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Original Article

Effect of Concomitant Use of Flutamide and Luteinizing Hormone Releasing Hormone (LHRH) Analogue Versus Flutamide Alone on Pituitary Gonadotroph Cells of Adult Male Albino Rats

Morsy A. Abo-Elgoud and Manal E. El-Sawaf

Anatomy Department, Faculty of Medicine, Tanta University

ABSTRACT

Background: The anti-androgen (flutamide) is widely used nowadays in the treatment of cancer prostate either alone or in combination with Luteinizing Hormone Releasing Hormone (LHRH) analogues. These drugs block androgen receptors, thus prevent growth of cancer cells. Meanwhile, gonadotroph cells of the anterior pituitary may be affected.

Aim of the work: To study the effects induced by flutamide administration in the presence or absence of concomitant use of LHRH analogue on gonadotrophs.

Materials and methods: Twelve adult male albino rats were divided into three groups: Group (I) rats were served as controls, Group (II) rats were given flutamide orally while Group (III) rats were given flutamide combined with LHRH analogue. The experiment lasted for 20 days after which the rats were sacrificed and pituitary glands were collected. Samples were processed for Hx.&E., immunohistochemistry and electron microscope examination.

Results: Gonadotrophs of Group (II) rats showed cytoplasmic vacuolation, castration cells, increased vascularization and decreased immunoreactive cells. E/M examination revealed reduction of secretory granules and dilatation of rER. Morphological changes of nuclei and disappearance of cell membrane were demonstrated. In rats of Group (III), some cells appeared normal while others showed cytoplasmic vacuolation with increased immunoreactive cells compared to Group (II). In E/M examination, most of the rER returned to normal appearance with partial sparing of secretory granules. Most cells showed normal nuclei.

Conclusion: Flutamide produced marked histological, immunohistochemical and ultrastructural changes of pituitary gonadotroph cells similar to castration effects which were improved by concomitant use of LHRH analogue.

Key Words: pituitary gland, gonadotrophs, flutamide, LHRH drugs.

Corresponding Author: Manal E. El-Sawaf, Anatomy Department, Tanta Faculty of Medicine. Email: manal_sawaf@yahoo.com, Mobile: 0187319509.

INTRODUCTION

The gonadotropins-Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)-are responsible for stimulation of both testes in male and ovaries in female. Although they are not necessary for life, they are essential for reproduction and secretion of gonadal hormones which in turn share in many vital processes. The secretion of these two hormones in rat takes place in one cell type called gonadotroph which belongs to basophils of chromophil population of the anterior pituitary gland (*Navarro et al., 1992).* However, some studies suggested that most gonadotrophs secrete either LH or FSH, but only some appear to secrete both hormones *(Childs, 1997; Engelmann et al., 2004).*

Gonadotrophin synthesis and secretion in male rats are regulated by hypothalamic-pituitary axis and testicular factors. The androgens are involved in the feedback regulation of gonadotrophin synthesis and secretion. They act at the hypothalamic level, at the pituitary level or at both sites *(Weirman, & Wang, 1990; Noguchi et al., 1996).*

Cancer prostate is a hormone-dependant tumor in which the tumor cells grow under the effect of androgens *(Scher, 2005).* Flutamide is a non- steroidal anti-androgen drug primarily used to treat cancer prostate. It competes with

testosterone for binding to androgen receptors in the prostate gland thus prevents growth of cancer cells. Flutamide blocks the androgen receptors at the hypothalamic-pituitary axis as well as at the peripheral level, hindering the feedback regulation of the androgens on the gonadotrophin synthesis and secretion. A consequent increase in serum LH in the presence of high testosterone concentrations results *(Chrousas et al., 2001; Segal et al., 2003).*

Flutamide may be given on its own or in combination with injections of LHRH analogues. This combination becomes the first treatment of choice because it prevents the undesirable hypersecretion of LH induced by the use of flutamide alone *(Letsch et al., 2004; Labrie et al.,2005).* LHRH drugs fill the receptors of the pituitary gland that normally receive internal body LHRH. For a period of seven to 10 days, the pituitary gland perceives the LHRH drugs as body LHRH and causes the testicles to produce large amounts of testosterone. This sudden rise of testosterone is known as tumor flare which may be painful and possibly dangerous to patients with advanced cancer prostate. Then, the LHRH drugs block the pituitary gland's receptors, while body LHRH has been metabolized and the production of LH has been suppressed. The pituitary gland stops stimulating the testicles to make testosterone. The level of testosterone then drops by 90 to 95 percent which is the castration level. Flutamide combination has the ability to prevent tumor flare *(*Labrie *et al., 1990; Lawson & Cohen, 1999; Thompson, 2001; Crawford et al., 2004).*

The purpose of the present study was to investigate the possible morphological changes induced by non- steroid anti-androgen (flutamide) on the gonadotrophs of the anterior pituitary and to compare them with the combined effects of both flutamide and LHRH analogues.

MATERIALS AND METHODS

Twelve adult male albino rats (200-250gm each) were used and were caged in a well-ventilated room and fed with a well-balanced diet at room temperature. The animals were divided into three groups (four rats each).

Group I: Was served as control and was injected with 0.9% saline subcutaneously.

- **Group II:** Was treated with 10mg/rat/day flutamide orally. Flutamide was available as Androxin tablets of 250 mg (Sigma pharmaceutical, Egypt). The tablet was crushed and dissolved in 50 ml sterile distilled water and each rat received 2ml/ administration by gastric intubation. The dose was adjusted according to *Console et al. (1999)* and was given for successive 20 days.

