



Tamoxifen Like Estradiol Attenuates Systemic Inflammation in Young and Aged Female Mice Fed with High-Fat Diet

Zeinab Farhadi^{1,2} , Mohammad Khaksari^{3*} ¹Department of Physiology, Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran²Neuroendocrine Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran³Endocrinology and Metabolism Research, and Physiology Research Centers, Kerman University of Medical Sciences, Kerman, Iran

Abstract

Background: Consumption of a high-fat diet (HFD) is associated with an increased incidence of inflammatory diseases and metabolic disorders. Also, these disorders will increase in women with aging and menopause, which is probably due to the reduced role of estradiol (E2). Selective estrogen modulators including tamoxifen (TAM), which acts through estrogen receptors, have important metabolic effects. This study aimed to determine whether TAM and E2 have protective effects on inflammation caused by HFD in young and aged mice.

Methods: Four-month-old (Sham and ovariectomized [OVX]) and 20-month-old female C57BL/6J mice were used in this study. After feeding them with HFD for 12 weeks, they were divided into nine groups consisting of Sham + Oil, Sham + TAM, Sham + E2, OVX + Oil, OVX + TAM, OVX + E2, Aged + Oil, Aged + TAM, and Aged + E2. TAM and E2 were injected subcutaneously every four days for four weeks. At the end of the experiments, the mice's blood was sampled. The serum cytokines tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-10 (IL-10) were also determined using ELISA kits.

Results: The results revealed that HFD increased inflammation by reducing IL-10 and increasing TNF- α /IL-10 and IL-6/IL-10 ratio in young and aged mice, and TAM and E2 therapy resulted in a significant decrease in TNF- α and IL-6, and an increase in IL-10 in young and aged mice.

Conclusion: In conclusion, the results of this study indicated that TAM, in addition to being used as an anticancer drug, can reduce HFD-induced inflammation in both young and aged mice. Therefore, probably it is a good candidate to substitute E2.

Keywords: Tamoxifen, Estradiol, Aging, Inflammation, High-fat diet

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Introduction

Chronic consumption of a high-fat diet (HFD), which causes diseases such as obesity, diabetes, and cancer, is one of the major health problems in today's society (1). Nowadays, it has been found that long-term consumption of HFD is associated with increased systemic and local inflammation in the metabolic tissues (2,3).

It has been approved that obesity is associated with functional changes in the reproductive systems of both women and rodents, which affects ovarian hormones (4). The 17 β -estradiol (E2), as the main ovarian hormone, has stabilizing anti-inflammatory effects in many tissues, including the brain (5) and heart (6). On the other hand, the increase in inflammation that occurs during menopause and ovariectomy can be reduced by E2 and its receptor agonists (7).

Aging is associated with changes in the distribution of body fat (8) and reduced physiological function (9,10). It also increases the occurrence of many metabolic diseases

such as obesity and insulin resistance (11). It has been found that there is a direct link between the consumption of HFD and aging (12), which is associated with tissue and systemic inflammation and general dysfunction of the body (13). On the other hand, the prevalence of inflammatory diseases in women is lower than in men, which is probably due to the effects of ovarian hormones, especially E2 (14,15). However, this protection decreases with age, menopause, and ovariectomy (16).

Tamoxifen (TAM), as a selective estrogen receptor modulator (SERM), has both antagonist and agonist effects on estrogen receptors (17). This compound acts as an antagonist in the breast tissue, and as an agonist in cholesterol metabolism as well as in the uterus, and bone tissue (5). It has been shown that TAM in postmenopausal conditions significantly reduces metabolic disorders (5) and cardiovascular diseases (18). Nevertheless, the effects of TAM (the prototypic SERM) on inflammatory conditions such as aging and obesity are not properly known (5).



Considering the above points, aging, menopause, and HFD consumption lead to structural and functional changes by increasing inflammation, and unlike E2, TAM has no side effects such as increasing the risk for breast cancer. Some studies have shown the anti-inflammatory properties of TAM in youth, so in this study for the first time, we investigated the anti-inflammatory effects of TAM in aged female HFD-fed mice.

