Research Article

Ovariectomy-Induced Obesity in Adult Albino Rats Could Be A Target for the Peptide Tyrosine Tyrosine ($PYY_{٣-٣٦}$); the $Y^{٢}$ Receptor Agonist

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Abstract
Objective: This study aimed to assess the post ovariectomy metabolic changes contributing to obesity as a menopausal model, their possible pathophysiologic mechanisms and the effect of a potent $Y^{٢}$ receptor agonist; $PYY_{٣-٣٦}$ on its development. **Methods**: Thirty adult female rats were divided into ٣ equal groups: **control** sham operated, **ovariectomized** (OVX) and **OVX+$PYY_{٣-٣٦}$** treated at a dose of ٥٠µg/kg by intraperitoneal injection twice daily during the ٥th week after ovarievtomy. All rats were fed standard diet *ad libitum* and followed by anthropometric measures. Finally, rats were sacrificed by decapitation after an overnight fast, blood samples collected for biochemical analysis, gastrocolic omentum fat (GCOF) excised and weighed, and hypothalamus taken for determination of neuropeptide Y (NPY) concentration. **Results and conclusion: O**variectomy resulted in significant higher body weight from two weeks after OVX till the end of the study with a significant higher food intake, Lee index, (GCOF), serum TC, LDL-c, glucose, leptin and hypothalamic concentration of NPY with a significant lowering in HDL-c and TGs. Except for serum lipid profile, the effects were reversed with $PYY_{٣-٣٦}$ treatment. **In conclusion**, $PYY_{٣-٣٦}$; the potent $Y^{٢}$ receptor agonist could prevent OVX-induced obesity and its hazards and could be a line of management in menopausal females at risk of hormonal replacement therapy (HRT).
Keywords: ovariectomy, obesity, $PYY_{٣-٣٦}$, NPY, metabolic risk factors

Introduction

Female sex hormones, especially estrogens play an important role in energy balance mechanisms including food intake versus energy dissipation through, basal metabolism, physical activity and thermo-genesis. That is why hormonal withdrawal following menopause is associated with progression of metabolic diseases such as obesity, diabetes, cardiovascular diseases, and bone rarefaction[١].

Energy balance mechanisms are multifactorial and complex. In females, the triad of hypothalamic appestat, peripheral adipose tissue and the connecting sympathetic innervation with the cross talks between them represent the backbone of the regulatory mechanisms. Many cell signaling molecules are involved including estrogens acting through estrogen receptors alpha and beta (ERα and ERβ), catecho-lamines acting through adrenergic receptors alpha and beta with their different subtypes, and the Y peptides including neuropeptide Y (NPY), peptide YY (PYY) and pancreatic polypeptide (PP) acting through five Y receptors ($Y^{١}$,$Y^{٢}$,$Y^{٤}$,$Y^{٥}$, and $Y^{٦}$) and others. The multitude of receptors with opposing effects both centrally in the brain and peripherally and the interactions between them makes such control very complex. In addition, Adipose tissue is either white (WAT) concerned with energy reserve store or brown (BAT) concerned with thermogenesis. In other way, subcutaneous fat differs from visceral (central fat) as regard the function and response to control mechanisms; that is why estrogen controls subcutaneous fat deposition to fit the female contour while in males central fat is more dominant[٢,٣,٤].

The pancreatic polypeptide family includes NPY, PYY and PP. These peptides are structurally and biologically similar;

being rich in tyrosine residues so given the Y name, formed in different tissues and act by binding to Y receptors [٥]. They play important role in gut-brain signaling mechanisms regulating energy balance. Neuropeptide Y is a hypothalamic neuro-transmitter co-released with agouti peptide from arcuate neurons and acting *via* Y١ receptors, it produces orexigenic effect. It is also co-released with catecholamines from sympathetic nerve endings[٦]. PYY is produced by the intestinal L-cells throughout the gut[٧]. In the circulation, PYY is truncated to $PYY_{٣-٣٦}$ which is a relatively selective Y٢ receptor agonist. It can cross the blood brain barrier (BBB). PP is post-prandially secreted from the endocrine F cells of the pancreatic islets. Peripheral administration of PP decreased food intake and body weight in obese rodents, while central administration produced opposite effects due to variations in receptor types and effects[٨]. In addition to regulating food intake, digestion and absorption of food they also regulate lipogenesis, lipolysis and thermogenesis in adipose tissue, adrenergic receptor activity and carbohydrate metabolism[٩].

