Assiut Vet. Med. J. Vol. 41 No. 81, April 1999

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THE EFFECT OF CHRONIC OPIOID AND ACUTE AMPHETAMINE ADMINISTRATION ON SOME METABOLIC AND GONADAL HORMONE LEVELS IN ADULT MALE RATS

(With 2 Tables and 8 Figures)

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(Received at 6/2/1999)

التأثير المزمن لحقن معضد الأفيون والتأثير الحاد لحقن الأمفيتامين على مستوى بعض الهرمونات الأيضية والجنسية لذكور الفئران البالغة

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أجريت هذه الدراسة على (٥٠) خمسين من ذكور الفئران البالغة تتراوح اوزانها من (١٧٠ – ١٩٠ جرام وزن جسم). وقد استهدفت هذه الدراسة توضيح تأثير الحقن المزمن لكبريتات المورفين بجرعة منخفضة (١٠ مللجم / لكل كجم من وزن الجسم) وكذا بجرعة عالية (٢٠ مللجم / لكل كجم من وزن الجسم) لمدة اسبوعين متتاليين. وكذلك التأثير الحاد لحقن الأمفيتامين (٣،٤– مثيلين داي أوكسي ميث أمفيتامين ، م د م أ) كجرعة واحدة (٥ مللجرام / كجم من وزن الجسم) على مستوى هرمونات التراي أيودو ثيرونين ، الثيروكسين ، الكورتيكوستيرون والتيستوستيرون في بلازما هذه الفئران. أدى الحقن المزمن (لكل من الجرعة المنخفضة والعالية) لكبريتات المورفين إلى انخفاض معنوي في مستوى بلازما هرمونات التراي أيودو ثيرونين، الثيروكسين و التيستوستيرون ، بينما ازادا مستوى هرمون الكورتيكوستيرون زيادة معنوية في بلازما ذكور هذه الفئران. بينما لم يؤدي سحب حقن المورفين لمدة أسبوع إلى تغييرات معنوية في مستوى هذه الهرمونات سواء الأيضية أو الجنسية. وقد أدى الحقن الحاد للأمفيتامين (م د م أ) إلى زيادة معنوية واضحة في كل من مستوى هرموني الكورتيكوستيرون والتيستوستيرون في بلازما ذكور هذه الفئران خلال فترات أخذ عينات التجربة (١ ، ٣ و ٢٤ ساعة) بعد حقن الأمفيتامين. بينما لم يكن هناك أى تأثير معنوي لحقن الأمفيتامين في ذكور تلك الفئران على مستوى هرمونات الغدة الدرقية (التراي أيودو ثيرونين و الثيروكسين) مقارنة بقيم المجموعات الضابطة.

SUMMARY

The present investigation was carried out on fifty adult mature male rats weighing between 170 - 190 g. b.wt. The aim of this study is to clarify the effect of chronic morphine sulphate administration at low dose (10 mg/kg b.wt) and high dose (20 mg/kg b.wt) for two weeks and also the effect of acute amphetamine treatment (3,4-Methylenedioxymeth-amphetamine, MDMA) at a dose (5 mg/kg b.wt) as a single shot on triiodothyronine (T_3), thyroxine (T_4), corticosterone and testosterone hormone levels in the rat plasma. Chronic morphine administration (both low and high doses), significantly decreased plasma T_3 , T_4 and testosterone levels, while the plasma corticosterone level was significantly increased in male rat plasma. One week later after stopping of treatment (morphine withdrawal), all the former changes were still prominent. Acute amphetamine administration (MDMA) significantly increased both plasma corticosterone and testosterone levels in male rat plasma throughout the experimentation sampling periods (1, 3 and 24 hours) post-amphetamine administration. However, no statistical significant alterations in plasma T_3 and T_4 levels in amphetamine-treated male rats as compared to respective control values.

Key words: *Morphine-Amphetamine-Thyroxine-Triiodothyronine-Corticosterone-Testosterone-Rats.*

INTRODUCTION

Hypothalamic neurotransmitters release may play a role in regulation of reproductive and gonadal hormones secretion, such as dopamine, neuropeptide K, exitatory amino acids as glutamate and aspartate and norepinephrine (Levine et al., 1991 and Nishihara et al., 1991). Similarly, hypothalamic endogenous opioid peptide (EOP) play a major role in regulation of reproductive function in adult male rat (Piva et al., 1986, Levine et al., 1991 and Nazian, 1992).