Methods

Animals

All laboratory works were performed according to the ethical guidelines of the Kerman University of Medical Sciences (Ethical code: 95/264 KA). Young and aged female (C57BL/6J) mice (4 and 19-21 months old, respectively) were purchased from Pasteur Institute in Tehran, Iran. The mice were housed in the Animal Center of Kerman University of Medical Sciences under a standard condition of temperature (22-23°C) and humidity (55%), with a 12:12-hour light-dark cycle and free access to food and water. Throughout the experimental period, the animals were fed HFD (Royan, Iran) consisting of 58.8% fat, 27.5% carbohydrates, and 14.7% proteins, with a total caloric value of ~5.9 kcal/g.

Bilateral ovariectomy and sham surgery

Before surgery, the animals were anesthetized with an intraperitoneal (ip) injection which was a mixture of ketamine and xylazine (80 mg/kg and 10 mg/kg, respectively). For ovariectomy, bilateral incisions were made on the back of each mouse, and the skin, fascia, and abdominal muscles were opened. Then ovaries were identified and removed. Finally, 2 mL of saline was poured into the abdomen and the skin was sutured. In the sham surgery, a similar incision was made on the abdominal area, but the ovaries were not removed. In aged mice, since their reproductive systems are quiescent (19) and studies show that E2 levels in aged mice are equal to ovariectomized (OVX) mice (20), ovariectomy was not performed.

Experimental design

Young animals were divided into two groups: ovarian-intact (Sham) and OVX mice. All animals including young (Sham and OVX) and aged mice were fed with HFD for a period of 12 weeks, then they were divided into nine groups of Sham + Oil, Sham + E2, Sham + TAM, OVX + Oil, OVX + E2, OVX + TAM, Aged + Oil, Aged + E2, and Aged + TAM. The mice received injections of E2 (2 µg/mice) (9) and TAM (1 mg/kg) (18) subcutaneously every four days for four weeks.

Measurement of pro- and anti-inflammatory cytokines in the serum

At the end of the study, the mice were anesthetized

with an ip injection of ketamine and xylazine (80 mg/kg and 10 mg/kg). Then, their blood was collected from the cardiac ventricles. The serum was separated by centrifugation (3000 rpm for 15 minutes) and stored at -80°C for later measurements. Serum cytokines of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10) were also determined using commercial ELISA kits (Eastbiopharm, China) according to the manufacturer's instructions. Briefly, ELISA plates coated with primary antibodies were used for the analysis. The standards or serum samples of cytokines (TNF-α, IL-6, and IL-10) from each mouse were added to the wells of the plates and were allowed to be incubated at room temperature for two hours. Plates were washed, and an enzyme conjugate was applied for 90 minutes. After a second wash, an amplification reagent was added to the wells, and the absorbance values were determined for each well. The cytokines concentration of each sample was determined by standard curves. Values have been expressed as pg/mg of total protein (21).

Statistical analyses

Data were analyzed by two-way ANOVA, followed by Bonferroni multiple comparisons using GraphPad Prism 6.0 software (GraphPad Software, San Diego, CA, USA). Results have been presented as mean ± SEM and $P < 0.05$ was considered statistically significant.

Results

The comparison of serum TNF-α levels in different HFD-fed groups is shown in Figure 1. As seen, treatment with TAM or E2 did not affect the serum TNF-α level in young-Sham and aged HFD-fed mice. In contrast, treatment with TAM or E2 resulted in a reduction in serum TNF-α levels only in young-OVX animals compared to the oil group ($P < 0.05$ and $P < 0.01$, respectively). Further analysis showed that young-OVX animals had higher serum levels of TNF-α compared to young-sham ($P < 0.01$) and aged animals ($P < 0.05$).

