.The average values of (AChE) activity in the brain tissue tended to decrease ($P \leq 0.01$) by cannabis dosing level whereby the decrease from 47.2, 49.8 and 44.6 in the control groups to 13.3, 11.6 and 10.0 after the 15, 30 and 45 days of treatment with cannabis extract, respectively

From the results obtained (Table 1) it is evident that the administration of cannabis extracts has significantly increased the total DA, NE and 5-HT content. The same dose of cannabis caused a highly significant decrease in 5-HIAA content. Our findings appear to indicate that cannabis extract produces significant changes in secretion, release and degradation of biogenic amines. It appears also that cannabinoids enhance the reuptake of DA, NE and 5-HT into nerve endings of the brain causing an increase in their levels, which support the findings of many authors (Schurr and Rigor, 1984; Ghosh *et al.,* 1980; Cheer *et al.*, 2003; Howlett *et al.*, 2004 and Park *et al.*, 2004).

Another possible mechanism that THC activates the adrenal gland steroid hormones possibly through a stress mechanism which agree with Norlo and Garcia (1974) who recorded that the administration of delta-9- tetrahydrocnnabinol (Δ-9- THC) in a dose of 5-20 mg /kg body weight, caused inhibition of growth hormone secretion and stimulation of ACTH secretion. They suggested that Δ-9-THC acts as a pharmacological stressor of hypothalamo-pituitary adrenal axis stimulation in rats.

It was suggested that Cannabinoids affect the ontogancy of various neurotransmitter systems leading to changes in different behavioral patterns. DA and endogenous opioids are among the neurotransmitters that result more effects by prenatal cannabinoid exposure. When animals mature, these Cannabinoids produce changes in motor activity, drug-seeking behavior, nociception and other mental processes (Fernandez *et al.*, 2004).

Table (1): Effect oral administration (5 mg/100 g body weight) of cannabis extract on the dopamine, norepinephrine, serotonin and 5-hydroxy indole acetic acid contents and acetylchlolinestrase activity in the whole brain tissue of male rats

Days of	DA (ng/g)			NE (ng/g)			5-HT (ng/g)			5-HIAA (ng/g)			Acetylcholinesterase (u mole/1 h/100 mg)		
adminis.	C	T	% change	C	T	% change	C	T	% change	C	T	% change	C	T	% change
15	613 ±13.5	646 ±1.5	+5.38	350 ±12	421 ±5**	+20.29	625 ±11	670 ±14*	+7.2	448 ±6	320 ±5**	-28.57	47.2 ± 6	13.3 ±4**	-71.82
30	615 ±14.2	654 ±6.4	+6.34	344 ±10	458 ±7**	+33.14	620 ±9	680 ±10*	+9.68	450 ±5	285 ±8**	-36.67	49.8 ± 8	11.6 ±8**	-76.71
45	608 ±10.8	756 ±5.2**	+24.34	346 ±8	460 ±11**	+32.95	627 ±13	730 ±7**	+16.43	420 ±8	271 ±3**	-35.48	44.6 ± 5	10.0 ±7**	-77.57

*: Significant; **: High significant; DA: Dopamine; NE: Norepinephrine; 5-HT: Serotonin; 5-HIAA: 5-hydroxy indole acetic acid.
C : Control; T: treaded

In the present study, the oral administration of the cannabis extract dose (5 mg/100 g body weight) caused an increase in DA, NE and 5-HT content and a decrease in 5-HIAA content in the brain tissue of rats (Table 1). From the present results, it seems clear that the increase in the whole brain contents of DA, NE and 5-HT after the administration of cannabis may be due to the fact that cannabis acts as a monoamine oxidase inhibitor. On the other hand, the decrease in 5-HIAA concentration may be due to the decrease in turnover of 5-HT. These results are in agreement with previous findings (Truitt *et al.*, 1963; Chakravarty *et al.*, 1976; Sofia *et al.*, 1971 and *S*churr and Rigor, 1984).

It is relevant to conclude that the decreasing in AChE activity in brain, the largest and the major component of the central nervous system, is a reflection of parallel changes in the other neurotransmitters in brain tissues.

B- Blood Biochemical Parameters

The average of blood glucose, (Table 2) tended to be increased by cannabis dosing level whereby the increase from 84.4, 80.6 and 82.0 (mg/dl) in the control groups to 94.5, 106.8 and 108.5 (mg/dl) in the 15, 30 and 45 days of cannabis treatment respectively. Moreover, treatment with cannabis methanol extract led to significant ($P \leq 0.01$) increases in G-GT (IU/L) from 7.92, 7.6 and 8.1 in the control groups to 8.99, 12.95 and 15.41 after 15, 30 and 45 days post-treatment respectively.