- **Group III:** Was treated with flutamide orally in the same previous dose. At the same time, LHRH analogue (zoladex) 3.6 mg depot was implanted subcutaneously into the anterior abdominal wall (Fig. 1) and according to *Redding and Schally (1985),* it was calculated to release a controlled dose of 25 µg/day. Zoladex was supplied as a biodegradable, white cylindrical rod which was available in a prefilled disposable syringe contained 3.6 mg goserelin acetate (LHRH) mounted on a 16-gauge hypodermic needle designed for subcutaneous use and allowed a sustained release depot (AstraZeneca UK Limited, United Kingdom).

In the morning next to the 20th day of treatment, all the animals were sacrificed by rapid decapitation and two pituitary glands from each group were rapidly dissected out and fixed in 10% formol saline. Paraffin sections were either stained with Haematoxylin and Eosin (Hx.&E.) stain or prepared for immunohistochemistry and examined by light microscope. Furthermore, the anterior lobes (lateral wings) of the remaining pituitary glands were cut in small pieces 1mm^3 and fixed in 2% buffered gluteraldehyde. Then, they were washed in phosphate buffer, post-fixed in 1% osmium tetra-oxide, dehydrated and embedded in epoxy resins. Semithin sections were prepared, stained with toluidine blue and observed by light microscope in order to select fields. Ultrathin sections were cut, mounted on copper grids, stained with uranyl acetate and lead citrate and examined by electron microscope JEOL100s E/M provided with a digital camera .

Immunohistochemistry:

Paraffin sections were obtained at different levels of the blocks and immunostained by means of a Dako En vision system. Sections were incubated for one hour at room tempera-

ture with primary antibody (Anti-LH), diluted 1:200. Thoroughly washed sections were treated for 30 minutes with a ready to use En Vision reaction system. The peroxide-sensitive chromogen was diaminobenzidine. The specificity of the primary antiserum was monitored by the ability to block the immunocytochemical reaction by preabsorption of the antibodies with an excess of the related antigen or by replacing that antiserum with normal rabbit serum or phosphate buffer saline. Immunoreactive cells were examined by a light microscope and photographed *(Console et al., 2001)*

RESULTS

Histological study of Hx.&E.- stained sections obtained from the anterior pituitary of group (I) (control) rats revealed that they were composed of anastomosing cords of epithelial cells surrounded by a rich network of sinusoidal capillaries (Fig. 2). Most of the cells were deeply stained (chromophils) while few cells were faintly stained (chromophobes). The chromophil cells were either acidophilic or basophilic. Gonadotroph cells which belonged to basophil population were hardly distinguished in ordinary stains. However, they could be considered as being the larger type of basophil cells that appeared polyhedral in shape with large rounded nuclei (Fig. 3).

Gonadotroph cells were immunolabeled. The immunoreactive cells appeared as brownish patches that were scattered throughout the anterior pituitary gland (Fig. 4).

The gonadotrophs were easily identified in electron microscopic study. The cells were found in clusters among other types of anterior pituitary cells. The gonadotroph cells possessed large rounded or oval euchromatic nuclei with dispersed chromatin and voluminous cytoplasm. Their nuclei were surrounded with normal nuclear envelope. Their cytoplasm had numerous rounded electron dense granules of variable sizes distributed all over the cytoplasm, but more concentrated at the periphery. The gonadotrophs were surrounded by a distinct cell membrane (Fig. 5). They contained a well- developed rough endoplasmic reticulum (rER) formed of narrow cisternae that were dispersed throughout the cytoplasm. The mitochondria were large and elongated (Fig. 6).

Hx.&E.-stained sections of the anterior pituitary of group (II) rats (treated with flutamide only) showed that the gonadotrophs possessed small dark nuclei and less staining intensity of their cytoplasm than that of the controls. Some cells showed vacuolated cytoplasm (hydrobic degeneration). Many cells contained a single large cytoplasmic vacuole which pushed the nuclei to one side giving them the signet ring appearance (castration cells) (Fig. 7). Also, there were dilatation and congestion of the sinusoidal capillaries (Fig. 8).

Gonadotroph- immunolabeled cells were decreased compared to that of the control. The majority of the anterior pituitary appeared devoid of these cells (Fig. 9).

Electron microscopic study of the gonadotrophs of the anterior pituitary of group (II) rats revealed loss of the cell membrane between adjacent cells leading to formation of syncytium like structure. The secretory granules were scanty and scattered in the cytoplasm (Fig.10). The rER was dilated and some of its cisternae were fused forming vacuoles of variable sizes which appeared electron lucent (Fig.11). Some nuclei became shrunken with margination of clumped chromatin and the mitochondria appeared swollen (Fig. 12). Other nuclei showed irregular contour with peripheral condensation of chromatin and disrupted nuclear envelope (Fig. 13).

Histological study of the gonadotroph cells of the anterior pituitary of group (III) rats (treated with flutamide and LHRH) demonstrated that some cells appeared normal with deeply stained cytoplasm and euchromatic nuclei, while others showed less intensely stained vacuolated cytoplasm (hydropic degeneration) (Fig. 14). However, no castration cells could be detected. Dilated and congested sinusoidal capillaries were demonstrated (Fig. 15).

Gonadotroph- immunolabeled cells were more than that observed in group (II) which were scattered throughout the anterior pituitary. However, they were apparently less than that of controls (Fig. 16).

Electron microscopic study of the gonadotrophs of the anterior pituitary of group (III) rats revealed large rounded euchromatic nuclei which appeared regular with clear nuclear envelope. The cells were separated with a distinct cell membrane. However, reduction of cytoplasmic secretory granules compared with that of the controls was manifest (Fig. 17). Vacuolization of rER decreased and many segments of rER returned back to normal compared to group (II). The mitochondria showed normal appearance (Fig. 18).