Menopause is frequently associated with obesity; a state in which energy intake exceeds energy expenditure over a prolonged period[٩], and there is increased risk of cardiovascular, neurodegenerative, and gall bladder diseases, increased incidence of metabolic syndrome, and diabetes mellitus. Hormone replacement therapy (HRT) during menopause will always be a mixed picture of benefits and risks including breast cancer, coronary heart disease, fracture, stroke, obesity, and deep venous thrombosis[١٠]. Therefore, research should be directed to substitute HRT with new drugs that target the pathophysiologic mechanism with least hazards.

The aim of the present study was to:

١- Characterize the changes in metabolic parameters over time after ovariectomy in rats, and examine the role of leptin production, leptin sensitivity and hypo-thalamic NPY concentration in these metabolic changes.

٢- Study the impact of a potent Y٢ receptor agonist; $PYY_{٣-٣٦}$, on the ovariectomy-induced metabolic changes.

Materials and methods

I-Animals

Thirty female adult albino rats (Sprague dawley strain) were used. Their weight ranged between ١٨٠-١٩٠ grams at the beginning of this study. Rats were housed in stainless steel mesh bottomed cages in groups of five rats/cage providing adequate space and light at room temperature with natural light\dark cycles for one week for acclimatization to lab conditions. Rats were fed a standard diet of commercial rat chow and tap water *ad libitum* until the time of the experiment. During the acclimatization period, daily food intake was measured to know the mean daily food intake per rat. All the procedures followed with the rats were in accordance with our institutional guidelines. The protocol was ethically approved by The Laboratory Animals Maintenance and Usage Committee of Faculty of Medicine in Minia University.

The rats were classified into the following equal and homogenous groups (١٠ rats each):

١-**Control sham operated group**: in which rats were sham operated and then, allowed standard rat chow diet for ٥ weeks without treatment.

٢-**Ovariectomized (OVX) non treated group;** in which rats were subjected to ovariectomy and then, allowed standard rat chow diet for ٥ weeks without treatment.

٣-**Ovariectomized treated (OVXT) group**: Rats were ovariectomized and allowed standard rat chow diet for ٥ weeks. During the fifth week after ovariectomy, each rat received Peptide $YY_{٣-٣٦}$ (Sigma Aldrich, USA) at a dose level of ٥٠µg per kg, by intraperitoneal injection twice daily. It was prepared by dissolving it in saline solution [١١].

II--Ovariectomy

The rat was anesthetized by ether inhalation, and then placed on the operating board in dorsal recumbence position with

its tail directed towards the operator. The ventral aspect of the lumbar region was shaved, and then cleaned with ٧٠% ethanol, followed by thorough scrubbing with ١٠٪ povidone iodine (Betadine). ١ cm long longitudinal ventral midline incision was made above the symphysis pubis, the skin edges were laterally retracted, and the abdominal muscle layer and peritoneum were incised. Both fallopian tubes were exposed and ligated; the ovary can usually be seen embedded in a pad of fat in the abdomen; then the ovaries were removed by cutting them with scissors, taking care not to rupture the ovarian capsules. The remaining tissues were replaced into the peritoneal cavity, and the incision was then closed using a sterile ٢/٠ suture. The excised ovaries were verified by histological sections[١٢]. In sham operated rats, the abdomem was opened and closed without excising the ovaries[١٣]. The surgical wound was cleaned daily with Betadine till healing was complete and rats were allowed standard rat chow diet *ad libitum* and daily monitored for food intake and weekly for body weight through a five weeks' experimental period.

III- Lee index:

Lee index is used to determine obesity in rats using weight and naso-anal length. It was measured at the beginning of the study, at the end of the ٤th week and at the end of the ٥th week. Lee index was calculated for each rat according to the following formula:

Cube root of body weight (g) X ١٠ / naso-anal length (mm)

Rats with Lee index ≥ ٠.٣ were considered obese [١٤].

At the end of the ٥th week, and after an overnight fast, rats were sacrificed by decapitation and blood samples were collected, allowed to clot at room temperature, and then centrifuged at ٣٠٠٠ rpm for ١٥ min. in a cooling centrifuge (Hettich centrifuge). The serum layer was then withdrawn into identified eppendorf tubes and stored at - ٢٠ °C till the time of assay.