There were significant decreases in testosterone concentration in treated rats. The higher reduction in the hormone level was observed after 45 days post-treatment.

Prolonged administration of cannabis (45 days) caused a highly significant increase in blood glucose level than short-term administration (15 days). This may reflect higher demands of energy and that THC administration causes an increase in the level of adrenaline in blood which is well known to affect the glycogen stores in the liver and convert glycogen to glucose in blood. These results are in agreement with those by Sanz *et al.* (1985) who indicate that cannabis increases the energetic requirements of the cell by mobilizing the enzymatic system which are necessary for its own metabolism, these actions occur at the expense of intracellular stores of glycogen. Similarly Wilber and Morrison (1955) and Mahfouz *et al.*

Table (2): Effect of oral administration (5mg /100 g body) of cannabis extract on the serum glucose and testosterone levels, and the G-GT activity in serum of male rats

Days of adminis.	Glucose (mg/dl)			Testosterone (ng /ml)			G-GT (IU/L)		
	C	T	% change	C	T	% change	C	T	% change
15	84.4 ±5	94.5 ±7*	+11.97	1.43 ±0.020	1.3 ±0.022*	-9.09	7.92 ±0.35	8.99 ±37*	+13.51
30	80.6 ±2	106.8 ±3**	+32.51	1.54 ±0.022	1.25 ±0.027**	-18.83	7.60 ±0.42	12.9 ±1.1**	+70.39
45	82.0 ±6	108.5 ±8**	+33.31	1.61 ±0.027	1.24 ±0.022**	-22.98	8..10 ± 0.36	15.41 ±1.6**	+90.25

*: Significant; **: High significant; G-GT: Gamma-glutamyl transpeptidase; C: Control; T: Treaded

(1975), concluded that the increase in blood glucose was obtained in the terminal stages of chronic parathion poisoning.

Our results indicate also that cannabis administration causes significant increases in the enzyme G-GT activity. These increases were higher after 30 and 45 days post-treatment, which could be an indicator for disrupted testicular function concomitant with sertoli cells plasma membrane damage and reduction in the spermatogenic activity, leading to oligospermia and infertility syndrome. The increased G-GT was accompanied also by a reduction in testosterone concentration which my reflect hazard effects on Leydig cells.Since, previous reports showed that G-GT activity is a sensitive marker for the incidence of primary and secondary carcinoma in liver (Whithy *et al.*, 1993) and testis functions (Caston and Sanborn, 1988) which support our findings. The decrease in the level of testosterone is expected to affect the biological activity of sertoli cells (Dyme, 1983). In this respect Rodin *et al.* (1987), mentioned that persisting depression of the free testosterone in treated male epileptics may be attributed to either Leydig cell exhaustion or direct toxic effect of anticonvulsant drugs on the testis, which in close agreement with our results. It appears also that cannabinoids effect on testosterone level is mainly due to their influence on GnRH release from the hypothalamus through the hypothalamic-pituitary–gonadal axis which in close agreement with Chakravarty and Ghosh (1981); Park *et al.* (2004) and Tasker (2004).

The results obtained for testosterone level are good indicator for the harmful effects of cannabis administration on semen quality traits and general sexual activity which is dependent upon testosterone level in blood which agree with and closely support the findings of Kreek *et al.* (2002).

C- General Activity

Table (3) shows the general activity and quiescence time of cannabis-treated and control rats. The experimental animals exhibited a significant reduction in their activity than the control group. Sexual activity of male rats, expressed as the time elapsed (min/h) in courtship, libido, mounting and intromission, was significantly decreased from 4.6 minutes after 15 days of cannabis treatment to 2.2 and 1.9 min at 30 and 45 days post- treatment respectively. A similar decrease was noticed for the non-sexual activity behavior. As a result of these behavioral changes, the quiescence time increased.

Table (3) : Effect of oral administration (5 mg/100 g body) of cannabis extract on general behavior (min/hr) of male rats

Days of adminis.	Sexual activity				Non sexual activity				Quiescence time			
	C	%	T	%	C	%	T	%	C	%	T	%
15	8.4 ±0.7	15.5	4.6 ±0.5*	7.7	14.0 ±1.2	23.5	9.8 ±1.8*	16.4	37.6 ±1.2	62.7	45.6 ±1.5*	76.7
30	10,1 ±0.7	16.8	2.2 ±0.6*	3.7	15.8 ±1.6	26.3	5.3 ±1.9*	8.8	34.1 ±1.3	56.8	52.5 ±1.7*	87.4
45	9.1 ±0.7	15.2	1.9 ±0.4*	3.2	13.6 ±1.3	22.7	4.7 ±0.9**	7.8	37.3 ±1.5	62.2	53.4 ±0.9*	9.0

*: Significant; **: High significant; Results are expressed as the mean ±S.E ; C: Control; T: Treaded

The present results clearly show that THC administration reduced sexual activity of males, and this response was higher after 45 days of treatment. Non sexual activities also decreased from 13.6 to 4.7 minutes after 45 days. It is well known that sexual activity depends upon the sex male hormone (testosterone) level in the blood, which in our results significantly decreased (Table-2).

