Effects of Ovariectomy and 17β-Estradiol Replacement on the Activity of Dopamine D2 Receptors in the Selection of Macronutrients Carbohydrates, Lipids and Proteins in Females Rats

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Abstract

17β-estradiol modulates the activity of D2 receptors in the regulation of food intake and body weight. The functional lack of 17β-estradiol in postmenopausal women could create a dietary imbalance and cause body weight gain. This study aimed to better understand the interferences that could exist between 17β-estradiol, D2 receptors and the selection of carbohydrate, fat and protein consumption, as well as their consequences on body weight gain by using an animal model of the menopause. Ovariectomy exacerbates the consumption of foods rich in lipids. Thus confirming an inhibitory action of 17β-estradiol (E2) on the consumption of these types of foods. This consumption stimulates body weight gain, which is promoted by the high caloric content of these foods and not by the amount consumed. Our results showed a direct involvement of D2 receptors in food choice. This choice would be made according to the two (2) isoforms of the D2 receptors. The D2/BR isoform directs towards a high carbohydrate consumption, without causing a gain in body weight. While D2/SUL, promotes high fat food consumption, causing an increase in body weight. In women, 17β-estradiol modulates the activity ratio between these two D2 receptor isoforms to ensure energy and homeostatic balance, stabilizing food intake and body weight.

Keywords

17β-Estradiol, D2 Receptors, Bromocriptine, Sulpiride, Carbohydrates, Lipids, Proteins, Body Weight, Menopause, Obesity

1. Introduction

The increase in sugar consumption and the industrialization of food manufacturing have greatly increased the availability of palatable foods [1]. Consumption of highly appetizing and energy-dense foods was a critical variable leading to excessive weight gain and increased risk factors for obesity [2] [3] [4]. This accessibility to high-calorie foods seems to disrupt brain reward centers and homeostasis mechanisms, thus contributing to the onset of food addiction [5]. It is widely accepted that obesity results from prolonged positive energy balance [6]. This is how obesity has reached epidemic prevalence and much research has focused on the homeostatic and hedonic mechanisms that underlie the overconsumption of food and the regulation of body weight. Previous studies have closely implicated dopamine D2 receptors in several addiction models, including sugar, alcohol, food, and drugs [7] [8] [9]. Thus the dopamine reward system plays a considerable role in the normal or disturbed eating behavior of individuals [10]. For example, in obese people, there is a considerable drop in the number of dopaminergic receptors at the central level accompanied by dysfunctions in eating behavior [11] [12]. Excessive sugar consumption leads to changes in the expression of dopaminergic genes characterized by a decrease in the rate of mRNA synthesis of D2 receptors in the nucleus accumbens (NAc) [13]. This reduction in the number of dopamine D2 receptors could induce food addiction leading to excessive weight gain [14] [15]. Interestingly, these observed reductions in central dopamine expression in response to sugar binge are similar to the dopamine dysfunctions observed in drug addiction and obesity [16] [17] [18] [19]. Proteins, lipids and carbohydrates are the main dietary macronutrients [20]. The World Health Organization (WHO) recommends consuming 55% - 75% of daily energy as carbohydrates, 15% - 30% as fat and 10% - 15% as protein [20]. Previous studies have reported some selective effects of dopamine D2 receptors on macronutrient uptake. For example, the ordemanding effects of DA injections have been demonstrated on the consumption of fats [21] and carbohydrates, in particular sucrose [22]. Endogenous dopamine levels were also increased in the nucleus accumbens (NAc) after fat or sugar consumption [23] [24], suggesting that an increase in dopamine in the NAc can lead to excessive consumption of foods high in fat and sugar. When exposed to the same high-fat diet, mice with lower D2 receptor density gained more weight than mice with higher D2 receptor density [25]. Animals fed a high-fat diet show decreased dopamine turnover in the NAc compared to those fed a standard low-fat diet [26].

According to other mechanisms, the functional absence of 17β-oestradiol in post-postmenopausal women would be a risk factor for obesity [27] [28]. Indeed, previous studies have shown that the incidence of obesity increases significantly after menopause [29]. Bâ and collaborators demonstrated that in ovariectomized rats there was interference between 17β-estradiol and dopamine D2 receptors in the etiology of obesity in women. These authors showed that 17β-estradiol would be involved in the regulation and stability of body weight, by directly

controlling food, sugar and alcohol consumption: E2 would modulate the activity of two isoforms of D2 dopaminergic receptors (D2S = short peptide chain and D2L = long chain) that it would activate or inhibit according to the needs of homeostasis [30] [31].

In rats, ovariectomy is the cause of a decrease in muscle mass [32] [33]. Estrogens play a significant role in muscle development, since in adolescent rats, ovariectomy decreases the size and speed of muscle development [34] [35]. This is associated with a decrease in the expression of the anabolic growth factor IGF-1 (Insulin Growth Factor) in muscle [36] [37] [38]. Similarly, there is a decline in muscle strength during the peri-menopausal and post-menopausal periods, which can be corrected by taking hormonal treatment, again suggesting the importance of hormonal regulation on the modulation of muscle physiology [39]. When a female rat is ovariectomized she is affected by the symptoms of menopause, we find mood changes with irritability, nervousness, mood swings [40]. This loss of E2 is associated with a greater susceptibility to affective and cognitive disorders [41] [42] [43], which in turn can alter food intake [44] [45]. In contrast to the clear cyclical effects of estradiol on total energy intake [46], several studies in rodent models have examined the effect of estradiol on diet choice and have given conflicting results. While some studies show no effect of oophorectomy on diet choice [47], others have shown that increased estradiol leads to increased fat intake [48] [49] and a decrease in carbohydrate but not protein intake [50]. In women, some studies have reported reductions in protein and carbohydrate intake coinciding with increased estrogen levels at the time of ovulation [51], while others have reported increased fat intake in the 10 days preceding menstruation [52]. However, no consistent effect of estradiol on macronutrient selection emerged [53].

We undertook these studies to better understand the role of 17β-estradiol and dopamine D2 receptors in carbohydrate, lipid and protein macronutrient selection in female rats. For this, we compared between control rats and ovariectomized rats, the effects of the administration of 17β-estradiol without or with co-treatment with an agonist (bromocriptine) or antagonist (sulpiride) of dopaminergic D2 receptors on daily consumption of six (6) types of food. With a potentially high nutritional value per 100 g in couples of macronutrients: carbohydrates-lipids, lipids-proteins, proteins carbohydrates; or in a single dominant macronutrient: carbohydrates, lipids or proteins [54] [55] [56]. Consumption of food types, as well as body weight, were measured daily in each treatment for ten (10) days. All six feed types were simultaneously available for each animal condition ad libitum.

2. Materials and Methods

2.1. Animals

Rats of the Wistar strain, three (3) months old, were reared under the conditions of our laboratories. These rats are maintained under standard laboratory condi-

tions, at an ambient temperature of 30°C ± 2°C, with light/dark cycles of 12 hours each and relative humidity reaching 85% ± 3%. Rats were housed individually in polypropylene cages (27 × 37 × 18 cm) with the bottom covered with wood shavings and fed a pellet-based diet and water ad libitum. A week before the start of the tests, they were acclimatized to the experimental conditions. All experiments were performed in accordance with the National Institutes of Health guide for the care and use of laboratory animals.

2.2. Chemicals and Doses Administered

The drugs and chemicals used in these experiments were: 17β-estradiol (estradiol or E2), bromocriptine mesylate, sulpiride, dimethyl sulfoxide (DMSO) manufactured by Sigma-Aldrich Chemie GmbH (Eschenstrasse 5, 82, 024 Taufkirchen, Germany). DMSO was the solvent used for all product dilutions. Bromocriptine mesylate and sulpiride have been used as a selective agonist and antagonist at central dopamine D2 receptors, respectively [57].

Seventy-two Wistar rats weighing an average of 200 ± 5 g, were divided into non-ovariectomized control rats or large control group (C) composed of 6 subgroups (C = 6 groups) and ovariectomized rats (OVX = 6 groups) which were subjected simultaneously to the following treatments: 17β-estradiol (5μg/kg body weight or bw; [58], bromocriptine mesylate (0.1 mg/kg bw; [59]), sulpiride (20 mg/kg bw; [60]) and concomitant administration of "17β-estradiol + bromocriptine" or "17β-estradiol + sulpiride", and the vehicle DMSO (0.7%; [61]).