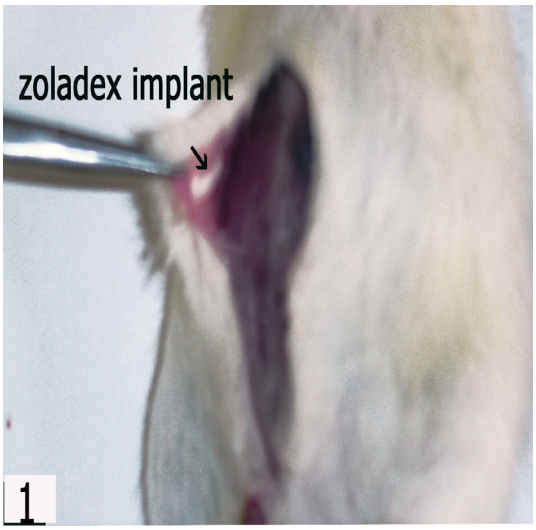

Fig. 1: A photograph of a male albino rat from group (III) showing the subcutaneous zoladex implant (arrow) under the skin of its anterior abdominal wall.

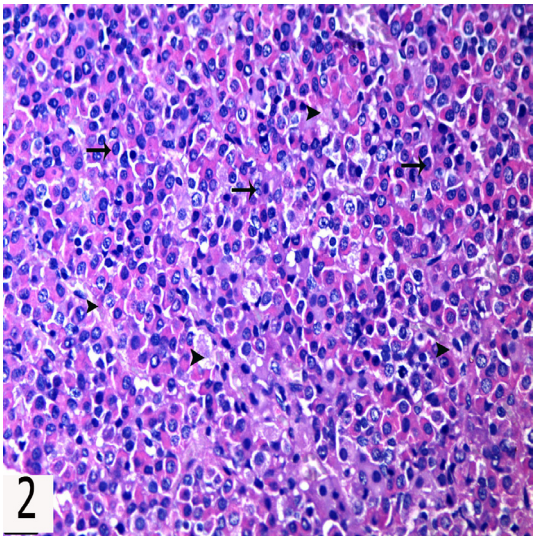

Fig. 2: A photomicrograph of a section of the anterior pituitary of a control rat showing cords of anastomosing epithelial cells (arrows) interspersed with sinusoidal capillaries (arrowheads). Hx.&E.; X200

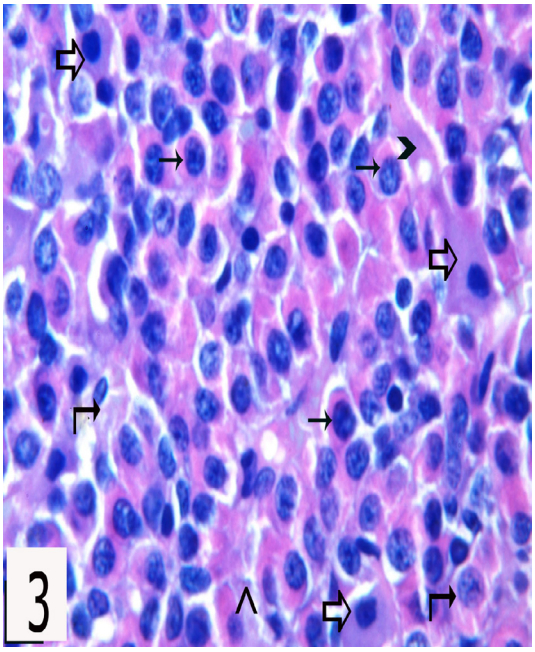

Fig. 3: A photomicrograph of a section of the anterior pituitary of a control rat showing most of the cells are deeply stained (chromophils). Some of them are acidophilic (arrows) while others are basophilic. The gonadotrophs are the largest basophils which appear polyhedral in shape with large rounded nuclei (open arrows). Few cells are faintly stained (chromophobes) (angled arrows). Notice the capillary sinusoids (arrowheads). Hx.&E.; X1000

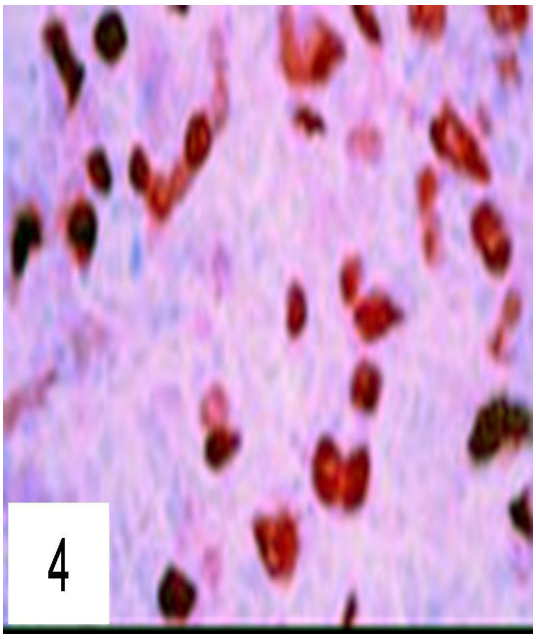

Fig. 4: A photomicrograph of a section of the anterior pituitary of a control rat showing specifically immunolabeled gonadotroph cells which appear as brownish patches. Anti- LH immunostain X1000