Morphine and methadone injection reduced serum leutinizing hormone (LH) and testosterone concentration (Piva et al., 1986). This action is mediated via pituitary-gonadal-axis as indicated by decreased concentrations of LH and testosterone (Cicero et al., 1976). Both opioid agonists and antagonists (morphine and naloxone) altered LH-RH receptors in rat pituitary tissue (Barken et al., 1983), but this changes in LH receptors were attributed after that to changes in endogenous LH-RH release (Shupnik,

1996), indicating neural rather than pituitary site of opioid action (Shacoori et al., 1992).

However, opiate-induced hyperprolactinaemia was accompanied by reduction in serum testosterone level via impairement of gonadotropin secretion as well as the direct effect of prolactin (PRL) on Leydig cell function (Tresguerres et al., 1985).

In males, it was found that intracerebroventricular injection of β-endorphine suppressed pulstile discharge LH in concious moving castrated rats (Bonavera et al., 1993). Similarly, β-endorphine inhibited K-evoked LH-RH release from mediobasal hypothalamic sites (Drouva et al., 1981). Dynorphine administration inhibited LH secretion in concious castrated rats (Kinoshita et al., 1982) and man (Delitala et al., 1983).

Peripheral administration of acute morphine and opioid peptides decreased basal and cold-stimulated thyrotropin (TSH) secretion in rats (Bruni et al., 1977, Sharp et al., 1981 and Rauhala et al., 1988) and increases rat prolactin (PRL) secretion (Rivier et al., 1977). Chronic methadone treatment (with no acute challenge dose of methadone) had been reported to decrease basal serum TSH levels in young adult rats (Kuhn and Bartolome, 1985). However, whether tolerance develops to the endocrine (TSH and PRL) effects of acute opiate action is unclear. Morley et al. (1980) claimed that no tolerance is developed to the acute morphine challenge on TSH secretion in rats. On the other hand, tolerance had been demonstrated to the effects of methadone challenge on TSH and PRL secretions (Kuhn and Bartolome, 1985). Development of tolerance to cold stimulated TSH secretion (+ 4°C) was driven by enhanced thyrotropin releasing hormone (TRH) activity in the hypothalamus (Männisto, 1983). Acute morphine administration led to depressent effect on cold-stimulated TSH secretion after (2 hrs) and consequently triiodothyronine (T_3) and thyroxine (T_4) (Männisto et al., 1994). Chronic cocaine administration enhanced corticosterone levels in male rat plasma (Budziszewska et al., 1996).

Systemic administration of MDMA resulted in a transit elevation of rat brain dopamine content (3 hrs) post-administration (Schmidt et al., 1985; Schmidt et al., 1987 and Stone et al., 1988) suggestive of drug-induced of dopamine release in vivo.

Behavioural excitation caused by amphetamine administration was antagonized by pre-treatment of rats with either opioid antagonist, naloxone or dopamine receptor antagonist, haloperidol. Amphetamine-induced excitation was not associated with elevation of thyrotropin releasing hormone or thyroid hormone secretion (Lin et al., 1983 and Little et al.,

1988). Chronic d-amphetamine administration, elevated cortisol levels in human abusers (Little et al., 1988) and plasma corticosterone in rats (Budziszewska et al., 1996).

The present investigation was carried out to clarify the effects of chronic morphine administration, morphine withdrawal and 3, 4-methylene dioxymethamphitamine, (MDMA) treatment on T_3, T_4, corticosterone and testosterone levels in male rat plasma.

MATERIAL and METHODS

Experiment I:

The experiment was carried out on thirty adult mature male Sprague-Dawley rats purchased from National Research Centre weighing from 170-190 g b.wt., food and water were available ad libitum. Rats were divided into three equal groups (10 rats each).