2.3. Methods

Experiment I: the large Control group (C = non-ovariectomized rats)

Thirty-six (36) nulliparous rats, individually housed, were divided into six (6) treatment groups (6 rats/treatment group), and treated for ten (10) consecutive days as follows:

- Group C (control proper) consisting of six (6) female rats not treated with the drugs, but injected with the vehicle DMSO, a liquid solvent.
- Group C + E2 (17β-estradiol) comprising six (6) rats having received a subcutaneous (s.c.) injection of 17β-estradiol (5 μg/kg bw).
- Group C + BR (bromocriptine) composed of six (6) female rats treated by intraperitoneal (i.p.) injection of bromocriptine mesylate (0.1 mg/kg bw), a dopamine D2 receptor agonist.
- Group C + SUL (sulpiride): Six (6) females treated by i.p. sulpiride (20 mg/kg bw), a dopamine D2 receptor antagonist.
- Group C + E2 + BR (17β-oestradiol + bromocriptine): six (6) rats receive a concomitant administration of 17β-oestradiol (5 μg/kg bw/s.c.) and bromocriptine (0.1 mg/kg bw/i.p.).
- Group C + E2 + SUL (17β-estradiol + sulpiride) includes six (6) females treated with concomitant administration of 17β-estradiol (5 μg/kg bw/s.c.) and sulpiride (20 mg/kg bw/i.p.).

Within each experimental group, the rats consumed six (6) types of food daily whose nutritional value per 100 g [54] [55] [56] is potentially high, either in pairs of macronutrients: *carbohydrates-lipids* (plantain banana chips: *carbohydrates* = 63.8 g; *lipids* = 29.6 g; *proteins* = 2.3 g; 531 Kcal), *lipids-proteins* (roasted salted peanuts: *carbohydrates* = 11 g; *lipids* = 51.2 g; *proteins* = 24.4 g; 619 Kcal), *proteins-carbohydrates* (white cornille bean: *carbohydrates* = 49 g; *lipids* = 2.1 g; *proteins* = 24 g; 331 Kcal); either in a dominant macronutrient: *carbohydrates* (yellow corn: *carbohydrates* = 62 g; *lipids* = 2.8 g; *proteins* = 10 g; 342 Kcal), *lipids* (coconut, dried almond: *carbohydrates* = 9.27 g; *lipids* = 65.1 g; *proteins* = 6.64 g; 374 Kcal), *proteins* ("meat + fish" flour pellets: *carbohydrates* = 0 g; *lipids* = 9 g; *proteins* = 25 g: 120 Kcal). The consumption of the food types, as well as the body weight, are measured daily in each cage during the ten (10) days of manipulation. In each cage, small feeders are fixed in which the different categories of food are served, so that each type of food is accessible to the animal ad libitum, without the feeder tipping over to soil the food. Each type of food has its feeder marked to avoid confusion when measuring the amount of the type of food eaten. A bottle of still water is also placed in each of the cages. The injections of the products and the various measurements of weight or food intake begin almost every day at the same time, 16:30 p.m. and end around 19:00 p.m., corresponding to the start of activities, rats being nocturnal animals. The same amount of each food category is served to all treatment groups (initial food mass = M_0). After 24 hours, the remaining mass of each type of food is measured in all the cages (remaining mass of food = M_{24}). The difference ($M_0 - M_{24}$) gives the daily quantity of food consumed by rat, by food category and in each cage; which makes it possible to determine the average food consumption per rat, per day, per food category and per treatment.

Experiment 2: Ovariectomy and replacement of 17β-estradiol (E2)

Thirty-six (36) nulliparous rats, individually housed, underwent oophorectomy. For the surgical procedure, rats were immersed in a glass jar and anesthetized by inhalation of ethyl ether. Then, rats underwent bilateral oophorectomy (OVX group) via a midline dorsal incision. After ligation of the ovaries, a dorsolateral longitudinal incision was made on the organ. The risk of postoperative infection was eliminated by applying an antibiotic cream and an alcoholic solution of Betadine twice a week for four (4) weeks. After this recovery period, the OVX rats are divided into (6) groups (n = 6/group) comprising: OVX (ovariectomized females, untreated, injected with the vehicle DMSO); OVX + 17β-estradiol (E2, s.c.); OVX + Bromocriptine (BR, i.p.); OVX + Sulpiride (SUL, i.p.); OVX + E2 + BR and OVX + E2 + SUL. The administration schedule of the products to the OVX rats was identical to that of the controls. The same food types served to the control females were also made available to the OVX females. During the ten (10) days of manipulation, as in control rats, daily food intake and body weight were measured. The animals had free access to different types of food and water.

2.4. Statistical Analyzes

Two-way ANOVA was used to compare the effects of treatments on oophorectomy (6 factors) and control (6 factors) × 10 days of treatment (10 factors). Post hoc tests (p = 0.05) were performed using the protected least significance difference (PLSD) for comparison of means [62]. The graphs only show the variations of the average values of the variables per day over 10 days of processing.

3. Results

3.1. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating Yellow Corn Intake

A two-way ANOVA test on daily consumption of yellow maize, comparing control rats (C) with ovariectomized rats (OVX) showed significant treatment effects [$F_{(11, 600)}$ = 257, p < 0.001], with significant changes depending on treatment days [$F_{(9, 600)}$ = 37.7, p < 0.001] and confirmed treatment × day interactions [$F_{(99, 600)}$ = 11.36, p < 0.001] (Figure 1). Scheffé's post hoc test (p's = 0.05) shows that all the treatments in the ovariectomized rats significantly increased the consumption of yellow maize compared to the untreated control females. The comparison of the means shows that the average level of yellow maize consumed per day in the untreated ovariectomized rats (OVX: 1.283 ± 0.082 g/rat/day) increases significantly compared to the untreated control rats (C: 0.816 ± 0.023 g/rat/day) [p < 0.001]. In ovariectomized rats, bromocriptine (OVX + BR: 2.4 ± 0.108 g/rat/day) strongly increase yellow maize consumption compared to untreated OVX rats [p < 0.001]. Treatment of OVX rats with 17β-estradiol alone (OVX + E2: 1.433 ± 0.050 g/rat/day) slightly and significantly increases the consumption of yellow maize compared to the OVX group [p = 0.002]. The administration of 17β-estradiol to ovariectomized rats treated with sulpiride (OVX + E2 + SUL: 1.333 ± 0.041 g/rat/day) reduced consumption of yellow maize compared to the OVX + SUL group [p < 0.001]. Similarly, the OVX + E2 + BR group (1.483 ± 0.036 g/rat/day) decreased its daily consumption of yellow maize compared to the OVX + BR group [p < 0.001]. These observations show that E2 reduces yellow maize consumption in ovariectomized rats by inhibiting both types of D2/SUL and D2/BR receptors.

These results show us that the absence of E2 caused by ovariectomy induces an overconsumption of sugar in OVX rats by disinhibition of the two types of D2 receptors. Administration of exogenous E2 partially restores the activities of these D2 receptors to normal.

