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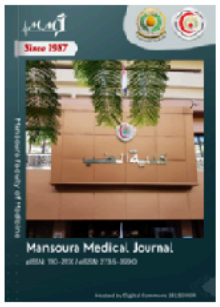

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INFLUENCE OF NICOTINE ON SEXUAL MATURATION AND UTERINE CONTRACTILE RESPONSE TO OXYTOCIN OR SEROTONIN IN FEMALE ALBINO RATS

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ABSTRACT

It has been found previously that nicotine inhibits ovulation and fertilization both in vivo and in vitro in rats. Furthermore the onset of puberty was reported to be associated with changes in pulsatile gonadotrophin - releasing hormones secretion in the hypothalamus. The objective of this study was to test the hypothesis that nicotine perturbs the onset of puberty and to explain the mechanism of this effect. In addition, it has been reported previously that nicotine may alter uterine fallopian tube function which mediate gamete and conceptus transport, so this work was also aiming at evaluation of difference in response of isolated rat uterus to either serotonin or oxytocin in nicotine pretreated and untreated female rats.

Nicotine in a dose of 0.5mg/kg/d. was injected I.P. to female rats from the day 15 of postnatal life induced retardation of the onset of puberty as assessed in terms of vaginal opening (64.3 ± 3.2 VS 43.5 ± 2.1 day in saline treated control). In addition the animals which have been given nicotine showed a significant decrease in serum levels of FSH, LH, oestrogen and progesterone beside increased serum level of prolactin as compared to saline treated control. The number of ova in the fallopian tubes released at first ovulation, weight of ovaries, uteri and whole body weight were significantly lower in comparison with nicotine untreated rats. Furthermore, postnatal life administration of nicotine in a dose of 0.5mg/kg/d, I.P. from the day 15 of age until the day of first ovulation induced a significant reduc-

tion in uterine contractile response to either oxytocin or serotonin (5 HT). Contractile properties of either oxytocin or 5HT on myometrium have had applications in obstetrics with the use of ergometrine (a partial agoinst of 5HT) to contract the uterus to reduce post partum haemorrhage, so the effect of ergometrine & oxytocin must be further studied in cases of cigarette smoking females.

INTRODUCTION

Nicotine has long been considered as the active agent in tobacco smoking (1). Nicotine is one of the few natural liquid alkaloids. It is a colourless volatile base that turns brown and acquires the odour of tobacco on exposure to air; nicotine is a highly toxic agent, 40-60mg may be lethal (2). It was concluded that nicotine inhibited ovulation, estradiol production and fertilization both in vivo and in vitro in rat models of ovulation (3). Both female and male smokers had elevated levels of adrenal androgens (3,4). It have been proposed that smoking directly influences steroid production and metabolism (4). The effect of smoking mothers on birth weight of their babies has been extensively studied (5). Many experiments on humans and animals were designed to relate smoking to birth weight and to explain the mechanism of this relation.

The preparation of the myometrium for parturition is dependent on the action of estrogens. An increase in the synthesis of oxytocin receptors are observed by the action of oestrogens (6). Oxytocin is recognised as a potent stimulant of myometrium contractility and contractile events of parturition (7). 5-hydroxytryptamine (5HT), stimulates myometrial smooth muscle cells to synthesize collagenase at the end of gestation which indicates that this amine has a possible contributary role in the ripening of the cervix and the timing of human parturation (8 & 9).

The objective of this work is to study the effect of nicotine administration to female rats during the prepubertal period on timing of sexual maturation and to study its effect on follicle stimulating hormone (FSH), leuteinizing hormone (LH) & prolactin (PRL) and female sex hormones (oestrogen & progesterone). Furthermore this work is aiming at evaluation of the difference in responses of isolated rat uterus to 5HT or oxytocin in nicotine pretreated and untreated female rats.