IV- The weight of gastrocolic omentum:

Rats were opened via ventral abdominal incision. Peritoneal omental adipose tissue was removed by lifting the intestines and cutting the intermediate fat free, starting at the distal end close to the appendix, the whole gastrocolic omentum was weighed[١٥].

V- Biochemical analysis

Total cholesterol (TC), triglycerides (TGs), low density lipoprotein (LDL-c), high density lipoprotein (HDL-c) and glucose were determined by enzymatic colorimetric methods, using kits purchased from Bio-diagnostic, EGYPT using spectrophotometer **(Spectronic ٢٠٠٠, BAUSCH & LOMB**). Leptin concentration was determined by enzyme-linked immunosorbent assay (**CUSABIO, CHINA**) using ELISA apparatus **(SLT-SPECTRA, Salzpurg).** The methods followed the instruction manual of the manifacturer.

VI- Analysis of brain homogenates:

The heads were dissected, then the brain was removed and the hypothalamus was isolated, weighed, and homogenized by ultrasonicate homogenizer **(٤٧١٠ series, Chicago)** in ٥٠٠ µL of ٠.٥ mol/L acetic acid (Prepared by mixing ٢٨.٦٢ ml glacial acetic acid (El Nasr pharmaceutical chemical company, Egypt) completed to ١٠٠٠ ml by adding distilled water) then the homogenate was boiled in a water bath for ١٥ min followed by centrifugation at ١٠,٠٠٠ rpm for ١٠ min at ٤°C. The supernatant was collected and stored at –٨٠°C until use [١٦]. Determination of Neuropeptide Y (NPY) concentration was done by enzyme-linked immunosorbent assay (Sigma Aldrich USA -Cat No RAB٠٣٨٧).

VII- Statistical Analysis

Statistical analysis was performed using Graph pad Prism ٥ software and significant difference between groups was done by one-way ANOVA followed by Tukey-Kramar post hoc test for multiple

comparisons with a value of P≤٠.٠٥ considered statistically significant

Results:

١. Changes in body weight, Lee index and food intake in the different groups:

Table (١) shows that:

- Ovariectomy (OVX) caused a significant higher body weight from the second week till the end of the study as compared to sham operated control group. Injection of $PYY_{٣-٣٦}$ caused a significant lower body weight as compared to OVX group (figure ١).
- The lee index was significantly higher in rats of OVX group as compared to control group; being > ٠.٣, they were considered obese. Injection of $PYY_{٣-٣٦}$ during the ٥th week did not decrease the lee index below ٠.٣ and rats were still obese, but the Lee index in OVXT group was significantly lower as compared to OVX group and insignificant as compared to sham operated control group.
- In ovariectomized groups, food intake was significantly lower during the first week then increased significantly till the end of the study as compared to control group. Injection of $PYY_{٣-٣٦}$ caused a significant lower food intake as compared to sham operated control and OVX groups (figure ٢).

Table ١: Changes in body weight (g), Lee index and food intake (g/day) in different groups

Parameters	Groups		
	Control (sham operated	OVX	OVXT
Body weight			
Initial	١٨٩.٧ ± ٢.٣	١٨٧.٧ ± ٣.٥	١٨٨.٧ ± ١.٧
After ٤ weeks	٢١٨.٥ ± ٠.٦	٢٣٧.٢ ± ٢.٠٥ a	٢٤٠.٢± ٠.٦ a
After ٥ weeks	٢١٩.٧ ± ٠.٤ c	٢٤١ ± ٠.٩ ac	٢٣٣.٥ ± ٠.٢ abc
Lee index			
Initial	٠.٢٩٤±٠.٠٠١	٠.٢٩٣±٠.٠٠١	٠.٢٩±٠.٠٠٢
After ٤ weeks	٠.٢٩٥±٠.٠٠٢	٠.٣١٥±٠.٠٠٢a	٠.٣٠٨±٠.٠٠١ a
After ٥ weeks	٠.٢٩٦±٠.٠٠٢	٠.٣١٦±٠.٠٠٢ a	٠.٣٠٠±٠.٠٠٢ b
Food intake			
Initial	١٣.٢ ± ٠.٣١	١٢.٠٥ ± ٠.٢٤ a	١٢.٠٨ ± ٠.٢٩ a
After ٤ weeks	١٣.١٨ ± ٠.٣١	٢٠.٥ ± ٠.٣ a	٢١.٢ ± ٠.٤ a
After ٥ weeks	١٣.٢١ ± ٠.٣٧	٢٠.٥ ± ٠.٣٢ a	١٠ ± ٠.٣١ ab

OVX= ovariectomized, OVXT=ovariectomized treated with Peptide $YY_{٣-٣٦}$ during ٥th week. Data are expressed as mean ± S.E.M. of ١٠ rats in each group.
a: Significant (P < ٠.٠٥) from sham operated control group, b: Significant from OVX group, c: Final value significant from its corresponding initial value.