3.2. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement Sulpiride (SUL) and Bromocriptine (BR) Regulating Dry Coconut Kernel Consumption

After ovariectomy of the rats, a two-way ANOVA on the average daily consumption of dried coconut kernels showed significant treatment effects [$F_{(11, 600)}$ =
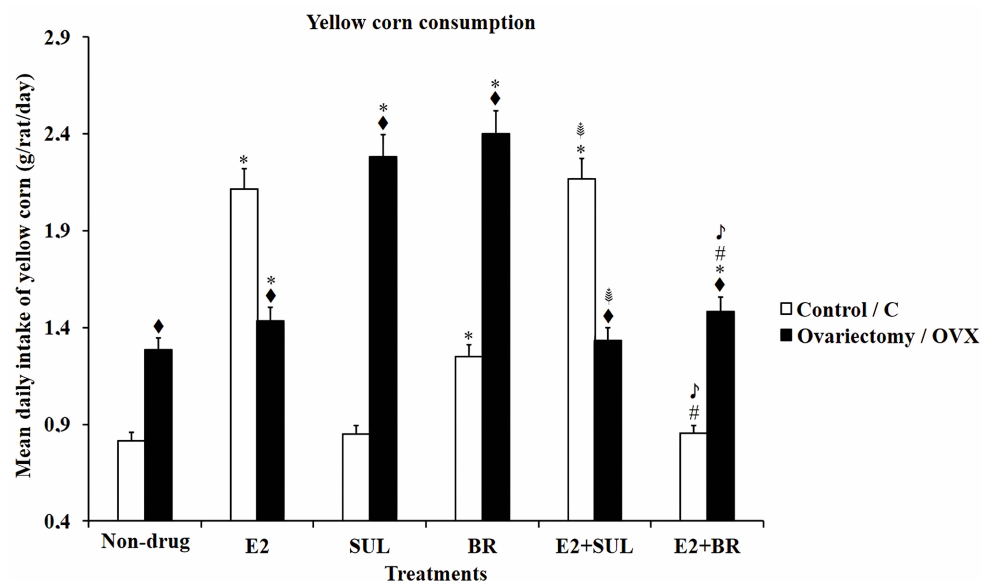
Figure 1. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of yellow maize consumption (carbohydrates = 62 g; lipids = 2.8 g; proteins = 10 g; 342 Kcal per 100 g) by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. Mean values over 10 consecutive days of treatment (g/rat/day ± SEM) of yellow maize consumption within each experimental group (N = 6 rats) were shown in control rats (C) and ovariectomized rats (OVX) submitted simultaneously to different treatments. The effects of the hormone (E2), the D2/SUL and D2/BR receptors and their respective interactions on the variations in the daily consumption of yellow maize are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, p < 0.001; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, p < 0.01; "⚕" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, p < 0.001; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, p < 0.001; "♪" Significantly different from E2 + SUL in control C rats and ovariectomized rats (p < 0.001). N = 6 rats in each of the six (6) treated groups in control rats and in ovariectomized rats.

185.85, p < 0.001], a significant variation of these averages as a function of the duration of treatment [F(9, 600) = 39.35, p < 0.001], as well as a significant "treatments × days" interaction [F(99, 600) = 14.36, p < 0.001] (Figure 2). The use of Scheffé's post hoc test (p's = 0.05) shows that the average daily consumption of dry coconut kernels increases significantly in untreated ovariectomized rats (OVX: 4.15 ± 0.078 g/rat/ day) compared to untreated control rats (C: 3.75 ± 0.165 g/rat/day), [p < 0.001]. In OVX rats, sulpiride (OVX + SUL: 4.483 ± 0.077 g/rat/day) increases the average daily consumption of dry coconut kernels compared to untreated ovariectomized rats (OVX), [p < 0.001] whereas, bromocriptine (OVX + BR: 3.816 ± 0.072 g/ratte/jour) reduces this consumption [p < 0.001]. The administration of 17β-estradiol alone to OVX rats (OVX + E2: 2.583 ± 0.051 g/rat/day) reduced the average daily consumption of dried coconut kernels
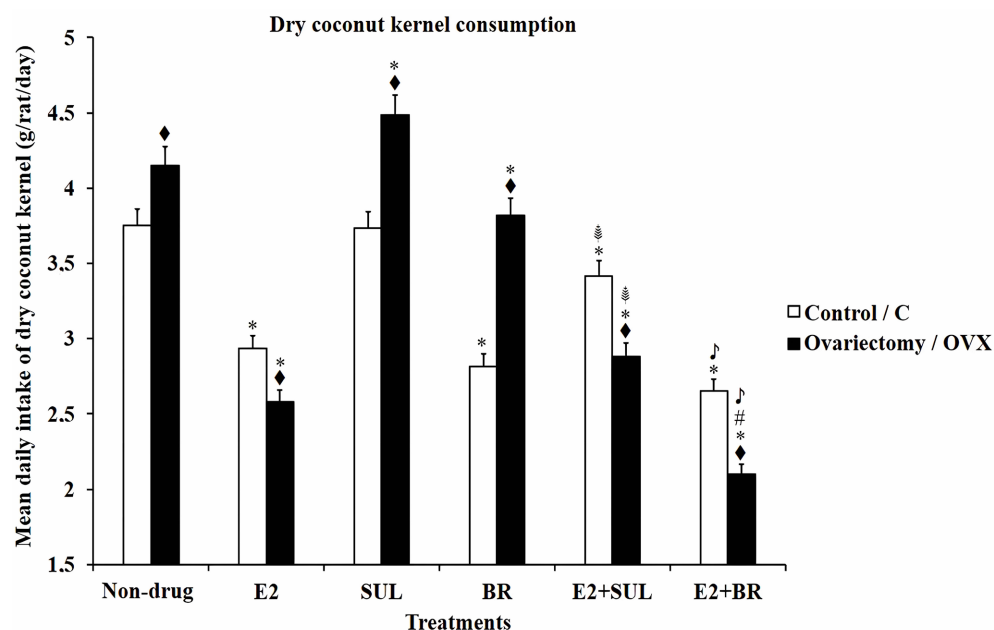
Figure 2. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of dry coconut kernel consumption (carbohydrate = 9.27 g; lipid = 65.1 g; protein = 6.64 g; 374 Kcal per 100 g) by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. Mean rates over 10 consecutive treatment days (g/rat/day ± SEM) of dry coconut kernel consumption in each experimental group (N = 6 rats) were plotted in control (C) and ovariectomized rats. (OVX) submitted simultaneously to different treatments. The effects of the hormone (E2), D2/SUL and D2/BR receptors and their respective interactions on variations in daily consumption of dry coconut kernels are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, p < 0.001; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, p < 0.001; "⧧" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, p < 0.001; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, p < 0.01; "♪" Significantly different from E2 + SUL in control C rats and ovariectomized rats (p < 0.001). N = 6 rats in each of the six groups treated in the control rats and in the ovariectomized rats.

compared to untreated ovariectomized rats (OVX) [p < 0.001]. The OVX + E2 + SUL group (2.88 ± 0.059 g/rat/day) decreased its daily consumption of dry coconut kernels compared to the OVX + SUL group [p < 0.001]. Comparison of the OVX + E2 + BR group (2.1 ± 0.065 g/rat/day) to the OVX + BR group [p < 0.001] also shows a reduction in the daily consumption of dry coconut kernels. Accordingly, the restoration of E2 in the OVX rat maintains the inhibition of the consumption of dry, lipid-rich coconut kernels (see **Figure 2**). These observations show that oophorectomy greatly increases the daily consumption of dry coconut kernels rich in lipids; on the other hand, E2 and BR alone reduce this daily consumption of dry coconut kernels in OVX rats with significant synergistic effects between E2 and BR. On the contrary, the SUL maintains a high daily consumption of dry coconut kernels, both in the control and in the OVX rat.

However, this effect of Sulpiride is countered by the administration of E2 in OVX females.

3.3. Effects of Ovarirectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating "Meat + Fish" Meal Pellet Consumption

After rat ovariectomy, a two-way ANOVA on daily consumption of "meat + fish" meal pellets showed significant treatment effects [$F_{(11, 600)} = 692.27$, $p < 0.001$], with significant changes over days [$F_{(9, 600)} = 3.23$, $p < 0.001$] and significant interactions between treatments and days [$F_{(99, 600)} = 4.64$, $p < 0.001$]; showing an exaggeration of the daily consumption of "meat + fish" meal pellets (Figure 3). The post-hoc comparison of the means shows that the untreated
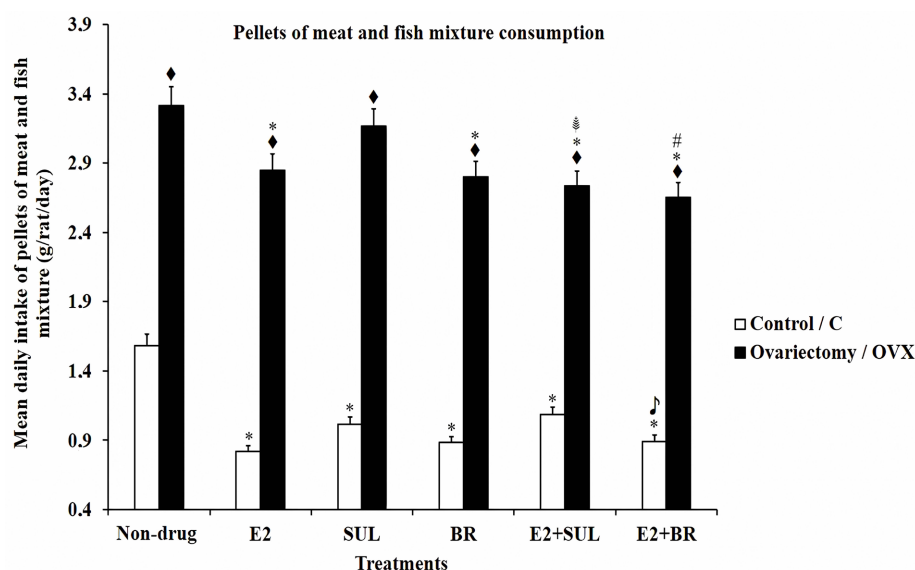