Morphine sulphate* was administered chronically once a day at 9.00 AM for two successive weeks. Rats of the first group were injected intra-peritoneally (i.p.) with a constant low dose morphine sulphate (10 mg / kg b.wt.). Rats of the second group were injected (i.p.) with a constant high dose morphine sulphate (20 mg / kg b.wt.). Rats of the third group were injected (i.p.) with equivalent volume of saline (0.5 ml 0.9% NaCl saline solution) and served as a control group. All rats were injected once-daily at 9.00 AM for two successive weeks (Rauhala et al., 1988). Rats were kept for another week (third week) without any treatment.

Blood samples were taken at the end of every week at 9.00 AM from each experimental group.

Experiment II:

The experiment was carried out on twenty adult mature male rats weighing 170-190 g b.wt. The rats were divided into two equal groups (10 rats each).

Rats of the first group were injected with 3,4-methylene dioxymethamphetamine, (MDMA**) as a single (s.c.) shot (0.2 ml 0.9% NaCl saline solution containing equivalent dose as 5 mg / kg b.wt.). Rats of the second group were injected s.c.once with (0.2 ml 0.9% NaCl saline

*Morphine sulphate was supplied by (Misr Co. for Pharm. Indust. A.R.E.)

**MDMA, 3,4-methylene dioxymethamphetamine supplied by (Sigma Chem. Co.)

solution) and served as a control group. All injections were occurred at a fixed time 9.00 AM (Stone et al., 1988).

Blood samples of both groups were taken after 1, 3 and 24 hour(s) either post-amphetamine or post-saline administration respectively.

Blood sampling:

All blood samples were collected by orbital sinus technique into polyethylene tubes containing 50 i.u. heparin*. Individual plasma samples were separated by centrifugation at 3500 r.p.m. for 15 minutes and kept at (-20°C) till hormonal assay was carried out.

Hormonal assay:

(a) Plasma triiodothyronine (T_3) was assayed using (DPC, RIA) kit according to the method adopted by Uiger (1980).

(b) Plasma thyroxine was determined using (DPC, RIA) kit according to the method adopted by Wenzel (1981).

(c) Plasma corticosterone concentration was determined flurometrically using spectroflurometer according to the method of Matinglay (1962).

(d) Plasma testosterone was assayed using (DPC, RIA) kit according to the method adopted by Vreeburg et al., (1984).

Statistical analysis:

Data were subjected to ANOVA test and LSD calculation, while the difference between means were subjected to "t" test (Snedecor and Cochrane, 1980).

RESULTS and DISCUSSION

The significant decrease of both plasma triiodothyronine (T_3) and thyroxine (T_4) as a result of chronic morphine administration (Table, 1 and Fig. 1 & 2) assured the marked suppression of thyrotropin and thyroid hormones secretion (Berglund et al., 1990, del-Valle-Soto et al., 1991 and Dou and Tang, 1993).

Berglund et al. (1990) found that the morphine-induced suppression of TSH release requires circulating thyroid hormone. When thyroidectomized (THX) rats were chronically-treated with morphine or placebo, then injected s.c. (with saline or 1, 10 or 100 μg T_4/kg b.wt.) 24 hrs prior to serum collection, morphine treatment alone did not affect TSH in THX rats. T_4 replacement caused a dose-dependent decrease in serum TSH in both morphine and placebo rats. However, TSH was suppressed significantly

*MDMA, 3,4-methylene dioxymethamphetamine supplied by (Sigma Chem. Co.)

more in morphine than in placebo rats. While, chronic morphine treatment is ineffective in suppressing of TSH in THX rats, morphine interacts with thyroid hormone to reduce TSH release. Berglund et al., 1990 and del-Valle-Soto et al., 1991) suggested that morphine may exert its inhibitory effect on TSH secretion by increasing the negative feedback sensitivity to thyroid hormones. Later, the thyroid hormones secretion was lower in opioid-treated than non-morphine treated rats (control animals). Moreover, del-Valle-Soto et al. (1991) found that the morphological changes in the pituitary TSH cells and thyroid cells of morphine treated rats (10 μg / kg b.wt.) were of minimal activity and were not modified by morphine antagonist "naloxone" (10 mg/ kg b.wt.) pretreatment. Plasma TSH levels in morphine-treated rats showed a significant decrease ($P<0.05$), which was not blocked by naloxone pretreatment. No significant changes in plasma T_3 or T_4 levels were found in either morphine-treated or morphine-treated animals pretreated with naloxone (del-Valle-Soto et al., 1991).