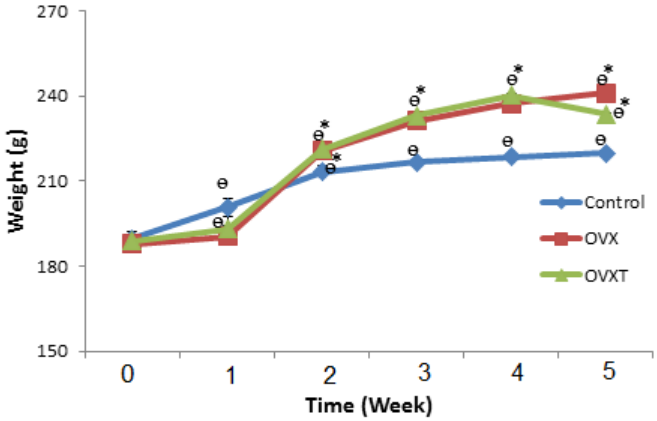

Figure (١): Time course changes in body weight (g) in OVX groups. OVX: ovariectomized, OVXT: ovariectomized treated with Peptide $YY_{٣-٣٦}$ during ٥th week.

* Significant from its previous week, ɵ Significant from its initial body weight. Values are expressed as mean ± S.E.M. of ١٠ rats in each group

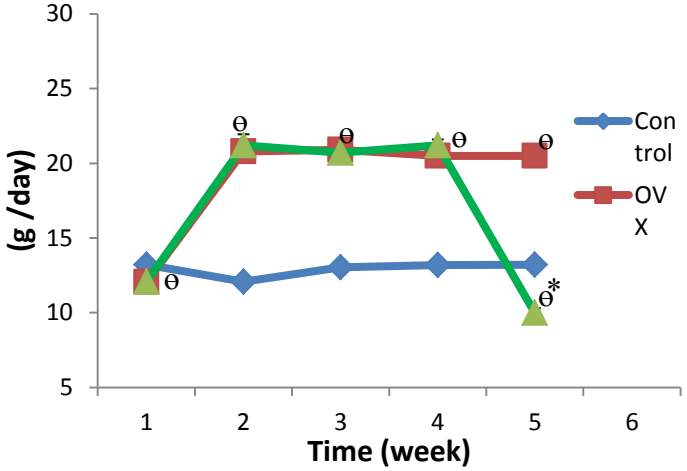

Figure (٢): Time course changes in food intake (g/day) in OVX groups. OVX: ovariectomized, OVXT: ovariectomized treated with Peptide YY٣-٣٦ during ٥th week.
* Significant from OVX group, **ɵ** Significant from control group. Values are expressed as mean ± S.E.M. of ١٠ rats in each group.

٢- Changes in weight of the gastrocolic omentum (GCOF) in the different studied groups:

In OVX group, the weight of the GCOF was significantly higher as compared to the control group. Injection of PYY٣-٣٦ caused a significant lower weight of the GCOF as compared to the OVX group; however, it was still significantly higher than the sham operated control (figure ٣).

٣- Changes in Serum glucose, leptin and lipid profile in different studied groups:

Table (٢) shows:

- Serum glucose and leptin levels were significantly higher in ovariectomized groups as compared to control group. On the other hand, injection of PYY٣-٣٦ caused significant lower levels in OVX treated group as compared to non treated group; however, the levels were still significantly higher than the control group.
- In ovariectomized groups, in comparison to the sham operated control group, the serum levels of TC and LDL-c were significantly higher associated with a significant lower serum levels of TGs and HDL-c. Injection of PYY٣-٣٦ to ovariectomized rats caused insignificant differences on serum lipid profile as compared to the OVX non-treated group.