Figure 3. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of consumption of "meat + fish" meal pellets (carbohydrates = 0 g; lipids = 10 g; proteins = 30 g; 120 Kcal per 100 g) by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. Mean values over 10 consecutive days of treatment (g/rat/day ± SEM) of "meat + fish" meal pellet consumption within each experimental group (N = 6 rats) were plotted for rats from control (C) and ovariectomized (OVX) submitted simultaneously to different treatments. The effects of the hormone (E2), the D2/SUL and D2/BR receptors and their respective interactions on the variations in the daily consumption of "meat + fish" meal pellets are compared between control rats and rats. ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, $p < 0.001$; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, $p < 0.01$; "≸" Represents a significant difference between the direct stimulating effect of the D2/SUL receptor (SUL) and that of the combination of the receptor and the hormone (E2 + SUL) in control rats and ovariectomized OVX rats , $p < 0.001$; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, $p < 0.01$; "♪" Significantly different from E2 + SUL in control C rats and ovariectomized rats ($p < 0.001$). N = 6 rats in each of six treatment groups in control rats and ovariectomized rats.

ovariectomized rats (OVX: 3.316 ± 0.066 g/rat/day) increase their daily consumption of "meat + fish" meal pellets compared to the untreated control females (C: 1.583 ± 0.044 g/rat/day) [p < 0.001]. In OVX rats, the administration of sulpiride (OVX + SUL: 3.166 ± 0.074 g/rat/day) has no effect on the daily consumption of "meat + fish" meal pellets compared to untreated ovariectomized rats (OVX) [p = 0.067], whereas bromocriptine (OVX + BR: 2.8 ± 0.05 g/rat/day) reduces this daily consumption [p < 0.001].

Treatment of OVX rats with E2 (OVX + E2: 2.85 ± 0.048 g/rat/day) reduced consumption of "meat + fish" meal pellets compared to untreated ovariectomized rats (OVX) [p < 0.001]. These observations show that in OVX rats, 17β-estradiol and BR oppose excessive protein consumption with similar intensity. Replacing E2 slightly but significantly reduces protein consumption in OVX rats treated with bromocriptine (OVX + E2 + BR: 2.65 ± 0.041 g/rat/day) compared to OVX rats treated with bromocriptine alone (OVX + BR) [p = 0.003]. Similarly, the administration of E2 to OVX rats treated with sulpiride (OVX + E2 + SUL: 2.733 ± 0.042 g/rat/day) reduces the consumption of "meat + fish" flour pellets compared to the group (OVX + SUL) [p < 0.001]. In conclusion, the functional absence of E2 caused by ovariectomy removes the tonic inhibition induced by E2 on the consumption of protein-rich food. Under physiological conditions, modulating activity of E2 on dopamine D2 receptors is zero on protein consumption, whereas this modulating activity appears weakly when E2 is administered to the OVX rat (see the appearance in Figure 3). Thus, it appears that the activities of the SUL and BR receptors as well as the modulating effect of E2 on these D2 receptors are weakly involved in the regulation of protein consumption. Consequently, protein consumption would be regulated by another hormonal pathway different from E2.

3.4. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating the Consumption of White Currant (Black-Eyed) Bean

A two-way ANOVA on the consumption of the dry mature seed of the white bean (black-eyed) yielded large treatment effects [F(11, 600) = 1533.39, p < 0.001]; substantial change over days of treatments [F(9, 600) = 2.08, p = 0.029], as well as significant "treatments × days" interactions [F(99, 600) = 1.90, p < 0.001]. The results show a total collapse in the daily consumption of white cornille bean at all treatment levels in rats after ovariectomy (Figure 4). These results suggest that under normal physiological conditions, a basal tone of 17β-estradiol is essential for the consumption of this type of food rich in pairs of carbohydrate-protein macronutrients. The post-hoc comparison of the means, using the Scheffé F test shows that the untreated ovariectomized rats (OVX: 0.7 ± 0.026 g/rat/day) considerably reduce their daily consumption of white beans compared to the untreated control rats treated (C: 3.016 ± 0.073 g/rat/day) [p < 0.001]. Compared to untreated ovariectomized rats (OVX), OVX females treated with bromocriptine (OVX + BR: 0.55 ± 0.038 g/rat/day) reduced their daily bean consumption
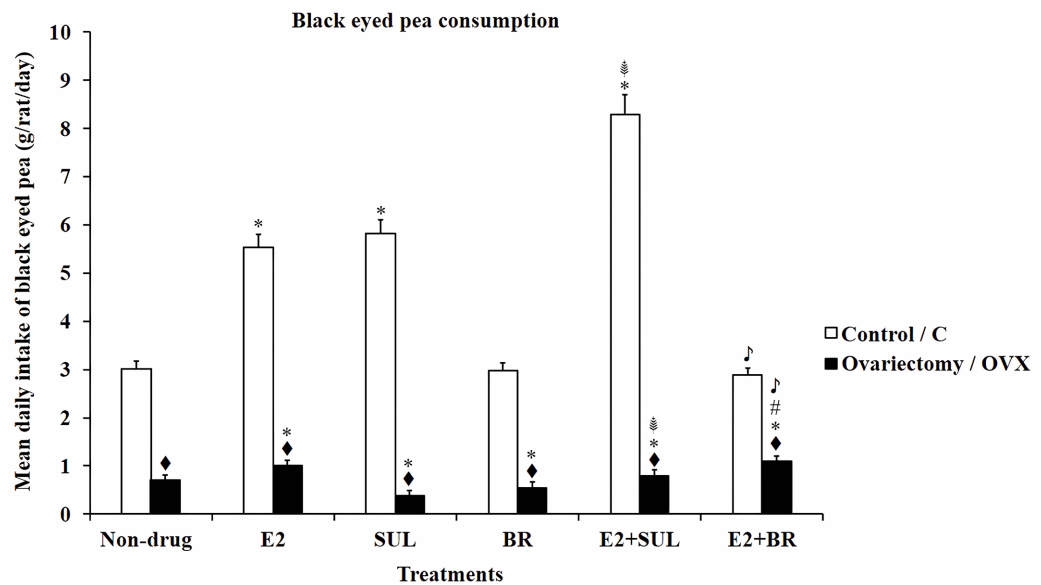
Figure 4. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of white cornille (black-eyed) bean consumption (carbohydrates = 49 g; lipids = 2.1 g; proteins = 24 g; 331 Kcal per 100 g) by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. Mean daily rates over 10 consecutive treatment days (g/rat/day ± SEM) of white bean consumption in each experimental group (N = 6 rats) were plotted in control (C) and ovariectomized (OVX) rats subjected simultaneously to the various treatments. The effects of the hormone (E2), D2/SUL and D2/BR receptors and their respective interactions on variations in daily white bean consumption are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, p < 0.01; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, p < 0.05; "♪" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, p < 0.05; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, p < 0.05; "♪" Significantly different from E2 + SUL in C control rats and OVX ovariectomized rats (p < 0.01). N = 6 rats in each of six treatment groups in control rats and ovariectomized rats.

cornelian white [p < 0.001]; those treated with sulpiride (OVX + SUL: 0.383 ± 0.017 g/rat/day) reduced their daily consumption of white beans even more [p < 0.001].