However, Dou and Tang (1993) found that in hypothyroid rats (either by propylthiouracil treatment or by thyroidectomy); the decrease in serum TSH levels to acute morphine (5 to 20 mg / kg b.wt.) administration was not abolished owing to the lack of negative feedback action of thyroid hormones indicating that the hypothalamic factors are probably unimportant in the regulation of TSH secretion.

The results of the present investigation are in agreement with aforementioned results of (Berglund et al., 1990 and del-Valle-Soto et al., 1991). While, our results are disagreement with Budziszewska et al. (1996) who found that neither acute nor repeated administration of cocaine had any significant effect on the level of thyroid hormones (T_3 & T_4). So, the hypothalmo-pituitary-thyroid (HPT) axis seems to be more resistant to cocaine administration.

Regarding morphine withdrawal, the results (Table, 1 and Fig. 1 & 2) revealed that both plasma levels of T_3 and T_4 were still significantly lower than those of control values ($P<0.01$). A statistical significant difference between plasma values of T_4 in (low and high dose) morphine-withdrawn rats was detected. On the contrary, there was no significant difference between plasma T_3 values in (low and high dose) morphine-withdrawn rats ($P<0.01$). The explanation of this result may be attributed to rapid utilization rate of triiodothyronine (T_3) with low T_4 / T_3 conversion rate.

Concerning plasma corticosterone level (Table, 1 and Fig. 3) in male rats treated with morphine sulphate; both low and high doses induced a significant elevation in its level at $P<0.01$ after one and two weeks treatment.

The present results are disagreement with those of Block et al. (1991) who found that chronic marijuana use (frequent, moderate and infrequent) in either men or women did not lead to significant alterations in plasma cortisol levels. Moreover, Dygalo et al. (1992) found that opioid receptor agonist (morphine 10 mg/kg/day) to pregnant rats throughout the 15-18 days of gestation, caused a long lasting inhibition of the testes and activation of the adrenals of neonatal offspring. The block of opioid receptors by naloxone (10 mg/kg/day) prevented the prenatal stress on the adrenal and elevation of the plasma corticosterone levels in 2-month-old male rats born by morphine-exposed females. The present results of this investigation (Table, 1 and Fig. 3) are in agreement with those of Budziszewska et al. (1996) who found that acute and chronic cocaine (15 mg/kg B.W., i.p. once an hour for 3 hr for 8 days) elevated the corticosterone level. These results indicated that repeated cocaine administration enhanced the activity of the hypothalamo-pituitary-adrenal (HPA) axis in male rats. Moreover, corticosterone elevation had a direct inhibitory effect on testicular weight and serum testosterone concentration owing to the marked suppression of serum LH and FSH in intact male rats (Bambino and Hsueh, 1981, Welsh et al., 1982 and Vreeburg et al., 1984).

Results of plasma testosterone levels (Table, 1 and Fig. 4) showed a significant reduction in its values by both low and high doses of morphine sulphate as compared to control values ($P<0.01$). These results are in agreement with Adams et al. (1993) who found that morphine exerts drastic effects on testicular function that are independent of its effects on LH. They furthermore support the hypothesis that both endogenous and exogenous opioids disrupt two major aspects of testicular function: testosterone secretion and testicular interstitial fluid (TIF) formation. Because of the role of TIF in maintaining testicular function, they suggested that opioid-induced changes in testosterone secretion into TIF and TIF formation. Moreover, Paice et al. (1994) concluded that intraspinal therapy of opioid into patient subjects lead to adverse effects on sexual libido and supression of serum testosterone due to testicular dysfunction. Additionally, Siddiqui et al. (1995) found that male offsprings (120 d age) born from female rats subjected to intrauterine morphine exposure at premating period had a complete abolition of spermatogenesis and drastic reduction of testicular steroidogenesis. Their plasma LH levels were low and hypothalamic noradrenaline was high. Budziszewska et al. (1996) concluded that repeated cocaine administration decreased the level of androgens in male rats suggesting that cocaine lead to a decrease in hypothalamo-pituitary-gonadal (HPG) axis activity.