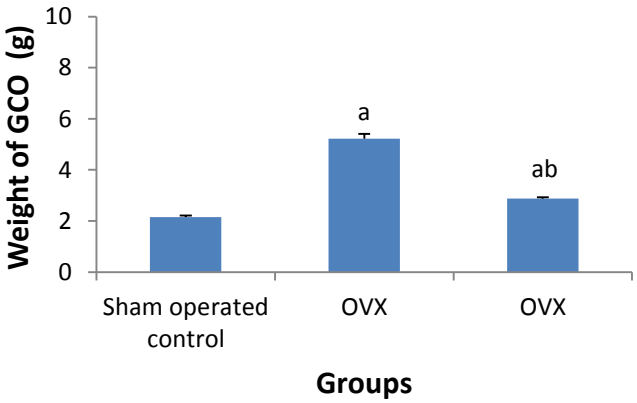

Figure (٣): The weight of gastrocolic omentum fat (GCOF) in OVX groups. OVX: ovariectomized, OVXT: ovariectomized treated with Peptide YY٣-٣٦ during ٥th week. a:

Significant from sham operated control group. b: Significant from OVX group. Data are expressed as mean ± S.E.M. of ١٠ rats in each group.

Table ٢: Serum lipid profile, glucose, and leptin concentrations in the different studied groups.

Parameters \ Groups	Sham operated control	OVX	OVXT
TC (mg/dl)	١٣٤.٣ ± ١.٧	١٥٨.٦ ± ٣.٠٤ [a]	١٥٧.٦ ± ٢.٩ [a]
TGs (mg/dl)	٩٥.٠٨ ± ٠.٩	٩١.٣ ± ١.٠٩ [a]	٨٩.٩ ± ٣.١ [a.]
HDL-c (mg/dl)	٥٥.٥ ± ٠.٦	٣٩.٣ ± ٠.١ [a]	٣٩.٢ ± ٠.٢ [a]
LDL-c (mg/dl)	٦٦.٢ ± ٠.٦	٧٣.٠٥ ± ١.٤ [a]	٧١.١ ± ١.٢ [a]
Serum glucose (mg/dl)	٧١.٣ ± ١.٤	١٢٤.٢ ± ٠.٩ [a]	١١٣.٦ ± ٣.٦ [ab]
Serum leptin (ng/ml)	٥.٤ ± ٠.١	٢٧.٠٧ ± ١.٤ [a]	١٣.٢١ ± ٠.٦ [ab]

OVX= ovariectomized, OVXT=ovariectomized treated with Peptide YY٣-٣٦ during ٥th week. Data are expressed as mean ± S.E.M. of ١٠ rats in each group. a: Significant from sham operated control group, P < ٠.٠٥.

٤- Hypothalamic neuropeptide Y (NPY) concentrations in the different studied groups:

Hypothalamic NPY was significantly higher in OVX group as compared to sham operated control group. Injection of PYY٣-٣٦ caused a significant lower hypothalamic NPY level in OVX group as compared to both control and non treated groups as shown in figure(٤)

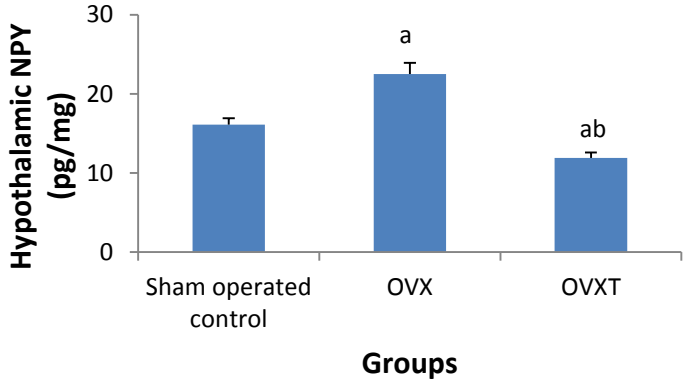

Figure (٤): Hypothalamic NPY concentration in OVX groups. NPY: neuropeptide Y, OVX: ovariectomized, OVXT: ovariectomized treated with Peptide YY٣-٣٦ during ٥th week. a: Significant from sham operated control group. b: Significant from OVX group. Data are expressed as mean ± S.E.M. of ١٠ rats in each group.