Treatment of OVX rats with 17β-estradiol (OVX + E2: 1 ± 0.038 g/rat/day) slightly and significantly increases the daily consumption of white beans compared to untreated ovariectomized rats (OVX), [F(1, 100) = 96.709, p < 0.001]. Simultaneous administration of sulpiride + 17β-estradiol to OVX rats (OVX + E2 + SUL: 0.8 ± 0.048 g/rat/day) increases the daily consumption of white beans compared to OVX rats treated with sulpiride alone (OVX + SUL) [p < 0.001]. Simultaneous treatment of OVX rats with bromocriptine + 17β-estradiol (OVX + E2 + BR: 1.1 ± 0.038 g/rat/day) increases the daily consumption of white beans compared to OVX females treated with bromocriptine alone (OVX + BR) [p < 0.001]. These results show that in the absence of the basal tone of E2, the D2/SUL receptors no longer respond to the activation of E2 and that all the desires to increase the consumption of foods rich in couples of carbohydrate-protein macronutrients

are triggered, either by E2 alone, or by its attempts to activate D2/BR receptors.

3.5. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating Plantain Chip Consumption

A two-way ANOVA on the daily consumption of plantain chips showed significant treatment effects $[F_{(11, 600)} = 181.02, p < 0.001]$; with significant changes depending on the days of treatment $[F_{(9, 600)} = 9.1, p < 0.001]$ and a treatment × day interaction that significantly varies the consumption of plantain chips $[F_{(99, 600)} = 8.17, p < 0.001]$ (Figure 5). These results also show a total collapse in daily plantain consumption at all treatment levels in rats after ovariectomy. Indeed, Scheffé's post hoc test (p's = 0.05) shows that untreated ovariectomized
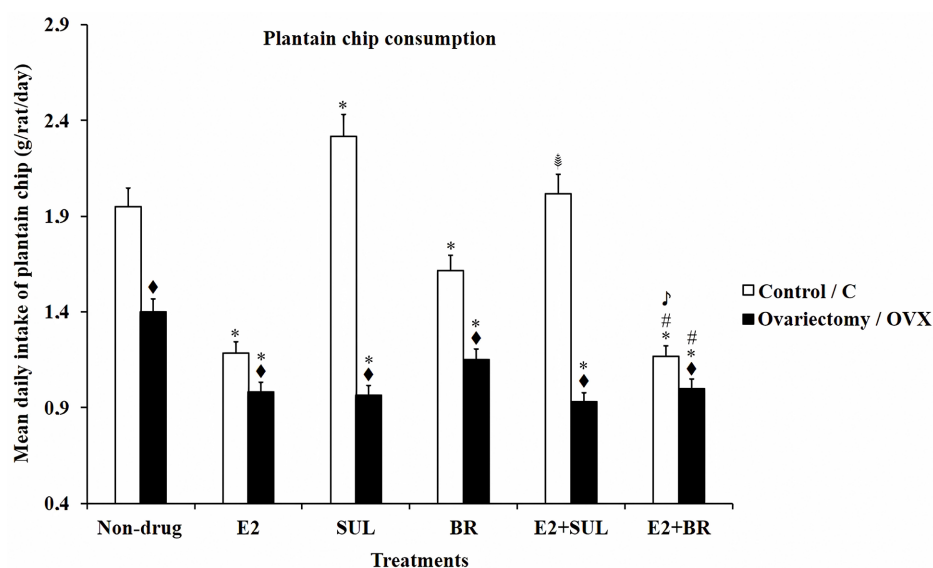

Figure 5. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of plantain chip consumption (carbohydrate = 63.8 g; fat = 29.6 g; protein = 2.3 g 531 Kcal per 100 g) by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. The mean daily values during 10 consecutive days of treatment (g/rat/day ± SEM) of the consumption of plantain banana chips within each experimental group (N = 6 rats) are represented in the control rats (C) and ovariectomized (OVX) submitted simultaneously to different treatments. The effects of the hormone (E2), D2/SUL and D2/BR receptors and their respective interactions on variations in the daily consumption of plantain chips are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, p < 0.001; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicule) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicule) OVX group, p < 0.01; "⁂" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, p < 0.01; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, p < 0.01; "♪" Significantly different from E2 + SUL in control C rats and ovariectomized rats (p < 0.05). N = 6 rats in each of six treatment groups in control rats and ovariectomized rats.

rats (OVX: 1.4 ± 0.022 g/rat/day) reduce their daily consumption of plantain chips compared to rats untreated control (C: 1.95 ± 0.073 g/rat/day) [p < 0.001]. In OVX females treated with sulpiride (OVX + SUL: 0.966 ± 0.053 g/rat/day), the daily consumption of plantain banana chips decreased compared to untreated OVX rats (OVX), [p < 0.001]. Similarly, OVX rats treated with bromocriptine (OVX + BR: 1.15 ± 0.04 g/rat/day) reduced their daily consumption of plantain chips compared to untreated OVX rats (OVX), [p < 0.001]. In the OVX + E2 group (0.983 ± 0.031 g/day) the daily consumption of plantain chips is reduced compared to the OVX group, [p < 0.001]. These results show that the consumption of foods with a codominance of carbohydrate-lipid nutrient pairs requires a basal tone of E2. In addition, replacement of 17β-estradiol did not restore estrogen receptor activity in rats ovariectomized for consumption of plantain chips. Thus, the co-treatment of OVX rattles with E2 + SUL (OVX + E2 + SUL: 0.933 ± 0.038 g/ratte/day) shows no variation in the daily consumption of plantain banana chips compared to the OVX + SUL treatment, [p = 0.362]. On the other hand, the OVX + E2 + BR group (1 ± 0.034 g/ratte/day) reduced the consumption of plantain banana chips compared to the OVX + BR group, [p < 0.001]. These results show that the disappearance of basal estrogen tone caused by ovariectomy cannot be established by replacement of exogenous E2, which leads to E2 dysfunctions in the regulation of D2 receptors to control the consumption of couple-rich foods, carbohydrate-lipid macronutrients. Mention may be made, for example, of the inversion of the effect of D2/BR receptors and its synergistic control by E2 in the consumption of this type of food in OVX rats.

3.6. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating the Consumption of Roasted and Salted Peanuts

After rat ovariectomy, a two-way ANOVA on the mean daily consumption of roasted and salted peanuts showed significant effects of the treatments [$F_{(11, 600)}$ = 230.89, p < 0.001], a significant variation of these averages according to the duration of treatment [$F_{(9, 600)}$ = 17.02, p < 0.001] as well as proven "treatments × days" interactions [$F_{(99, 600)}$ = 10.21, p < 0.001] (see Figure 6). Scheffé's post hoc comparisons (p's = 0.05) show that ovariectomy reduces the daily consumption of roasted and salted peanuts in untreated ovariectomized rats (OVX: 0.566 ± 0.034 g/rat/day) compared to control rats untreated (C: 1.083 ± 0.047 g/rat/day), [p < 0.001], which indicates a low consumption of roasted and salted peanuts in ovariectomized rats.