MATERIALS & METHODS

Drugs used:

Nicotine: Nicotine 95% (obtained from Hopkin Williams and LTD, England), it was diluted by normal saline.

5-hydroxytryptamine creatinine sulphate (5HT): The powder was dissolved in distilled water to obtain a concentration of 2400 NM/ml. (Sigma Co.).

Oxytocin: Commercial oxytocin distributed by Sandoz laboratories as 10 IU/ml solution.

Animals used:

Albino rats were obtained from the animal house of Mansoura Faculty of Medicine on the day of birth (day 0). All litters were kept with their mothers until day 15. They were maintained under similar housing conditions of humidity, temperature and photoperoid of 14H light and 10H dark. At day 15 females were separated from males. Female rats were divided into 2 groups:

Group (I): Control group, comprised 20 female rats injected daily with 0.5ml saline (IP) from the day 15 until the onset of puberty.

Group (II): Consisted of 20 female rats, injected daily, IP. with 0.5mg/kg nicotine daily from the day 15 until the onset of puberty (2).

Onset of puberty in female rats was detected by the day of first ovulation and vaginal opening (VO). The later was being assessed by daily inspection of female rats from the day 15 for the first sign of vaginal membrane rupture as previously reported (10).

Body weights were recorded every 2 days until the day of VO. Half of both groups was sacrificed on the day 35 & the other half was sacrificed on the day of first ovulation. Before decapitation, body weight of all animals was recorded. After decapitation the oviducts were dissected and flushed with sterile saline & the number of ova was counted under the microscope (9). In addition the weight of ovaries & uteri were determined. Blood was collected & the sera were separated for hormonal assays. Serum FSH, LH & PRL were analyzed by diagnostic ELISA kit supplied by Eurogenetics Co. (11). Serum oestrogen (E2) & progesterone were determined by ELISA using the Fertigenix - Easia kit, (12).

The uteri were dissected to be put in an isolated organ bath for recording response to oxytocin or

serotonin. De Jalon's solution(13) was used & the bath was aerated with carbogen (95% oxygen & 5% carbon dioxide). The experiments were started after the preparation had been allowed to equilibrate for about 60 minutes. Serotonin applied in concentrations of 50, 100 & 200NM/ml of water bath at 1.5 minute periods of application & 15-20 minutes intervals (6). Oxytocin was applied at intervals of 15-20 minutes for 1.5 minute in concentrations of 20, 40 & 80 NM/ml (6).

Statistics:

Results are presented as mean ±SE. Statistical evaluation of data was performed by using student's t-test, P-value of 0.05 or less was regarded as significant (14).

RESULTS

Nicotine administration to female rats daily in a dose of 0.5 mg/kg I.P. from the day 15 of postnatal life to the onset of ovulation, induced a significant decrease in body weight, weights of ovaries, uteri & number of ova. Furthermore, it induced a significant decrease in serum FSH, LH, E_2 & progesterone associated with a significant increase in serum PRL as shown in Tab. (1) & (2).

Nicotine administration as previously mentioned, produced a decrease in isolated uterine contractile response to either oxytocin or 5HT as compared to isolated uteri of rats that were not pretreated with nicotine as shown in (Fig. 1, 2, 3 & 4) & (Tab. 3 & 4).

Tab. (1): Effect of nicotine administration on age of vaginal opening (VO), body weight, weight of uteri, ovaries and number of ova in female albino rats (Mean ± SE)

Group	Age at VO	Body weight (g)	Uterine weight (mg)	Ovary/pair (mg)	Number of ova
Saline treated (0.2 ml/day I.P.)	43.5 ± 2.1	116.8 ± 3.9	152.3 ± 0.9	30.7 ± 1.1	5.7 ± 0.2
Nicotine treated (0.5 mg/kg/day) I.P. from day 15 up to VO	64.3 ± 3.2	95.8 ± 4.2	140.1 ± 0.8	25.1 ± 1.3	3.2 ± 0.1
P	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

- SE = standard error
- P = significance of difference between nicotine treated & saline treated female rats

Tab. (2): Serum concentrations of follicle stimulating hormone (FSH), leutinizing hormone (LH), oestrogen (E2), progesterone & prolactin of female rats treated prepubertally with saline or nicotine (M ± SE).