Discussion

The present results revealed that OVX was followed by significantly lowered food intake during the first week following the operation propbably due to the stress of ssurgical trauma, anesthesia and manipulation of internal viscera. These stressors may result in activation of short neuronal circuits in the hypothalamus and brain stem that release the anorexic peptides; prolactin releasing peptide and glucagon like peptide-١ according to Maniscalco et al.,[١٧]. Food intake then was significantly increased till the end of the study as compared to the control group. Estrogens directly and indirectly modulate the activity of hypothalamic neurons controlling food intake. ERα is abundantly expressed in the rodent brain hypothalamic nuclei modulating food intake including the ventromedial nucleus; VMN, the arcuate nucleus; ARC, the paraventricular nucleus;

PVN, and the medial preoptic area. ERβ is found in the same hypothalamic nuclei, but ERβ expression is significantly lower relative to ERα. Estrogen stimulates ERα on preopiomelanocortin (POMC) neurons in ARC to release alpha melanocyte stimulating hormone that inhibits food intake through melanocortin ٤ receptor (MC٤)[١٨]. These effects are compatible with the reports of Lizcano and Guzmán[٣] that deletion of ERα in POMC neurons in mice leads to hyperphagia without directly influencing energy expenditure or adipose tissue distribution**,** In addition, ERα mRNA levels fluctuate over the course of the estrous cycle, with the most dramatic increase on the day of proestrus, when estrogen concentration is highest. This explains why estrogen withdrawal by ovariectomy in the present work increased food intake.

In the present work, body weight significantly increased hand in hand with the increased food intake in OVX rats. This is in agreement with Li et al.,[١٩] and Posa et al.,[٢٠]. Estrogen can mediate its inhibitory effect on body weight through different mechanisms: (i) by potentiating anorexigenic signaling in the hypothalamus to decrease food intake[٢١], (ii) by enhancing cholecystokinin (CCK) binding to receptors on vagal afferents of pylorus and proximal duodenum that initiate a negative feedback satiation signal reducing meal size and overall food intake[٢٢], and (iii) by promoting lipolysis and suppressing lipogenic activity in visceral adipocytes[٢٣]. Therefore, estrogen withdrawal by OVX in the present work significantly increased body weight.

In addition, estrogen withdrawal by OVX affected body fat distribution and function. The weight of (GCOF) was significantly higher as compared to the control group. This was associated with a significantly higher Lee index >٠.٣ indicating obesity, a significantly higher serum leptin level, and an atherogenic lipid profile with increased TC, LDL-c and decreased HDL-c and TGs.

Estrogen is responsible for body fat distribution with more deposition in subcutaneous depots than visceral fat during reproductive age and its reversal after menopause. GCOF is a type of visceral fat that is why it increased in OVX rats of this study. The distribution of body fat depends on the type of receptors present. Subcutaneous and visceral adipose tissues express both ERα and ER[٢٤]**.** On the other hand, adrenergic receptors on adipocytes control adipose tissue metabolism with lipolysis controlled primarily by the action of $\beta_٣$-adrenergic receptors (lipolytic) and antilipolysis by $\alpha_٢$-adrenergic receptors (antilipolytic). In subcutaneous adipocytes Estradiol directly increases the number of antilipolytic $\alpha_٢$-adrenergic receptors, while in visceral adipose tissue, it increases $\beta_٣$-adrenoreceptor expression through ERα, but has no effect on $\alpha_٢$-adrenergic receptor mRNA expression[٢٥,٣]. This receptor variability allows estrogen to enhance lipolysis in visceral adipocytes and lipogenesis in subcutaneous ones.

Previous studies reported favorable changes in lipid metabolism and blood lipoprotein profile by estrogen administration through the following effects: ١- it may inhibit hydroxy methyl glutaryl coenzyme A (HMG-CoA) reduc-tase, which is the first enzyme in cholesterol biosynthesis, ٢- it promotes FFA uptake and β-oxidation in muscles, and reduces liver TG storage so, preventing hepatic steatosis, by stimulating the expression of peroxisome proliferation activator receptor-delta (PPARδ) and by activating AMP-activated protein kinase (AMPK), ٣- it may induce inhibition of hepatic lipase which destroy HDL-c, ٤- it also stimulates hormone sensitive lipase and inhibits endothelial lipoprotein lipase which catabolizes blood triglycerides in visceral adipose tissue in favor of lipolysis, and finally it increases insulin sensitivity which enhances lipogenesis in subcutaneous adipocytes and improves glucose oxidation[٢٦,٢٧,٢٨]. These estrogen effects can explain why estrogen withdrawal by ovariectomy produced a significant higher serum level of TC and LDL-c, and a significant lower serum level of TGs and HDL-c.