OVX rats treated with bromocriptine (OVX + BR: 0.6 ± 0.031 g/rat/day) show no difference in daily consumption of roasted and salted peanuts compared to untreated OVX rats (OVX) [p = 0.332], confirming the non-involvement of D2/BR receptors in the consumption of this type of food. Compared to untreated OVX rats (OVX), treatment of OVX rats with sulpiride (OVX + SUL: 1.633 ± 0.063 g/rat/day) increases the daily consumption of roasted and salted peanuts [p < 0.001]. Ovariectomized rats treated with E2 (OVX + E2: 1.65 ±
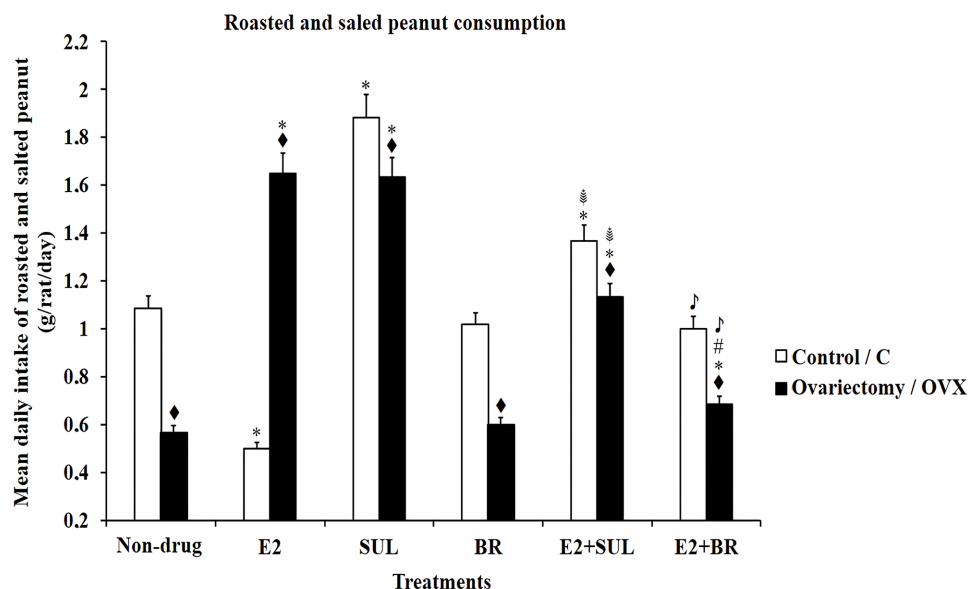
Figure 6. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of roasted and salted peanut consumption (carbohydrate = 11 g; fat = 51.2 g; protein = 24.4 g; 619 Kcal per 100 g) by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. Mean daily rates over 10 consecutive treatment days (g/rat/day ± SEM) of roasted and salted peanut consumption in each experimental group (N = 6 rats) were plotted in control (C) and ovariectomized rats (OVX) submitted simultaneously to different treatments. The effects of the hormone (E2), D2/SUL and D2/BR receptors and their respective interactions on variations in daily consumption of roasted and salted peanuts are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, p < 0.001; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, p < 0.05; "≋" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, p < 0.001; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, p < 0.05; "♪" Significantly different from E2 + SUL in control C rats and ovariectomized rats (p < 0.01). N = 6 rats in each of six treatment groups in control rats and ovariectomized rats.

0.043 g/rat/day) increased their daily consumption of roasted and salted peanuts compared to untreated OVX rats (OVX), [p < 0.001]. The OVX + E2 + BR group (0.683 ± 0.034 g/rat/day) slightly and significantly increased its consumption of roasted and salted peanuts compared to the OVX + BR group [p < 0.001]. The OVX + E2 + SUL group (1.133 ± 0.059 g/rat/day) reduced their consumption of roasted and salted peanuts compared to the OVX + SUL group [p < 0.001]. We also observe in this experiment that the absence of estrogenic tone created by ovariectomy leads to dysfunctions of E2 in the regulation of D2 receptors to control the consumption of foods rich in couples of lipid-protein macronutrients. In this case, we also note the inversion of the effect of the D2/BR receptors and its synergistic control by E2 in the sense of an increase in the consumption of this type of complex food in the OVX rats.

3.7. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating Regulating Food Intake

Daily food consumption was calculated from a summation of the residual consumption of each food category per rat and per day. This involves adding up the quantities of corn, coconut kernels, "meat + fish" flour granules, cornille white beans, banana chips, peanuts, consumed daily by each rat and per treatment.

A two-way ANOVA test on daily food intake showed large treatment effects [$F_{(11, 600)} = 146$, $p < 0.001$], significant changes in daily food intake over treatment days [$F_{(9, 600)} = 4.3$, $p < 0.001$], as well as confirmed treatment × day interactions [$F_{(99, 600)} = 1.3$, $p = 0.031$], (Figure 7). Scheffé's post hoc test (p's = 0.05) shows that untreated ovariectomized rats (OVX: 10.426 ± 0.11 g/rat/day)
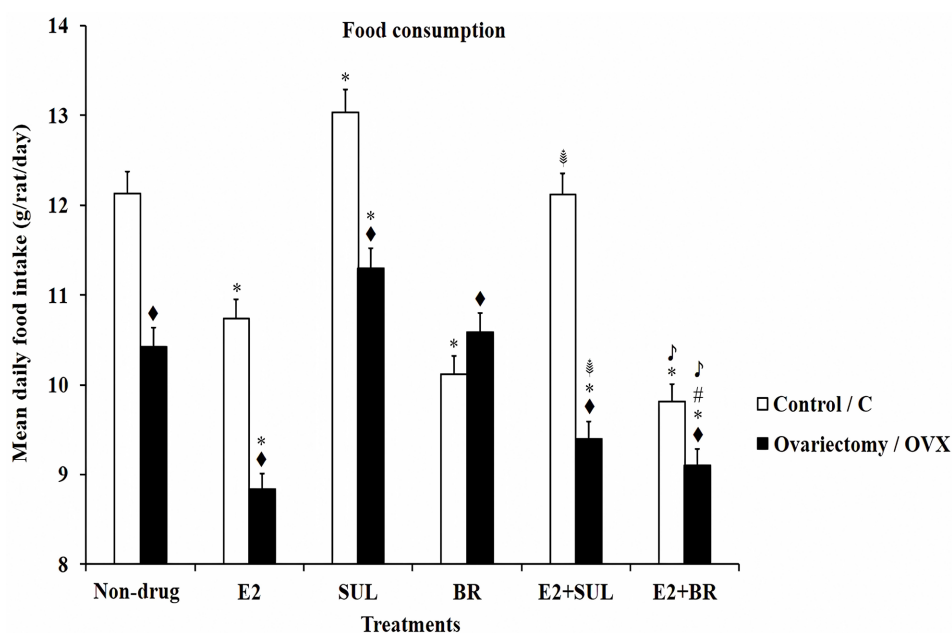

Figure 7. Effects of ovariectomy and 17β-estradiol (E2) replacement on the regulation of food intake by sulpiride (SUL) and bromocriptine (BR) in ovariectomized rats. Mean daily values of food consumption (g/rat/day ± SEM) over 10 consecutive days of treatment within each experimental group (N = 6 rats) were plotted in control rats (C) and ovariectomized rats (OVX) subjected simultaneously to the various treatments. The effects of the hormone (E2), D2/SUL and D2/BR receptors and their respective interactions on variations in daily food consumption are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, $p < 0.05$; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, $p < 0.01$; "⚕" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, $p < 0.001$; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, $p < 0.05$; "♪" Significantly different from E2 + SUL in C control rats and OVX ovariectomized rats, ($p < 0.05$). N = 6 rats in each of six treatment groups in control rats and ovariectomized rats.

reduce their daily food consumption compared to untreated control rats (C: 12.133 ± 0.16 g/rat/day), [p < 0.001]. The OVX + SUL group (11.296 ± 0.108 g/rat/day) increased its daily food consumption compared to the untreated OVX rats (OVX), [p < 0.001]. On the other hand, the OVX + BR group (10.583 ± 0.084 g/rat/day) did not modify its food consumption compared to the OVX group [p = 0.226], showing that estrogen tone is essential for blocking BR on food consumption.

Administration of E2 to ovariectomized rats (OVX + E2: 8.833 ± 0.083 g/rat/day) further reduces food consumption compared to untreated OVX rats (OVX), [p < 0.001]. D2/BR and D2/SUL receptors are blocked in ovariectomized rats by replacement of E2, when comparing the OVX + BR group to the OVX + E2 + BR group (9.101 ± 0.087 g/rat/day), [p < 0.001] and The OVX + SUL group to the OVX + E2 + SUL group (9.4 ± 0.087 g/rat/day) [p < 0.001]. However, E2 blocking is preponderant on D2/SUL receptors relative to D2/BR receptors. In conclusion, these results show that 17β-estradiol and BR inhibit food consumption independently and without synergistic effect between E2 and BR. Consequently, D2/BR receptors would not be involved in the regulation of appetite and food intake. They would moderately undergo the regulatory influence of 17β-oestradiol on appetite, but could be solicited on the contrary by the factors triggering satiation. On the other hand, SUL greatly increases food consumption alone or under the hormonal influence of17β-estradiol, which can increase or inhibit the activity of D2/SUL receptors depending on homeostatic needs. However, the functioning of D2/SUL receptors would require basal estrogen tone, given the involvement of these receptors in the choice of consumption of complex foods. D2/SUL receptors are thought to be involved in the regulation of appetite and food intake.