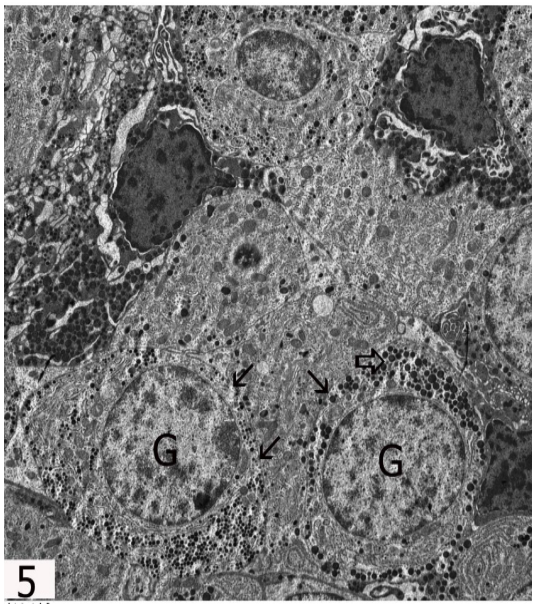

Fig. 5: An electron micrograph of a group of cells of the anterior pituitary of a control rat showing two gonadotrophs (G) distinguished by their large oval nuclei with dispersed chromatin and clear nuclear envelope. Their cytoplasm is filled with numerous electron dense secretory granules of variable sizes (open arrow) which appear mainly at one side of the cells. Distinct cell membrane is recognized (arrows). X1000

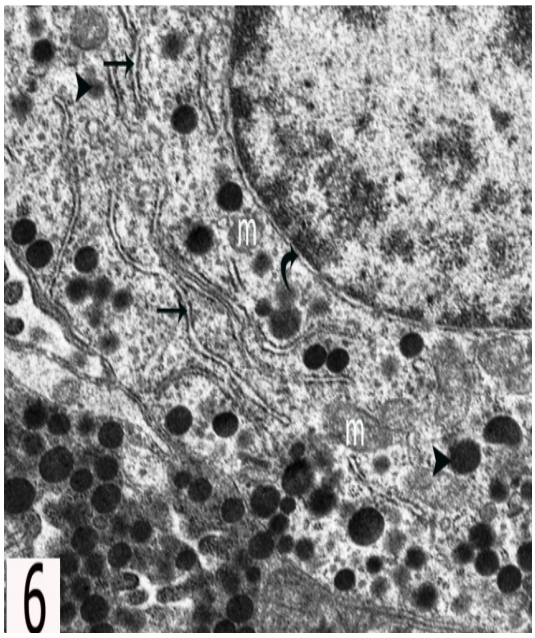

Fig. 6: An electron micrograph of a gonadotroph cell of the anterior pituitary of a control rat showing its nucleus is surrounded with normal nuclear envelope (curved arrow) and its cytoplasm contains variable sized granules (arrowheads), well developed rER (arrows) and large elongated mitochondria (m). X5,000

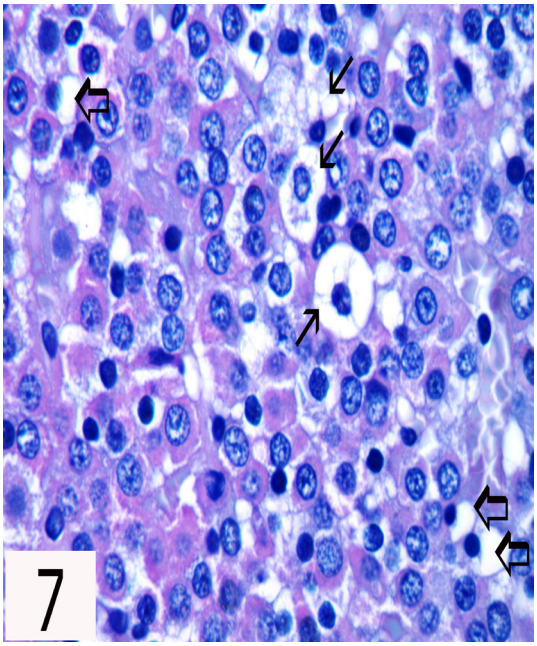

Fig. 7: A photomicrograph of a section of the anterior pituitary of a rat from group (II) (treated with flutamide) showing enlarged gonadotrophs (arrows) with vacuolated cytoplasm (hydropic degeneration). Other cells contain a single large vacuole in their cytoplasm which pushes their nuclei to one side forming a signet ring appearance (castration cells) (open arrows). Hx.&E.; X 1000

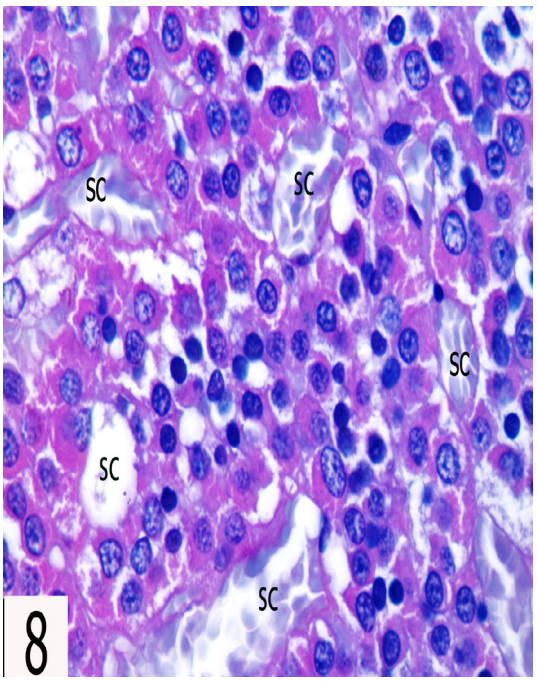

Fig. 8: A photomicrograph of a section of the anterior pituitary of a rat from group (II) showing dilatated and congested sinusoidal capillaries(sc). Hx.&E.; X1000