The present investigation (Table, 1 and Fig. 4) revealed that morphine withdrawal did not alter the drastic effect of morphine administration on testosterone production.

Regarding the effect of acute amphetamine administration on thyroid activity (T_3 & T_4 secretion). The present results (Table, 2 and Fig. 5 & 6) showed no statistical significant alterations in plasma T_3 and T_4 levels of amphetamine-treated rats in comparison with their respective control throughout the experimental sampling times (1, 3 and 24 hours). Our results in the present study are in agreement with Budziszewska et al. (1996) who found that neither acute nor repeated amphetamine administration in male rats had any significant effect on the level of plasma T_3. While, they added that chronic amphetamine only, led to reduction in plasma T_4. Moreover, Little et al. (1988) suggested that d-amphetamine abuse caused excessive secretion of TSH and T_4. Such an amphetamine-induced effect might be noradrenergic-mediated in the hypothalamus. No acute effect of d-amphetamine administration on plasma TSH, T_3 or T_4 levels.

Concerning the effect of acute amphetamine administration (Table, 2 and Fig. 7), amphetamine-treated male rats had a significantly ($P<0.01$) higher plasma corticosterone levels than those of control allover the 24 hours experimentation period. The results of the present investigation are in agreement with those of Little et al. (1988) who found that d-amphetamine abuse in human elevated cortisol levels at 180 min. post-injection. Budziszewska et al. (1996) concluded that either acute or chronic amphetamine administration elevated the level of corticosterone at 2 hours in male rats.

Plasma testosterone levels (Table, 2 and Fig. 8) at 1, 3 and 24 hours post-amphetamine administration were significantly ($P<0.01$) higher than those of controls. Present results are in agreement with Budziszewska et al. (1996) who found that acute amphetamine administration increased both testosterone and androstenedione plasma levels in male rats.

In conclusion, chronic morphine administration has a depressing effect on both thyroid and testicular hormonal levels and a stimulating effect on corticosterone production. Acute amphetamine administration has a stimulating action on both adrenal and testes secretions in male rats.

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Table 1 : Effect of chronic morphine administration and morphine-withdrawal on plasma levels of some metabolic and gonadal hormones in adult male rats.

Hormones	T_3 (ng / dl)			T_4 (ug / dl)			Corticosterone (ng / ml)			Testosterone (ng / ml)		
Duration / Group	1 week treat.	2 weeks treat.	1 week with.	1 week treat.	2 weeks treat.	1 week with.	1 week treat.	2 weeks treat.	1 week with.	1 week treat.	2 weeks treat.	1 week with.
Control (saline)	120.0 ± 4.36	124.8 ± 5.27	126.0 ± 3.62	5.00 ± 0.13	5.30 ± 0.13	5.20 ± 0.14	170.0 ± 5.55	164.0 ± 4.28	161.0 ± 4.26	3.30 ± 0.06	3.50 ± 0.14	3.40 ± 0.10
Low dose (10 mg/kg b.wt.)	80.00[a] ± 6.27	73.00[a] ± 4.14	100.00[a] ± 3.28	3.50[c] ± 0.14	3.00[c] ± 0.05	4.62[c] ± 0.09	245.0[e] ± 8.62	280.0[e] ± 6.09	180.0[e] ± 4.42	2.90 ± 0.08	2.70[g] ± 0.09	3.00[g] ± 0.07
High dose (20 mg/kg b.wt.)	70.00[b] ± 2.30	58.00[b] ± 2.72	92.00[b] ± 3.47	2.70[d] ± 0.06	2.00[d] ± 0.05	4.10[d] ± 0.11	320.0[f] ± 6.56	384.0[f] ± 8.01	193.0[f] ± 4.81	2. 60[h] ± 0.08	2.25[h] ± 0.10	2.50 ± 0.06
F-value	28.96	61.97	23.20	90.93	38.22	41.78	100.25	267.40	11.22	20.67	28.67	29.14
L.S.D. (for column)	17.47	15.82	13.12	0.42	0.34	0.34	26.62	23.92	17.07	0.28	0.42	0.30

- Data indicate Means ± S.E., (Treat.) = treatment, (with.) = withdrawal.
- Values having the same letter within the same raw are significantly different at $P<0.01$.