3.8. Effects of Ovariectomy and 17β-Estradiol (E2) Replacement on Sulpiride (SUL) and Bromocriptine (BR) Regulating Regulating Regulating Body Weight

A two-way ANOVA on body weight showed large treatment effects [F(11, 600) = 12, p < 0.001], but no change over treatment days [F(9, 600) = 1, p = 0.31] and established treatment × day interactions [F(99, 600) = 2, p < 0.001] (Figure 8). Post hoc comparisons using the Scheffé test (p's = 0.05) show that ovariectomy (OVX: 202.241 ± 0.23 g/rat/day) causes an increase in body weight in rats compared to female rats. Control (C: 201.426 ± 0.25 g/rat/day), [p = 0.008]. The administration of sulpiride to ovariectomized rats (OVX + SUL: 202.259 ± 0.47 g/rat/day), does not cause any variation in body weight compared to untreated OVX rats (OVX: 202.241 ± 0.23 g/rat /day), [p = 0.971]. It is important to note that the comparison of the OVX + SUL and C + SUL groups (202.483 ± 0.225 g/rat/day) shows no difference in body weight variation in the rats [p = 0.673]. These observations show that sulpiride does indeed promote weight gain. Compared to untreated OVX rats (OVX: 202.241 ± 0.23 g/rat/day), bromocriptine prevented increased body weight in ovariectomized rats (OVX + BR: 201.426 ±
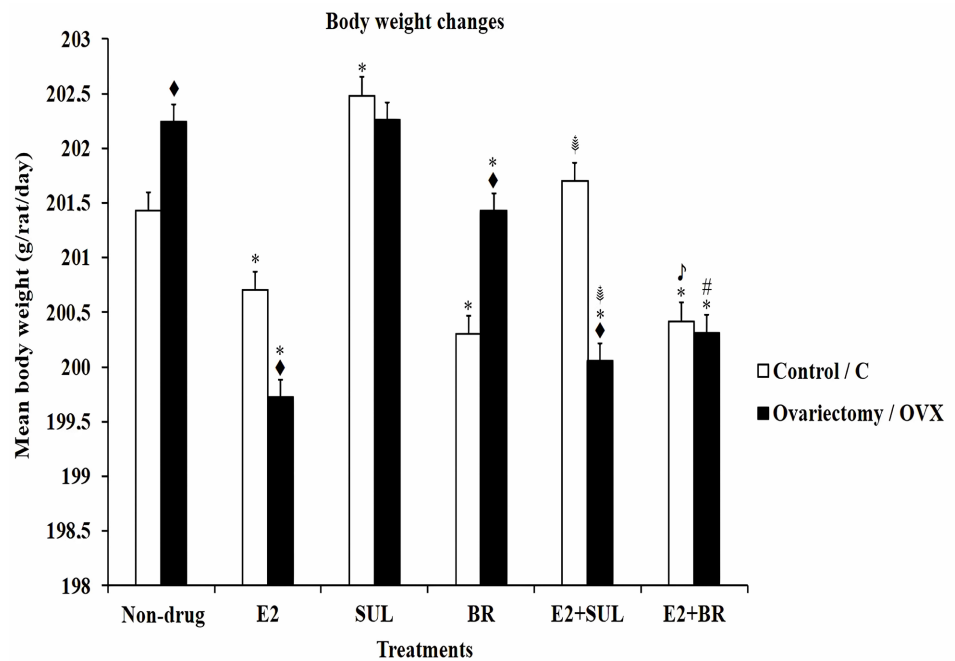
Figure 8. Effects of ovariectomy and 17β-estradiol (E2) replacement on body weight regulation by bromocriptine (BR) and sulpiride (SUL). Daily variations in mean body weight over 10 consecutive days of treatment (g/rat/day ± SEM) within each experimental group (N = 6 rats) are shown in control (C) and ovariectomized (OVX) rats subjected to simultaneously with different treatments. The effects of the hormone (E2), the D2/SUL and D2/BR receptors and their respective interactions on the variations in mean body weight are compared between control rats and ovariectomized rats. "♦" Indicates a significant difference between control (C) and ovariectomized (OVX) rats subjected to the same treatments, $p < 0.05$; "*" Differences in significance: between the treated groups of control C and the Non-drug-treated (DMSO vehicle) group of control C; between the OVX-treated groups and the Non-drug-treated (DMSO vehicle) OVX group, $p < 0.01$; "♪" Represents a significant difference between the direct stimulation effect of D2 receptor/SUL (SUL) and that of the combination of receptor and hormone (E2 + SUL) in control C rats and ovariectomized rats OVX, $p < 0.05$; "#" Corresponds to a significant difference between the direct stimulation effect of the D2/BR receptor (BR) and the effect of association of the receptor and the hormone (E2 + BR) in the control rats C and the OVX ovariectomized rats, $p < 0.05$; "♪" Significantly different from E2 + SUL in C control rats and OVX ovariectomized rats, ($p < 0.05$). N = 6 rats in each of six treatment groups in control rats and ovariectomized rats.

0.261 g/rat/day), [$p = 0.014$], with no real reduction relative to the mean body weight of control females (C: 201.426 ± 0.25 g/rat). On the other hand, the comparison of the C + BR (200.301 ± 0.309 g/rat/day) and OVX + BR (201.426 ± 0.261 g/rat/day) groups shows an increase in weight in ovariectomized rats [$p = 0.002$] which remains at the same level as the control females (C: 201.426 ± 0.25 g/rat), indicating that the absence of E2 would cause a dysfunction of the D2/BR receptors which lose their effectiveness in inhibition of body weight. Replacement of E2 in ovariectomized rats promotes a strong reduction in body weight (OVX + E2: 199.722 ± 0.337 g/rat/day) compared to untreated OVX rats (OVX: 202.241 ± 0.23 g/rat/day), [$p < 0.001$]. The comparison of the OVX + BR (201.426 ± 0.261 g/rat/day) and OVX + E2 + BR (200.314 ± 0.268 g/rat/day)

groups shows a recovery in the activity of the D2/BR receptors which returns to a level normal [p < 0.001].

Similarly, the replacement of E2 prevents an increase in weight when comparing the OVX + SUL (202.259 ± 0.47 g/rat/day) and OVX + E2 + SUL (200.056 ± 0.257 g/rat/day) groups [p < 0.001], showing that E2 is more effective in controlling D2/SUL receptors. Our results indicate that under normal physiological conditions, increases in food consumption and body weight are induced by 17β-estradiol-controlled D2/SUL receptors, whereas D2/BR receptors cause specific inhibition of food consumption and body weight gain, independent of 17β-estradiol control. In the ovariectomized rat, our studies show a decrease in the general level of food consumption certainly caused by an abolition of estrogenic tone, in contrast to the increase in body weight. The increase in weight in OVX rats would be caused by a dietary imbalance oriented towards a massive consumption of foods with a single dominant macronutrient. The abolition of basal estrogen tone would also lead to a dysfunction of the D2/BR receptors, or even a reversal of their role, all of which would trigger an increase in body weight. Replacement of E2 reduces body weight and this action would induce inhibition of D2/SUL receptor activity and enhancement of D2/BR activities. Overall, these observations show that 17β-estradiol may play an important role in the stability of body weight in women by regulating the fixed set point of body weight by modulating the activities of dopamine D2 receptors.