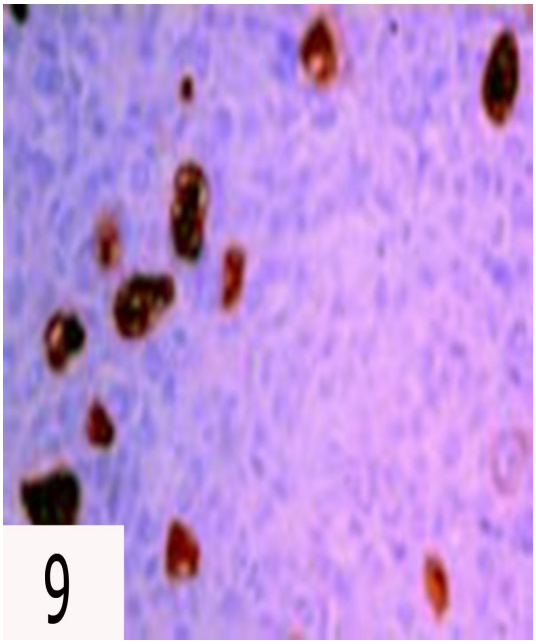

Fig. 9: A photomicrograph of a section of the anterior pituitary of a rat from group (II) showing reduction of specifically immunolabeled gonadotroph cells compared to that of the controls. Anti- LH immunostain. X1000

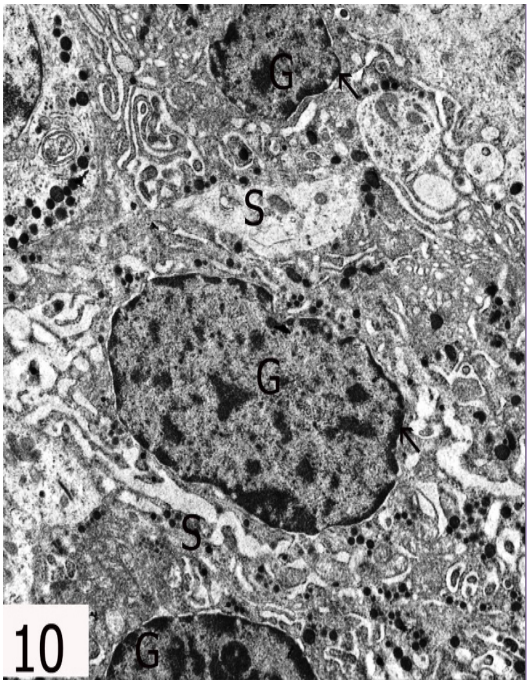

Fig. 10: An electron micrograph of gonadotroph cells of the anterior pituitary of a rat from group (II) showing loss of cell membrane of adjacent three gonadotrophs (G) leading to syncytial formation (S). The nuclei show irregular outlines (arrows). Notice the scanty secretory granules. X2,000

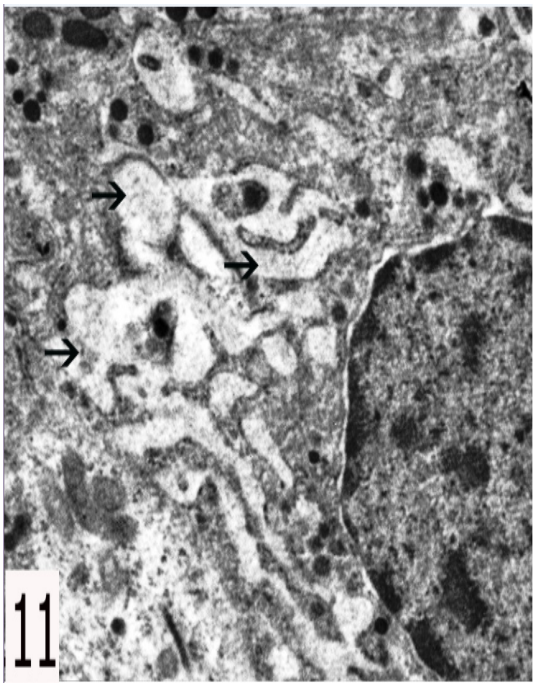

Fig. 11: A higher magnification of a gonadotroph cell of the previous figure showing electron lucent vacuoles of variable sizes formed by dilated rER (arrows). X5,000

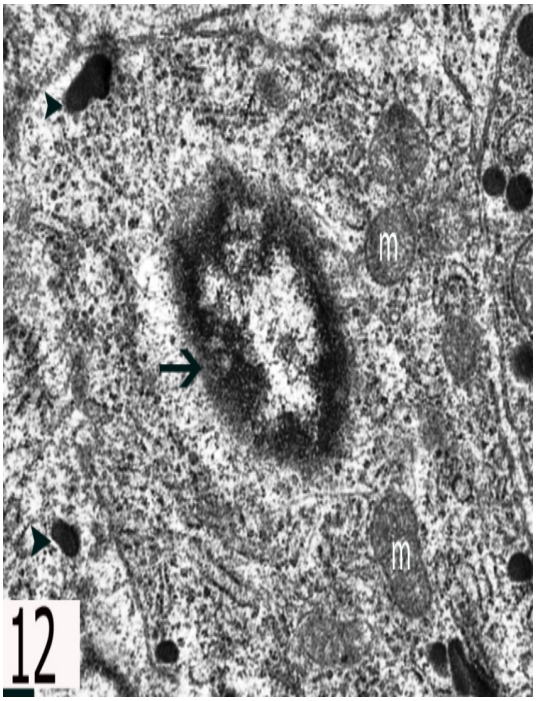

Fig. 12: An electron micrograph of a gonadotroph cell of the anterior pituitary of a rat from group (II) showing a small dense nucleus with margination of clumped chromatin (arrow) and swollen mitochondria (m). Notice the scanty secretory granules (arrowheads). X5,000