Table 2 : Effect of acute amphetamine administration on plasma levels of some metabolic and gonadal hormones in adult male rats.

Hormones / Group	T_3 (ng / dl)		T_4 (ug / dl)		Corticosterone (ng / ml)		Testosterone (ng / ml)	
	Cont.	Treat.	Cont.	Treat.	Cont.	Treat.	Cont.	Treat.
One hour post-treatment	118.70 ± 2.79	120.0 ± 3.86	5.20 ± 0.27	5.10 ± 0.29	172.0^a ± 5.73	614.0^a ± 37.51	3.83^b ± 0.22	5.60^b ± 0.10
3 hours post-treatment	121.0 ± 4.98	125.8 ± 6.42	5.00 ± 0.23	5.30 ± 0.25	183.0^c ± 4.85	305.0^c ± 16.18	3.75^d ± 0.18	5.10^d ± 0.25
24 hours post-treatment	123.0 ± 4.47	125.0 ± 4.64	4.85 ± 0.15	5.14 ± 0.23	178.0* ± 5.57	200.0* ± 6.40	3.70^e ± 0.18	4.80^e ± 0.19
F-value	0.23	0.30	0.55	0.16	0.92	79.33	0.11	3.02
L.S.D. (for column)	N.S.	N.S.	N.S.	N.S.	N.S.	85.88	N.S.	0.70

- Data indicate Means ± S.E., (Treat.) = treatment, (with.) = withdrawal.
- Values having the same letter(s) in the same raw are significantly different from each other at $P<0.01$.
- (*) values are significantly different at $P<0.05$.
- N.S. = non- significant, (Cont.) = control, (Treat.) = treated group.

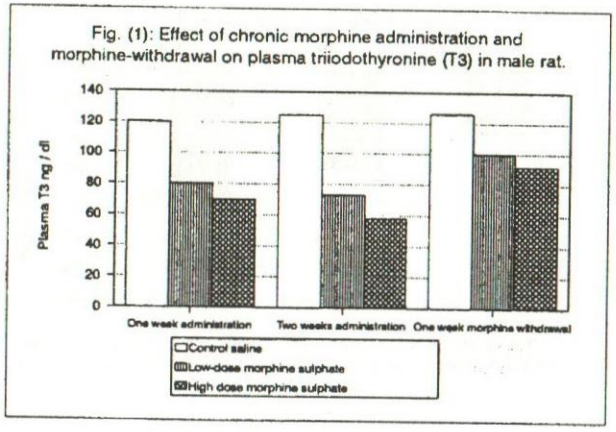
Fig. (1): Effect of chronic morphine administration and morphine-withdrawal on plasma triiodothyronine (T3) in male rat.
Plasma T3 ng / dl
140
120
100
80
60
40
20
0
One week administration
Two weeks administration
One week morphine withdrawal
Control saline
Low-dose morphine sulphate
High dose morphine sulphate

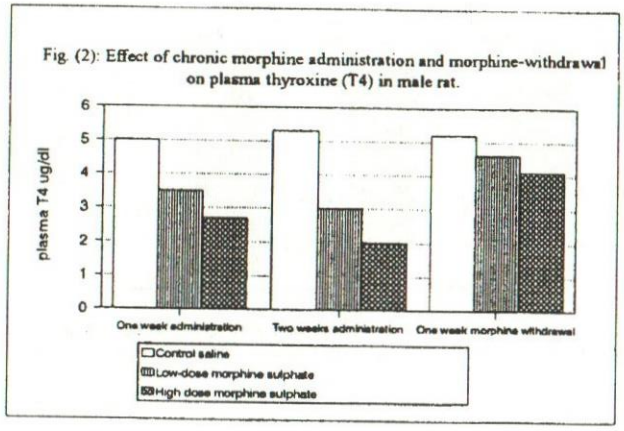
Fig. (2): Effect of chronic morphine administration and morphine-withdrawal on plasma thyroxine (T4) in male rat.
plasma T4 ug/dl
6
5
4
3
2
1
0
One week administration
Two weeks administration
One week morphine withdrawal
Control saline
Low-dose morphine sulphate
High dose morphine sulphate