Changes in the serum IL-6 levels in different HFD-

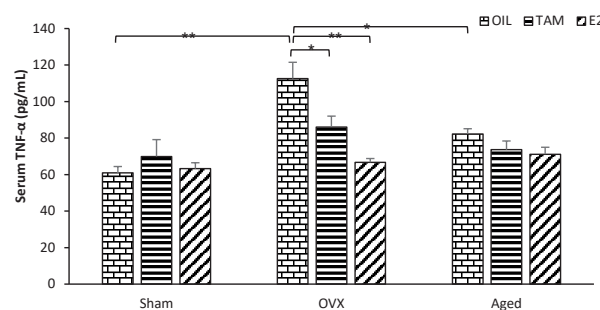


Figure 1. Effects of administration of TAM and/or E2 on the serum levels of tumor necrosis factor-alpha (TNF-α) in young (Sham and OVX) and aged HFD-fed animals. Results are expressed as mean ± SEM (n=6). * $P < 0.05$ and ** $P < 0.01$. E2: 17-β estradiol, OVX: Ovariectomy, Sham: Ovarian intact, TAM: Tamoxifen

fed groups are shown in Figure 2. As seen in the young-sham group, both TAM and E2 resulted in a significant decrease in serum IL-6 levels compared to the oil group ($P < 0.05$ and $P < 0.01$, respectively). Also, in the young-OVX group, only E2 could reduce the serum level of IL-6 compared to the oil group ($P < 0.05$). But, in the aged animals, none of the TAM or E2 made any significant difference in serum IL-6 level.

The changes in the serum IL-10 level in various HFD-fed groups for four weeks while receiving OIL, TAM, and E2 injections are shown in Figure 3. TAM and E2 treatment in young-sham animals caused an increase in serum IL-10 level compared to young-sham animals treated using oil ($P < 0.01$ and $P < 0.05$, respectively). Similar to the young-sham group, treatment with both TAM and E2 in the young-OVX group also increased their serum IL-10 level compared to the oil group ($P < 0.001$). Figure 3 shows that similar to the last two groups, TAM and E2 treatment in aged animals also increased their serum IL-10 level ($P < 0.05$). Further analysis showed that ovariectomy reduced serum IL-10 (OVX+Oil vs. Sham+Oil, $P < 0.05$), and with regard to age, no significant change was observed in serum IL-10 level. Also, the aged group treated with TAM (Aged+TAM) had lower levels of IL-10 compared to the sham group treated with TAM (Sham+TAM, $P < 0.01$).

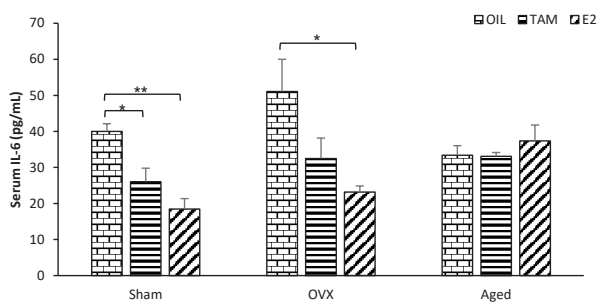


Figure 2. Effects of administration of TAM and/or E2 on the serum levels of interleukin 6 (IL-6) in young (Sham and OVX) and aged HFD-fed animals. Results are expressed as mean \pm SEM (n=6). * $P < 0.05$ and ** $P < 0.01$. E2: 17- β estradiol, OVX: Ovariectomy, Sham: Ovarian intact, TAM: Tamoxifen

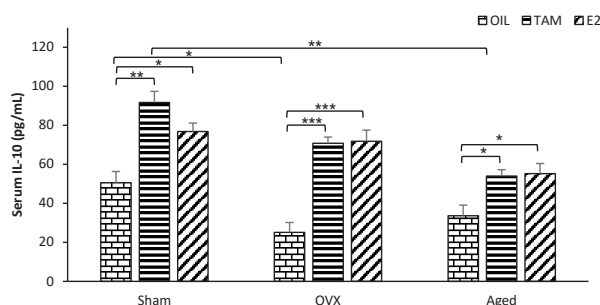


Figure 3. Effects of administration of TAM and/or E2 on the serum levels of interleukin-10 (IL-10) in young (Sham and OVX) and aged HFD-fed animals. Results are expressed as mean \pm SEM (n=6). * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. E2: 17- β estradiol, OVX: Ovariectomy, Sham: Ovarian intact, TAM: Tamoxifen