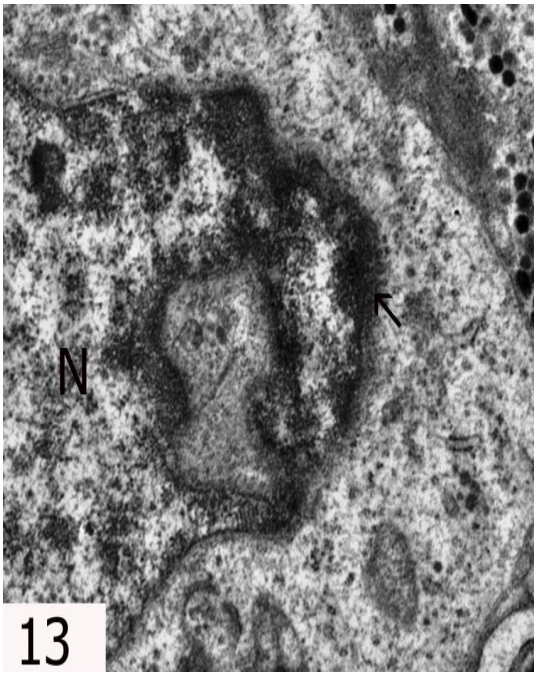

Fig. 13: An electron micrograph of a gonadotroph cell of the anterior pituitary of a rat from group (II) showing irregularly shaped nucleus (N) with disrupted nuclear envelope (arrow) and peripheral condensation of the nuclear chromatin. X5,000

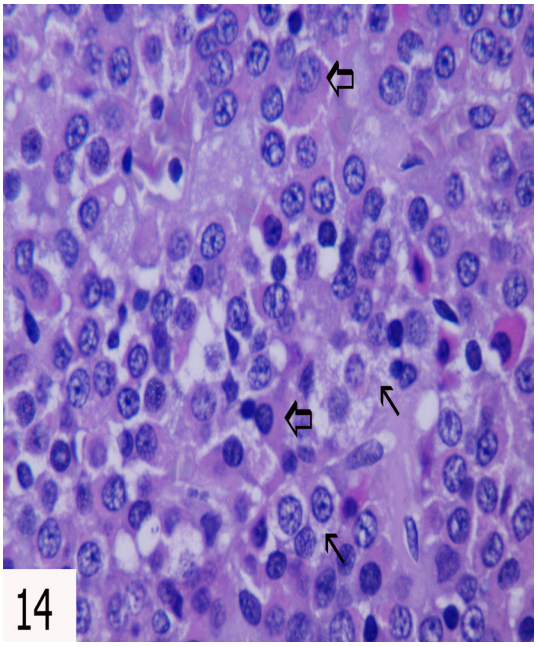

Fig. 14: A photomicrograph of a section of the anterior pituitary of a rat from group (III) (treated with flutamide and LHRH) showing some gondotroph cells are normal with deep basophilic stained cytoplasm and rounded large nuclei (open arrows) while others showing vacuolated less intensely stained cytoplasm (arrows). Hx.&E.; X1000

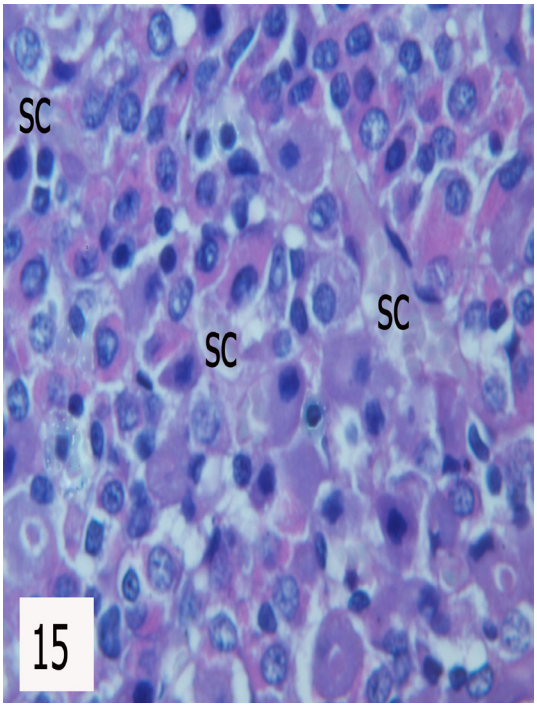

Fig. 15: A photomicrograph of a section of the anterior pituitary of a rat from group (III) showing dilated and congested sinusoidal capillaries (sc). Hx.&E.; X1000

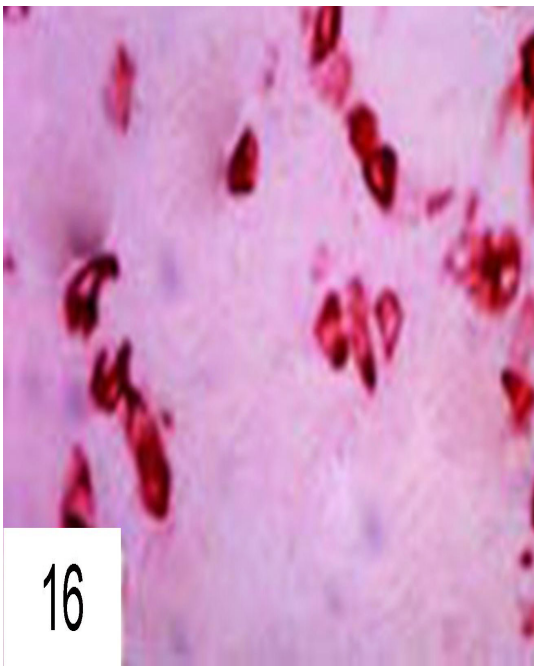

Fig. 16: A photomicrograph of a section of the anterior pituitary of a rat from group (III) showing increased specifically immunolabeled gonadotroph cells compared to that of group (II) but still less than that of the controls. Anti -LH immunostain. X1000