Group		FSH mIu/ml	LH mIu/ml	E2 pg/ml	Progesterone ng/ml	Prolactin ng/ml
Saline (0.2 ml, I.P.) at day 35		4.3 ± 0.11	1.6 ± 0.08	5.1 ± 0.12	0.21 ± 0.03	6.7 ± 0.3
Saline (0.2 ml I.P.) at day of ovulation	P	8.2 ± 0.16 < 0.01	11 ± 0.2 < 0.01	17.1 ± 0.33 < 0.01	0.9 ± 0.03 < 0.01	26.8 ± 0.28 < 0.01
Nicotine (0.5 mg/kg/d I.P.) at day 35	P P	4.3 ± 0.18 NS < 0.01	1.9 ± 0.07 NS < 0.01	6.4 ± 0.27 < 0.01 < 0.01	0.52 ± 0.02 < 0.01 < 0.01	26.3 ± 0.22 < 0.01 NS
Nicotine (0.5 mg/kg/d) at day of ovulation	P P	5.8 ± 0.2 < 0.05 < 0.01	6.7 ± 0.3 < 0.05 < 0.01	8.7 ± 0.3 < 0.05 < 0.01	0.57 ± 0.01 < 0.05 < 0.01	22.1 ± 0.3 < 0.01 < 0.05

- Nicotine treatment started on day 15 of postnatal life.
- SE standard error
- P significance of difference as compared to saline treated at day 35
- P significance of difference of nicotine treated as compared to saline treated rats at day of ovulation

Tab. (3): Effect of prepubertal nicotine treatment (0.5 mg/kg/day, I.P.) on uterine contractile response to oxytocin in rats (Mean ± SE).

	Uterine contractile response to oxytocin in rats pretreated with saline			Uterine contractile response to oxytocin in rats pretreated with nicotine		
Concentration of oxytocin in water bath	20 NM/ml	40 NM/ml	80 NM/ml	20 NM/ml	40 NM/ml	80 NM/ml
Uterine contractile response (cm)	1.1 ± 0.07	2.3 ± 0.03	2.8 ± 0.09	0.5 ± 0.02 $P_1 < 0.05$	1.2 ± 0.02 $P_2 < 0.05$	1 ± 0.07 $P_3 < 0.05$

- SE standard error.
- P_1 test of significance between nicotine pretreated and saline pretreated rats in presence of oxytocin concentration of 20 NM/ml.
- P_2 test of significance between nicotine pretreated and saline pretreated rats in presence of oxytocin concentration of 40 NM/ml.
- P_3 test of significance between nicotine pretreated and saline pretreated rats in presence of oxytocin concentration of 80 NM/ml.

Tab. (4): Effect of prepubertal nicotine treatment (0.5 mg/kg/day I.P.) on uterine contractile response to serotonin (5HT) in rats (Mean ± SE).

	Uterine contractile response to 5HT in saline pretreated rats			Uterine contractile response to 5HT in nicotine pretreated rats		
Serotonin concentration in water bath	50 NM/ml	100 NM/ml	200 NM/ml	50 NM/ml	100 NM/ml	200 NM/ml
Uterine contractile response (cm)	0.4 ± 0.02	0.4 ± 0.02	0.4 ± 0.02	0.2 ± 0.01 $P_1 < 0.05$	0.2 ± 0.01 $P_2 < 0.05$	0.2 ± 0.01 $P_3 < 0.05$

- SE. standard error.
- P_1 significance between saline pretreated and nicotine pretreated in presence of 5HT in a concentration of 50 NM/ml.
- P_2 significance between saline pretreated and nicotine pretreated in presence of 5HT in a concentration of 100 NM/ml.
- P_3 significance between saline pretreated and nicotine pretreated in presence of 5HT in a concentration of 200 NM/ml.