In the last part of the study, the inflammatory balance was calculated by dividing the pro-inflammatory cytokines (TNF- α and IL-6 levels) by the anti-inflammatory cytokine (IL-10 level) ratio, which provided important information about the state of inflammation (Figure 4). Figure 4A shows that treatment with both TAM and E2 reduced the ratio of IL-6/IL-10 in both the young-OVX ($P < 0.001$) and aged ($P < 0.05$) groups. In the young-Sham group, only E2 therapy could reduce this ratio ($P < 0.01$). Also, Figure 4A shows that both ovariectomy (OVX+OIL) and aging (Aged+OIL) increase the IL-6/IL-10 ratio compared to the young-Sham group ($P < 0.01$ and $P < 0.05$, respectively). The TNF- α /IL-10 ratio is shown in Figure 4B. As seen in this figure, similar to the IL-6/IL-10 ratio, TAM and E2 therapy reduced the ratio of TNF- α /IL-10 in both young-OVX ($P < 0.001$) and aged groups ($P < 0.05$) compared to the OIL group, but in the young-Sham group it had no effects on the TNF- α /IL-10 ratio. In addition, as shown in Figure 4B, both ovariectomy (OVX+OIL) and aging (Aged+OIL) increase the TNF- α /IL-10 ratio compared to the young-Sham group ($P < 0.001$ and $P < 0.05$, respectively).

Discussion

The prevalence of metabolic disorders caused by HFD is higher in older and postmenopausal women than in premenopausal women, possibly due to E2 depletion or impaired E2 signaling following menopause and aging.

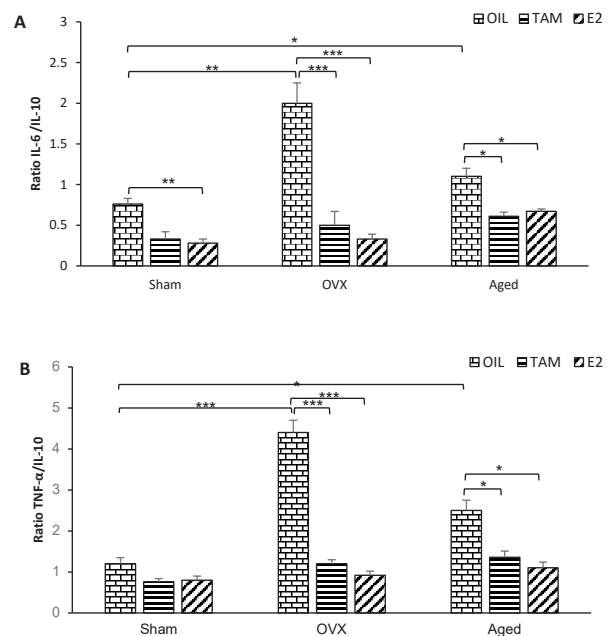


Figure 4. Effects of administration of TAM and/or E2 on the serum ratio of IL-6/IL-10 (A) and TNF- α /IL-10 (B) in young (Sham and OVX) and aged HFD-fed animals. Results are expressed as mean \pm SEM (n=6). * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. E2: 17- β estradiol, OVX: Ovariectomy, Sham: Ovarian intact, TAM: Tamoxifen

This study aimed to evaluate the anti-inflammatory effects of TAM and E2 in aged and young female HFD-fed mice. The main findings of the present study are as follows: (a) Consumption of HFD increased inflammation in both young-OVX and aged mice. (b) TAM, like E2, decreased pro-inflammation cytokines and increased anti-inflammatory cytokines in both young-OVX and aged mice.