The non–sexual activities such as feeding, walking and behavioral responses are depending, however, on the biogenic amines in the brain which increased significantly in our results. This may explain the lower activity of treated rats as a result of cannabis administration. In agreement with the findings of many authors who found that both biogenic amines, especially DA and 5-HT are related to different behavioral activities via hypothalamic pituitary-gonadal or adrenal axis, however, the quiescence time being related mainly to serotogenic activity in brain (Jackson and Murphy, 1997; Kreek *et al.*, 2002; Howlett *et al.*, 2004; Park *et al.*, 2004 and Tasker, 2004).

From the data obtained in this work it is suggested, that long–term cannabis methanol extract oral administration could stimulate dopaminergic, adrenergic and serotonergic reurons causing an increase in their levels in brain tissues. At the same time the cholinergic activity decreased. These responses are proposed to suppress the sexual behavior of male rats via different neuroendocrine (DA, NE, 5-HT and testosterone); biochemical (G-GT and glucose levels) and behavioral aspects (quiescence syndrome).

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تأثيرتناول (تعاطى) مستخلص القنب (البانجو) على الامينات الحيوية في المخ والسلوك التناسلى لذكور الجرذان

حمدي أحمد مكاوى* – دولت علي سلامه – إبراهيم الوردانى*****

** المركز القومي للبحوث الاجتماعية والجنائية- الزمالك- القاهرة - مصر*

*** قسم الكيمياء الحيوية- كلية الزراعة- جامعة عين شمس- القاهرة - مصر*

**** قسم انتاج الدواجن- كلية الزراعة- جامعة عين شمس- القاهرة - مصر*

- اجريت هذه الدراسة علي ذكور الجرذان لمعرفة تاثير تناول مستخلص نبات القنب (البانجو) عن طريق الفم وذلك لفترات زمنيه مختلفة (١٥،٣٠،٤٥ يوما) علي السلوك التناسلي وبعض الامينات الحيوية في نسيج المخ وكذلك بعض الهرمونات والانزيمات ذات الصلة بوظائف الجسم.
- تم استخدام جرعة واحده من المستخلص هي ٥ ملليجرامات لكل ١٠٠جرام من وزن الجسم بينما اعطيت مجموع المقارنة محلول فسيولجي بنفس الطريقة (توين-٨٠).
- اخذت عينات من نسيج المخ ومن الدم لتقدير الامينات الحيوية وبعض الانزيمات والهرمون الذكري وذلك بعد الفترات الزمنية السابقة.
- إتضح من النتائج حدوث زيادة معنوية في محتوي نسيج المخ من الدوبامين،السيروتونين، والنورادرينالين بينما إنخفض مستوي انزيم الاسيتيل كولين استريز وحمض هيدروكسي إندول استيك وكان لطول فترة التعاطي تأثير كبير في هذا الشأن وبصفة خاصة بعد ٣٠ و ٤٥ يوما من بداية التجربة
- حدثت زيادة معنوية في مستوي سكر الدم مع زيادة في نشاط انزيم جاما – جلوتاميل ترانسبتيديز كدليل علي تدهور وضعف نشاط الخصية في تكوين وانتاج الحيوانات المنوية.
- إنخفض مستوي الهرمون الذكري (التستوستيرون) معنويا وبصورة كبيرة وبصفة خاصة مع زيادة فترة التعاطي.
- كان للنتائج المعملية السابقة تأثير سيئ علي النشاط الجنسي لذكور الجرذان حيث إنخفضت الرغبة الجنسية لديها كما تأثرت الانشطة الاخرى (التغذية- الشرب- المشي....الخ) واصيبت الجرذان بالخمود وازدادت فترات الخمود وضوحا بزيادة فترة التعاطى.

اتضح من نتائج هذه الدراسة: إن تعاطي مستخلص نبات القنب (البانجو) لفترات زمنية مختلفة (بالجرعة التي تم تجربتها) كان له تأثير منبه لزيادة الامينات الحيوية – انزيم جاما- جلوتاميل ترانسبتيديز واخر مثبط لإنزيم اسيتل كولين استيريز اضافة الي انخفاض مستوي الهرمون الذكري وكان لهذه التغيرات تأثير علي الاتزان الفسيولوجي للجرذان وانخفاض نشاطها العام والذى يعتبر كمؤشر علي تدهور قدراتها الاخصابية.

تحكيم : أ.د./ سلوى احمد عيد و أ.د./ احمد ابراهيم ابو شادى