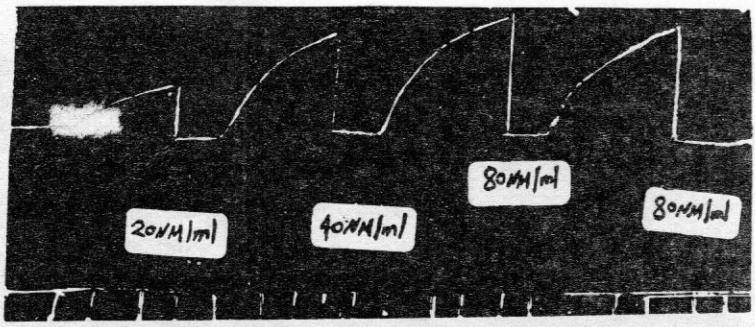

Fig. 1 : Uterine contractile response to oxytocin (saline pretreated) in rat..

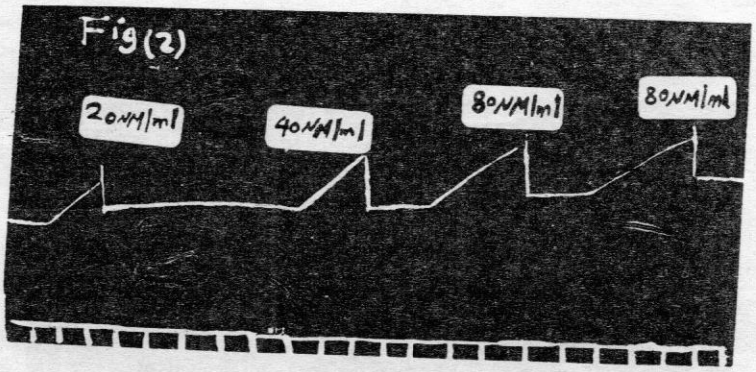

Fig. 2 : Uterine contractile response to oxytocin (nicotine pretreated) in rat..

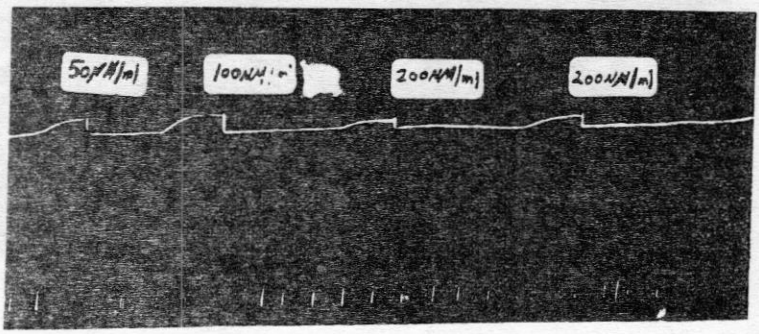

Fig. 3 : Uterine contractile response to serotonin "5HT" (saline pretreated) in rat.

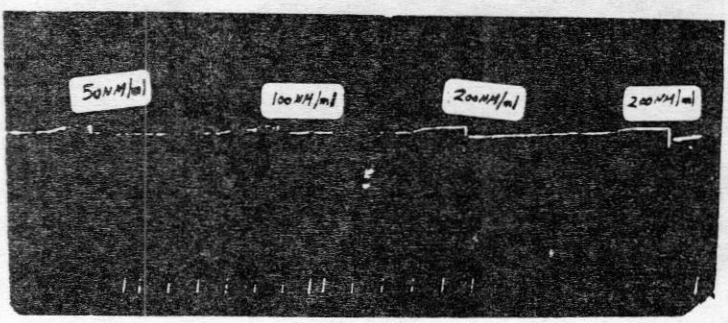

Fig. 4 : Uterine contractile response to serotonin "5HT" (nicotine pretreated) in rat.