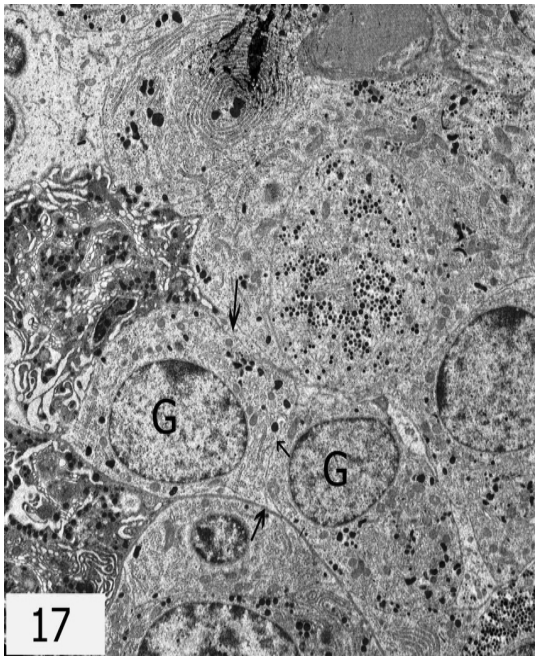

Fig. 17: An electron micrograph of a group of cells of the anterior pituitary of a rat from group (III) showing two gonadotroph cells with normal euchromatic nuclei (G) and distinct intercellular membrane (arrows). The secretory granules appear less than that of the controls. X1000.

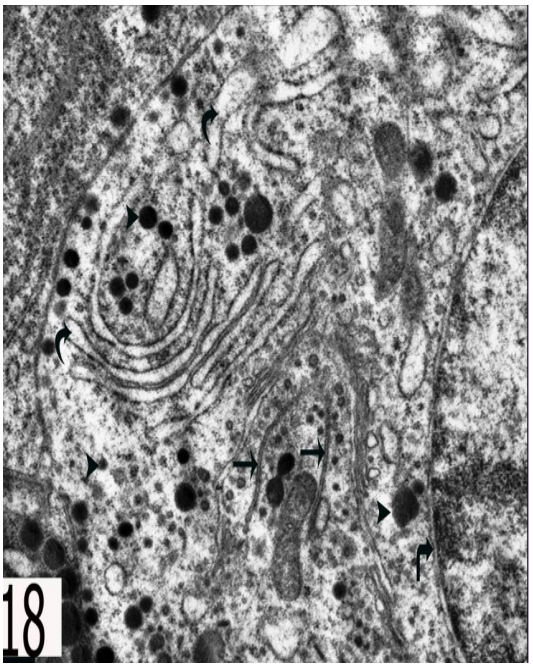

Fig.18: An electron micrograph of a gonadotroph cell of the anterior pituitary of a rat from gtroup (III) showing some rER are dilated (curved arrows) and others are normal (arrows). Notice secretory granules of variable sizes (arrowheads), normal nuclear envelope (angled arrow) and normal elongated mitochondria. X5,000

DISCUSSION

Many researches are found in the literature describing the morphological changes induced by flutamide on the pituitary gonadotroph cells *(Watanabe et al., 1993; Rulli et al., 1999; Console et al., 2001)*. However, although a combination therapy of flutamide and LHRH analogue is widely used recently *(Labrie et al., 2005),* data describing their compined morphological effects on gonadotrophs are hardly found. Thus, our concern in this work was to study the effects of flutamide alone or in combination with LHRH analogue on the gonadotrophs.

The present study showed that flutamide produced manifest histological, immunohistochemical and ultrastructural changes on the gonadotroph cells of the rat anterior pituitary. These observations are in accordance with *Console et al. (2001)* who mentioned that the anti-androgens through changes in the hormonal milieu produced a clear impact on the immunohistochemistry and ultrastructure of the gonadotroph population of the rat adenohypophysis.

In the current study, some gonadotrophs of the anterior pituitary of group (II) rats (treated with flutamide) revealed vacuolation of their cytoplasm (hydropic degeneration) suggesting dilatation of the rough endoplasmic reticulum (rER). *Altiparmak et al. (2002)* as well as *Levine and Saltzman (2004)* suggested that flutamide produced hyponatremia which in turn induced hydropic degeneration in the anterior pituitary gland. However, *Mannaa et al. (2005)* postulated that this hydropic degeneration was due to oxidative stress caused by flutamide metabolites. The gonadotroph cells showed also decreased staining intensity indicating diminished cytoplasmic secretory granules. Dilated congested blood sinusoids were also seen. Our results coincide with *Murakoshi et al. (2000)* who stated that flutamide stimulated the cells of pituitary gland to produce increase of LH. This stimulation led to hypersecretion and further to functional exhaustion and secretory granule depletion with increased glandular vascularization. Besides, in this group, some gonadotrophs showed signet ring appearance that was also demonstrated by *Console et al. (2001)* in castrated animals.

Immunohistochemical study of group (II) rats confirmed the histological findings. The immunolabeled gonadotrophs were markedly decreased compared to those of the controls. This finding matches with what was found by *Console et al. (2001)* who mentioned that on appearance of signet ring cells, the immunoreactivity of the anterior pituitary gland decreased.