In this study, it was found that consumption of HFD in young-OVX and aged mice increased pro-inflammatory and decreased anti-inflammatory cytokines. Similar to this study, there are reports indicating that diabetes and HFD consumption increase TNF- α and decrease IL-10 levels in many tissues of young-OVX and old animals, including the heart (22) and the brain (5). Also, in this study, it was found that the consumption of HFD in young-OVX animals could not increase IL-6 levels. Similarly, it has been shown that chronic consumption of HFD in OVX animals does not increase IL-6 (5), and it has also been shown that the main cytokine involved in estrogen deficiency is not IL-6 but rather TNF- α (18). Several studies provide evidence that chronic consumption of HFD increases inflammatory cytokines by increasing Toll-like receptors (23) and nuclear factor kappa B (NF- κ B) signaling (24), among which TNF- α plays a more prominent role as a marker of inflammation caused by chronic HFD consumption, diabetes, or obesity (25). Similar to our results, it has been shown that the induction of the menopausal model increases TNF- α /IL-10 and IL-6/IL-10 ratios, and also ovariectomy (26) and menopause in women (27) are associated with increased systemic inflammation. In addition, it is now known that consumption of HFD causes inflammatory conditions in the body by increasing inflammatory cytokines such as TNF- α and IL-6 and decreasing anti-inflammatory cytokines such as IL-10 (28). The possible mechanisms for this increase include stimulation of the suppressor of cytokine signaling-3, activation of endoplasmic reticulum stress, mitochondrial dysfunction, and ROS accumulation (28).

Today, it has been established that aging is a low-grade inflammatory condition (29) and is also a strong risk factor for most diseases (30). In agreement with our study, there are reports suggesting that aging is associated with increased levels of TNF- α and IL-6 and decreased levels of IL-10 in HFD-fed animals (5). Also, it has been shown that an increase in expression and secretion of inflammatory markers such as IL-6 occurs during menopause and aging (31). The exact mechanism by which aging increases inflammation is not fully understood; however, studies have shown that aging can increase inflammatory markers such as IL-6 and TNF- α by altering glucose homeostasis, increasing cellular stress, and decreasing SIRT6 expression (30).

In connection with determining the effects of TAM

on the inflammatory status of young-OVX and aged animals, this study showed that treatment with TAM, like E2, decreased inflammatory cytokines, and increased anti-inflammatory cytokines. Similar to the present study, treatments with TAM or E2 derivatives have been shown to inhibit inflammatory cytokines (5) or other inflammatory agents such as NO and ROS (32). Other studies have also shown that treatment with TAM or E2 reduces inflammation caused by traumatic brain injury in both young and old animals (33). On the other hand, it has been reported that various cytokines change in response to sex hormones, and TAM has also been shown to have anti-inflammatory effects on many tissues of the body, including the cardiovascular system, hypothalamus, and hippocampus (5). So far, little is known about the anti-inflammatory mechanisms of TAM. But it is possible that TAM can reduce inflammation by affecting TNF- α receptor expression (17), decreasing adrenalin levels, and corticosterone levels (5). However, there are reports indicating that the anti-inflammatory properties of SERMs are mediated through estrogen receptor-independent mechanisms such as their effect on the MAPK, AKT, and PKC messaging pathways (34).

Conclusion

In summary, the results of the present study showed that HFD consumption leads to inflammation in both young-OVX and aged mice, possibly by altering TNF- α , IL-6, and IL-10 levels. Also, treatment with TAM, like E2, improved inflammation by reducing serum levels of TNF- α and IL-6, increasing IL-10 levels, and improving inflammatory balance in favor of anti-inflammation. Future studies comparing the anti-inflammatory effects of TAM in young and middle-aged female HFD-fed mice, as well as other inflammatory and anti-inflammatory cytokines are suggested.

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Authors' Contribution

Conceptualization: Zeinab Farhadi, Mohammad Khaksari.

Data curation: Mohammad Khaksari.

Formal analysis: Zeinab Farhadi, Mohammad Khaksari.

Funding acquisition: Mohammad Khaksari.

Investigation: Zeinab Farhadi.

Methodology: Zeinab Farhadi, Mohammad Khaksari.

Project administration: Zeinab Farhadi, Mohammad Khaksari.

Supervision: Mohammad Khaksari.

Validation: Mohammad Khaksari.

Visualization: Zeinab Farhadi, Mohammad Khaksari.

Writing - original draft: Mohammad Khaksari.

Writing - review & editing: Mohammad Khaksari.

Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

Kerman University of Medical Sciences Institutional Animal Care Committee guidelines (No: 95/264 KA).

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