DISCUSSION

In humans and in several animal species, puberty results from changes in pulsatile gonadotrophin - releasing hormones (GnRH) secretion in the hypothalamus. In particular, the frequency of pulsatile GnRH secretion increases at onset of puberty (15). The mechanism controlling that increase in frequency of pulsatile GnRH secretion at the onset of puberty is not fully elucidated. This mechanism could consist of either switching off an inhibitory control such as that of opioid peptides & or switching on a facilitatory control such as proposed for the excitatory amino acids, gultamate & aspartate (15). Dopamine is involved in the central effects of nicotine. It was reported that nicotine elicited a dose - dependent increase in dopamine release in the striatum and in the nucleus accumbens (16). Chronic administration of nicotine affected the circadian rhythm of dopamine in the striata of mice & this might affect the function regulated by this transmitter such as PRL level (17). Dopamine containing neurons in hypothalmus play an important role in regulating hypothalamo - hypophyseal function, so nicotine through its relation to dopamine may modulate gonadotrophins release. Cigarette smoking has been associated with decreased fertility in females. These effects of smoking may be related to adverse effects of nicotine (1).

In the present study serum FSH, LH, PRL, E_2 and progesterone levels in saline treated group on day of vaginal opening, which is the sign of first ovulation, were significantly higher than the same control group at day 35. These findings are consistent with data obtained previously (15). It was stated that first ovulation in pubertal female rats, which occur on the morning of vaginal opening, is caused by spontaneous surge of FSH & LH. This is brought about by a surge of GnRH acting upon the pituitary. These changes are associated with increase in serum oestrogen. Steroidogenic granulosa and theca cells cooperate under gonadotrophin control to produce estrogens by stimulating synthesis of steroidogenic enzyme messenger RNAs. Steroid synthesis is amplified further by local growth factors and follicular cell multiplication. Estrogen synthesis is directed by FSH, and only small amounts of LH are needed to amplify the follicular estrogenic potential (18, 19). The present study showed that VO of control animals happened at age of (43.5

±2.1) days while it occurred on day 64.3±3.2 in nicotine treated rats.

In the current study nicotine treatment during prepubertal period produced significant decrease in E_2 serum level. This finding is consistent with previous study (1). It was reported that nicotine has a direct anti-oestrogenic effect through inhibition of oestrogen synthesis and induction of its metabolism. The present study revealed hyperprolactinaemia in nicotine treated rats. The effect of nicotine on the level PRL may be produced through the inhibition of hypothalamic prolactin inhibitory factor (20). This factor has been shown to be dopamine (16).

The body weight at first ovulation was significantly lower in nicotine treated animals in comparison to saline treated rats. This can be explained by decrease in the secretion of growth hormone (GH) as a result of exposure to nicotine in the first weeks of life which represented the period of rapid growth that depends on GH in rats (21). The weight of ovaries & uteri were significantly lower in nicotine treated group. It has been reported that decreased level of pituitary gonadotrophins is responsible for the reduction of weight of ovaries & uteri (22). Also, estrogen synergizes with FSH at the ovarian level to increase the number of FSH receptors per granulosa cells. This process involves both induction & maintenance (23), which can be quantified by ovarian weight augmentation (19). The reduction in number of ova within the fallopian tube found in nicotine treated rats in the present study is consistent with the previous in vivo study showed that nicotine reduced the ovulation rate and perturbed the rate of oocyte maturation (24).

Oxytocin is a very potent stimulator of myometrial contraction, it acts by inhibition of calcium binding to myometrial microsomes, which results in an increase in intracellular free calcium & myometrial contraction through the formation of calmodulin calcium complex. Oxytocin acts also by inhibition of calcium-magnesium ATP-ase activity and increase of intracellular calcium level. This inhibition was found to be parallel to the increased oxytocin receptors in myometrium in late pregnancy (7). In the present study, there is a decrease in uterine contractile response to oxytocin in nicotine treated rats. This

decreased response can be due to decreased number of oxytocin receptors secondary to lower level of oestrogen & progesterone (6).