The ultrastructural changes that were found in the present study in group (II) rats in the form of dilatation of rER and reduction of secretory granules reflected the hypersecretory pattern of the gonadotroph cell population after flutamide administration. *Watanabe et al. (1998) and Console et al. (2001)* stated that dilated rough endoplasmic reticulum and fewer granules indicated a higher secretory activity of the gonadotrophs. In this study, the dilated rER fused to form large vacuoles. Our findings are quite similar to what was reported by *Lindzey et al. (1998)* after a surgical or chemical damage of the gonads. The current study also revealed shrunken nuclei with margination of clumped chromatin and change of nuclear contour. Some adjacent gonadotrouphs lost their cell membrane and their cytoplasm fused together forming a syncytium. These findings denote cell degeneration which was also found by *Murakoshi et al. (2000)* who demonstrated cell degeneration as a result of functional exhaustion.

In the present work, the concomitant use of LHRH analogue with flutamide in group (III) rats decreased most of the morphological effects of the use of flutamide alone. The histological study revealed that most of the gonadotrophs appeared normal, while some showed hydropic degeneration. However, castration cells could not be demonstrated in this group. Similarly, *Console et al. (2001)* revealed that castration cells were completely absent from pituitaries of rats treated with LHRH drugs suggesting that these cells were formed as a result of increased release of gondotrophin hormones and depletion of the secretory granules.

The present study also showed increased immunoreactivity of gonadotrophs in group (III) rats than that of group (II). This finding denotes sparing of secretory granules. *Dungan et al. (2006)* mentioned that LHRH drugs decreased the hypersecretory activity of gonadotrophin cells. This, in turn, protected the secretory granules from depletion and hence the gonadotroph cells from degeneration.

Electron microscopic study of the gonadotrophs in group (III) rat pituitaries showed decreased dilatation of the rER than those of group (II) with no further formation of large vacuoles. The secretory granules were partially spared and most of the nuclei appeared normal. These results are supported by *Thrasher et al. (2000)* and *Letsch et al. (2004)* who stated that LHRH drugs decreased the undesirable effects of flutamide on the pituitary gland.

In conclusion, flutamide is better to be given in combination with injections of LHRH analogues. This combination would prevent the side effects happening in the anterior pituitary gland in use of flutamide alone.

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تأثير الاستخدام المتزامن للفلوتاميد و نظير الهرمون المحرر لهرمون اللوتين (LHRH) مقابل الاستخدام المنفرد للفلوتاميد على الخلايا المحرضة لغدة التناسل (خلايا الجونادوتروفين) بالغدة النخامية فى ذكور الجرذان البيضاء البالغة

مرسى عبد الفتاح أبو الجود، منال السيد الصواف

قسم التشريح - كلية الطب - جامعة طنطا

ملخص البحث

يستخدم عقار الفلوتاميد المضاد للأندروجن بتوسع هذه الأيام فى علاج سرطان البروستاتا إما منفردا أو مقترنا بنظائر الهرمون المحرر لهرمون اللوتين. هذه العقاقير تكبت مستقبلات الأندروجن و بالتالى تمنع نمو الخلايا السرطانية. وقد تؤدى إلى تأثر خلايا الجونادوتروفين فى الغدة النخامية الأمامية. و لقد كان الغرض من هذا البحث، دراسة التأثيرات الناشئة عن عقار الفلوتاميد فى وجود أو غياب الإقتران بنظير الهرمون المحرر لهرمون اللوتين على خلايا الجونادوتروفين. و قد استخدم فى هذا البحث اثنا عشر جرذا ذكرا بالغا تم تقسيمها إلى ثلاث مجموعات، المجموعة الأولى استخدمت كمجموعة ضابطة و المجموعة الثانية تم اعطاؤها عقار الفلوتاميد، أما المجموعة الثالثة فتم اعطاؤها عقار الفلوتاميد مع نظير الهرمون المحرر لهرمون اللوتين. وقد استمرت التجربة عشرين يوما، ثم تم التضحية بكل الفئران و تجميع الغدد النخامية منها. بعد ذلك تم اعداد العينات و صباغتها و فحصها.

و قد أظهرت النتائج أن خلايا الجونادوتروفين فى المجموعة الثانية بها فجوات سيتوبلازمية كما تحول بعضها إلى خلايا اخصائية مع وجود زيادة فى الأوعية الدموية و نقص فى الخلايا المناعية. و قد أظهر الميكروسكوب الإلكترونى نقصا فى حبيبات الإفراز و اتساعا فى الشبكة الإندوبلازمية الخشنة و لوحظ أيضا تغيرات فى شكل الأنوية و اختفاء لغلاف الخلية. أما فى المجموعة الثالثة، فبعض الخلايا كانت عادية، بينما البعض الآخر كان به فجوات سيتوبلازمية مع زيادة فى الخلايا المناعية بالمقارنة بالمجموعة الثانية. و بالفحص بالميكروسكوب الإلكترونى فقد تبين أن أغلب الشبكة الإندوبلازمية الخشنة قد استردت مظهرها العادى مع الحفاظ الجزئى على حبيبات الإفراز. كما أظهرت أغلب الخلايا أنوية عادية.

نستخلص من هذا البحث أن عقار الفلوتاميد ينشأ عنه تغيرات هستولوجية و مناعية هستوكيميائية بالإضافة إلى تغير فى التركيب الدقيق لخلايا الجونادوتروفين فى الغدة النخامية مشابها لما يحدث فى حالات نزع الخصيتين، و تتحسن هذه التغيرات إذا ما اقترن استخدام هذا العقار بنظير الهرمون المحرر لهرمون اللوتين.