In the present study, plasma leptin was significantly higher after ovx as compared to control rats and this may be related to higher body weight, lee index and gastrocolic omental fat weight as found by[٢٠]. This is compatible with Tolba [٢٩] and Hsieh et al.[٣٠] who reported that leptin is primarily produced by adipose tissue, with circulating levels being positively correlated with total body fat in both human and rodents. Increased leptin could be a switch off mechanism to inhibit the hypothalamic feeding center to decrease food intake and increases energy expenditure through increased thermo-genesis. However leptin could induce insulin resistance which explains the hyperglycemia of the OVX group.

In the present study, estrogen withdrawal by ovariectomy increased hypothalamic NPY concentration. This is in agreement with Rivera et al.,[٣١] and Santollo et al.,[٣٢]. On the other hand, estrogen treatment decreases NPY release in the paraventricular nucleus of ovariectomized rats[٣٣] as well as NPY messenger RNA expression in the arcuate nucleus [٣٤]. These effects are mediated by stimulating ERa on NPY/agouti related peptide neurons of The hypothalamic ARC. On the other hand ERα on POMC neurons can stimulate α- and β- MSH which -can suppress NPY neurons whether directly or indirectly through stimulation of inhibitory GABA interneurons[٣٥].

Y٢ receptors are abundantly expressed on NPY neurons in the arcuate nucleus (ARC) of the hypothalamus. Mittapalli and Roberts[٣٦] reported that both Y٢ knockout mice and mice treated with Y٢-receptor antagonist showed increased food intake. That is why $PYY_{٣-٣٦}$ treatment in the present work exerted inhibition on food intake through a Y٢-receptor dependent manner. Y٢ receptors primarily act as presynaptic autoreceptors modulating endogenous NPY release. $PYY_{٣-٣٦}$ inhibits NPY neurons and reduces hypothalamic NPY mRNA and /or protein content as found in the present study and by previous research Holzer et al.,[٣٧]. Peripherally, stimulation of Y٢ receptors on vagal afferent neurons from the gut reduces both frequency and size of meals[٧]. Both the central and peripheral mechanisms could explain the decreased food intake, body weight, gastrocolic omental fat and serum leptin found in this study with improved insulin sensitivity indicated by the significant lowering of blood glucose level produced by $PYY_{٣-٣٦}$ treatment and agrees with the previous results[٣٨]. Diminished food intake in response to $PYY_{٣-٣٦}$ treatment may lower the insulin: glucagon ratio, increase lipolysis and decrease de novo lipogenesis[٣٩].

NPY and the different Y receptors are present in peripheral tissues. In adipose tissue, differentiated adipocytes release NPY. Furthermore, adipocytes express NPY receptors specially Y١, Y٢ and Y٥. NPY is cleaved to $NPY_{٣-٣٦}$; the selective Y٢ agonist by Dipeptidyl peptidase IV and was found to be elevated with Y٢ receptors in subcutaneous fat of obese mice. NPY was found to be a major contributor to adipose expansion through hyperplasic, adipogenic and antilipolytic effects together with stimulating adipose tissue angiogenesis[٤٠]. In addition, NPY coreleased from sym-pathetic nerve terminals inhibited β-adrenergic lipolysis in cell culture studies[٤١]. On the other hand, increased hypothalamic NPY in obesity was associated with decreased sympathetic activity in some obese models with consequent decreased lipolysis[٦]. They added that the effects of NPY on adipose metabolism is controversial depending on the nutritional status, hormonal balance, site of fat tissue and variability of Y receptors and sympathetic activity. In the present work, it is probable that $PYY_{٣-٣٦}$ treatment to ovariectomized rats through suppressing NPY release both centrally and peripherally increased sympathetic activity with more lipolysis, thus our findings of reduced GCOF weight and its consequences of reduced body weight, serum leptin and improved insulin sensitivity and reduced blood glucose level.

In conclusion, ovariectomy in rats produced a metabolic disorder of obesity, disturbed lipid profile and increased hypothalamic NPY levels. This picture can be corrected with intraperitoneal injection

of NPY_{3-36} through Y^2 receptor stimulation; an effect that could be considered as a substitution line of treatment to menopausal syndrome in patients at risk of HRT.

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