Serotonin induced uterine contractions through the subtypes of $5HT_{2A}$ receptors which are linked to phospholipase (C) with the generation of two second messengers; diacylglycerol which activates protein kinase (C) & inositol triphosphate which releases intracellular stores of calcium (25). The present study showed a decrease in uterine contractile response to 5HT in nicotine pretreated rats. It was suggested that uterine mast cells may mediate an oestrogen - oxytocin endocrine regulation of free 5HT concentration in the myometrium & inhibition in the rate of 5HT uptake which could affect the time of interaction of 5HT with its receptors (6).

Conclusions:

On the light of the present study, it could be concluded that prepubertal nicotine administration induced retardation in female rats sexual maturation. This retarded maturation may be due to decreased level of gonadotrophins, oestrogen and progesterone. In addition prepubertal nicotine administration to female rats decreased the uterine contractile response to either oxytocin or serotonin.

Contractile properties of oxytocin and 5HT on myometrium have had applications in obstetrics with the use of ergometrine (a partial agoinst of 5HT) to contract the uterus to reduce post partum haemorrhage. So the effect of ergometrine & oxytocin must be further studied in cases of cigarette smoking females .

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دراسة تأثير النيكوتين على النضوج الجنسى فى إناث الفئران البيضاء وإستجابة إنقباضات رحمها لكل من الأوكسيتوسين أو السيروتونين

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الملخص العربى

أجرى هذا البحث لدراسة تأثير إعطاء النيكوتين (باعتباره المادة الفعالة فى تدخين التبغ) لإناث الفئران البيضاء على النضوج الجنسى ومستوى هرمونات الغدة النخامية المسئولة عن تنظيم التبويض ومدى تأثيرة على وظائف المبيض وإنقباضات الرحم لكل من الأوكسيتوسين والسيروتونين.

قد لوحظ أن إعطاء النيكوتين بجرعة ٥ر٠ مجم/ك يومياً منذ اليوم ١٥ من العمر أخر البلوغ وحدوث التبويض الذى يلازم إنفراج المهبل الذى حدث فى اليوم ٦٤ بدلاً من اليوم ٤٣ من العمر وذلك فى المجموعة التى أعطيت نيكوتين بمقارنتها بالمجموعة الضابطة على الترتيب.وكان هذا التأخر فى النضوج مصحوباً بنقص ذو دلالة إحصائية فى وزن الجسم، المبيض والرحم، وعدد البويضات فى قناة فالوب وكذلك نقص فى مستوى كل من الهرمونات المنبهة لحويصلات المبيض وهرمون الإستروچين والبروجستيرون وذلك إلى جانب زيادة هرمون البرولاكتين، وذلك بالإضافة إلى إحداث تثبيط فى إستجابة عضلات الرحم المعزولة للإنقباضات تحت تأثير كل من الأوكسيتوسين أو السيروتونين ويرجع ذلك إلى قدرة النيكوتين على إنقاص هرمونى الإستروچين والبروجستيرون المسئولين عن تنظيم إنقباضات الرحم وإستجابته لكل من الأوكسيتوسين والسيروتونين. وحيث أن الخواص القابضة للرحم لكل من الأوكسيتوسين والسيروتونين لها تطبيق إكلينيكى فى علم الولادة وذلك لأن الأرجومترين (محفز جزئى لمستقبلات السيروتونين) يستخدم فى إحداث إنقباض الرحم وذلك لإيقاف نزيف مابعد الولادة، فإنه يجب المزيد من دراسة تأثيره فى السيدات المدخنات ، وكذلك أيضاً بالنسبة للأوكسيتوسين .