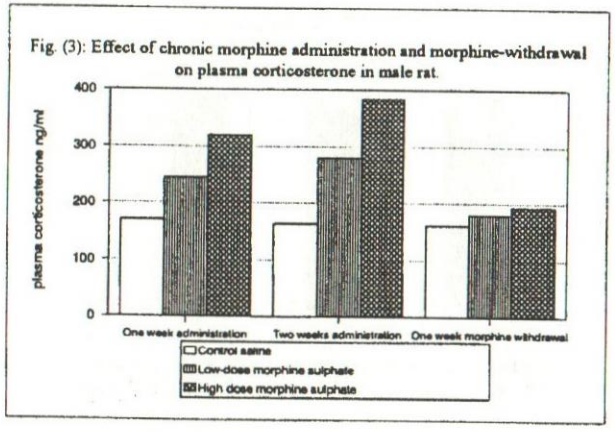
Fig. (3): Effect of chronic morphine administration and morphine-withdrawal on plasma corticosterone in male rat.
plasma corticosterone ng/ml
400
300
200
100
0
One week administration
Two weeks administration
One week morphine withdrawal
Control saline
Low-dose morphine sulphate
High dose morphine sulphate

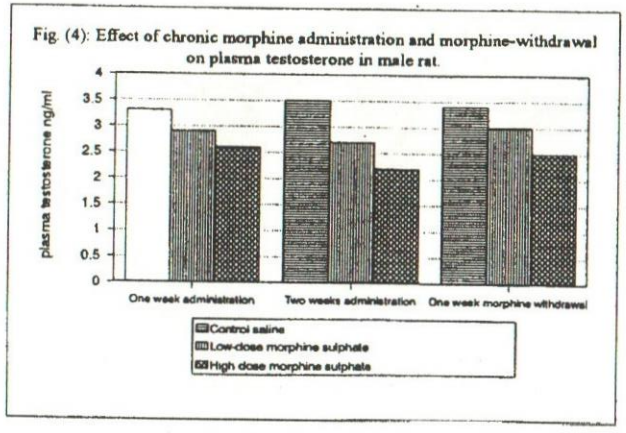
Fig. (4): Effect of chronic morphine administration and morphine-withdrawal on plasma testosterone in male rat.
plasma testosterone ng/ml
4
3.5
3
2.5
2
1.5
1
0.5
0
One week administration
Two weeks administration
One week morphine withdrawal
Control saline
Low-dose morphine sulphate
High dose morphine sulphate

Fig. (5): Effect of acute amphetamine (methylenedioxymethamphetamine) administration(MDMA) on plasma triiodothyronine (T3) in male rat plasma.

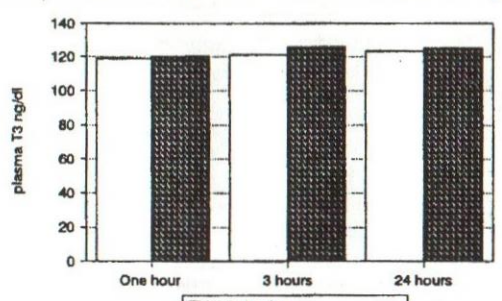

Fig. (6): Effect of acute amphetamine (methylenedioxymethamphetamine) administration(MDMA) on plasma thyroxine (T4) in male rat plasma.

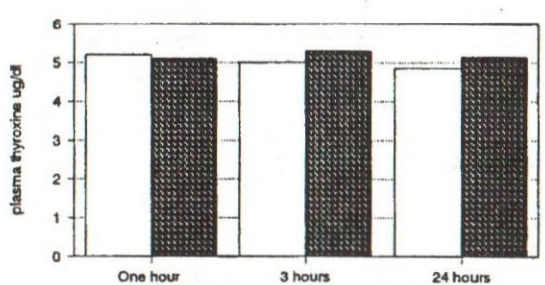

Fig. (7): Effect of acute amphetamine (methylenedioxymethamphetamine) administration(MDMA) on plasma corticosterone in male rat plasma.

Fig. (8): Effect of acute amphetamine (methylenedioxymethamphetamine) administration(MDMA) on plasma testosterone in male rat plasma.