4. Discussion

Our results show that the consumption of exclusively high carbohydrate foods, such as yellow corn, is triggered directly by 17β-estradiol or bromocriptine in control rats, while the administration of sulpiride alone has no significant effect. on the consumption of yellow maize. However, consumption of yellow maize is amplified by co-administration of "17β-estradiol + sulpiride" in control rats, whereas co-administration of "17β-estradiol + bromocriptine" reduces this consumption of yellow maize. Thus, 17β-estradiol controls the activities of D2/BR receptors but without synergistic effect with bromocriptine on the stimulation of carbohydrate consumption. The ovariectomy exploded the daily consumption of yellow maize, in all the treatment groups carried out. In addition, the replacement of 17β-estradiol by the administration of exogenous E2 to ovariectomized rats partially corrects this consumption of carbohydrate (yellow corn) compared to the untreated OVX group considered normal in the context of ovariectomy. These observations show us that the absence of E2 caused by ovariectomy induces an overconsumption of sugar in OVX rats by disinhibition of the two types of D2 receptors. Administration of exogenous E2 partially restores the activities of these D2 receptors to normal. Under hormonal induction of 17β-estradiol, bromocriptine more significantly reduced carbohydrate intake in control rats. Ovariectomy exacerbated carbohydrate consumption, expressing an inhibitory tone of 17β-estradiol on carbohydrate consumption. Similarly, bromocriptine

alone significantly increased carbohydrate consumption in OVX rats, demonstrating that bromocriptine is a specific inducer of carbohydrate consumption. However, replacement of 17β-estradiol in OVX rats treated with sulpiride or bromocriptine did not restore sugar intake to normal levels. Indeed, E2 exerts a tonic inhibition on D2/BR receptors which was released by OVX. In addition to the permanent inhibitory role played by 17β-estradiol on sugar consumption, it has also been shown that under hormonal induction of 17β-estradiol, D2/BR receptors effectively reduce sugar consumption. The involvement of 17β-estradiol in reducing sugar intake has been reported previously. Thus, removal of the ovaries has been shown to increase the supply of glucose solutions while replacement of 17β-estradiol reduces the glucose supply of ovariectomized rats [63]. On the one hand, previous studies have reported that systemic [64] [65] [66] [67] and intracerebral [67] of bromocriptine in insulin-resistant animals, decreased hepatic glucose production and gluconeogenesis, reduced adipose tissue lipolysis and improved insulin sensitivity [68]. On the other hand, [69] reported that D2 receptors were involved in the increased sugar consumption observed in obese OLETF rats. Indeed, the obese OLETF rat showed an exaggerated preference for high sugar concentration, expressing lower D2 receptors and exhibiting altered D2 receptor signaling [70]. Boswel and collaborators report that when Sprague-Dawley rats are given the opportunity to eat a mixture of chocolate and cake, they absorb a large amount of this mixture; often taking more than 20 g per rat in 24 hours. When these rats were given a dose of 17β-estradiol of 10 mg/kg, they absorbed more of the chocolate mixed with the cake than the control animals. These observations show that 17β-estradiol does indeed induce sugar consumption. But the effect of 17β-estradiol on sugar consumption is dose dependent [71]. Indeed, these authors showed that the consumption of a 0.25% sucrose solution was higher than the consumption of 2% sucrose [71]. These authors suggest that when the solution is pleasant to consume for the animal, it increases its consumption [71]. It can be deduced from these observations that 17β-estradiol induces sugar consumption, when the animal is in the context of a diet considered pleasant. This supports the hypotheses of some authors that 17β-estradiol encourages the consumption of tasty foods [46]. In general, our results show that the consumption of carbohydrate (yellow maize) is activated by all the treatments carried out both in control rats and ovariectomized rats. Estrogens and their receptors play a key role in the regulation of carbohydrate homeostasis. Indeed, numerous clinical studies have shown a positive correlation between the estrogen pathway and the main features of the metabolic syndrome (obesity, insulin resistance and hyperglycemia) [72]. Foods with a proportionate content of the three macronutrients with a predominance of sugar such as yellow corn, which can be described as a tasty or whole food, show an activation of their consumption by 17β-estradiol (E2) and bromocriptine (BR), both in control females and in ovariectomized rats. The consumption of these foods is therefore peremptory and does not seem to depend on a basal tone of E2. Some

authors have demonstrated that peripheral dopamine stimulates glucose uptake in vivo in insulin-sensitive tissues, such as adipose tissue, liver, and skeletal muscle, and that bromocriptine acts directly in adipose tissue, the liver and skeletal muscle to regulate, not only glucose uptake, but also insulin sensitivity and metabolic function [73]. According to our results, sulpiride D2/SUL receptors, which were not affected by sugar consumption in control rats, very significantly stimulate sugar consumption in ovariectomized rats. Some authors have demonstrated that blocking the D2 receptor with sulpiride releases another D2 isoform capable of actively reducing sugar consumption [74]. Some authors reported that D2 receptors were effective inhibitors reducing sugar consumption in rats, when exposed to high sugar intake [69]. These observations suggest that sulpiride binding to D2 receptors (D2/SUL), probably D2S (short chain), inhibits sugar intake in control rats when exposed to high sugar intake, and that this inhibition is induced under hormonal activation of 17β-estradiol. Indeed, as our studies show, 17β-estradiol activates bromocriptine more effectively than sulpiride to reduce sugar intake in control rats, showing functional differences between the two receptors [30] [75]. Therefore, 17β-estradiol exerts tonic inhibition on D2 receptor binding bromocriptine, such as long-chain D2L, which appear to be specific inducers of sugar consumption [30]. Under physiological conditions, 17β-estradiol blocks D2/BR receptors to maintain blood sugar levels. When glucose requirements were physiologically expressed, *i.e.* during hypoglycemia, tonic inhibition of 17β-estradiol on D2/BR (D2L) receptors was temporarily released, thereby triggering sugar consumption [30]. Conversely, during hyperglycemia, 17β-estradiol would induce D2/SUL (D2S) receptors to reduce glucose intake. Therefore, D2/SUL and D2/BR receptors participate in homeostasis of basal sugar level regulation under hormonal control of 17β-estradiol [30].

In controls, the consumption of foods rich in lipids was severely inhibited by 17β-estradiol or bromocriptine alone, or in combination (17β-estradiol + bromocriptine). Generally, the effects of 17β-estradiol and bromocriptine are synergistic in inhibiting high-fat foods. Unlike 17β-estradiol or bromocriptine, the consumption of foods with a high fat content, such as dried coconut kernels, is triggered directly by sulpiride. In addition, our study shows that ovariectomy increases the consumption of foods rich in lipids, indicating an inhibitory action of 17β-estradiol on lipid consumption, lifted by the elimination of the ovaries. Our study also shows that the administration of bromocriptine during ovariectomy also inhibits the consumption of foods rich in lipids and D2/BR appears as a specific inhibitor of lipid consumption. In the absence of E2, the SUL maintains a high daily consumption of lipid (dry coconut kernel); but the effect of Sulpiride is countered by the administration of E2 in OVX females. Thus, under physiological conditions E2 blocks the actions of SUL. In the event of menopause (absence of E2), the D2 receptors of the SUL appear as important mediators of obesity. Generally, the inhibiting effects of E2 are much stronger than those of BR. Moreover, synergistic effects between E2 and BR are not frequent.

Previous results indicate that the systemic injection of dopamine D2 receptor antagonists increases the consumption of foods rich in lipids. These observations show that sulpiride-sensitive receptors direct consumption towards foods with a potentially high lipid content. Jaber and collaborators, examined the chronic effects of the administration of sulpiride 100 mg/kg, for 14 days, in the pituitary gland and the striatum of rats. They observe that sulpiride increases dopamine D2 receptor mRNAs by more than 125%. In the striatum, sulpiride increased dopaminergic D2 receptor mRNAs by 72% [76]. These observations show that when the animal is exposed for a long time to a diet with a high energy potential in lipids, sulpiride can induce the synthesis of a subclass of D2 receptors which would promote the consumption of fat. This subclass of D2 receptor would be revealed in the presence of sulpiride blockade and could be short-chain D2 receptors (D2S) [30]. In addition, treatment with a dopamine antagonist preferentially increases the shorter isoform in the brain or pituitary [77]. However, recent studies have shown the involvement of short-chain D2 receptors in alcohol abuse and drug addiction [30]. It also appears that most of the inhibitions of E2 and BR on the consumption of energy foods, lipids in particular, is lifted in OVX rats. So after the ovariectomy there persists a residual activating activity of the D2/SUL receptors in the consumption of lipid. Thus causing a daily imbalance between food intake and energy expenditure, which thus promotes weight gain. Adipose tissue is preferentially stored in the form of subcutaneous adipocytes; but if the energy intake is too high, the body will store the fat in the form of intra-abdominal visceral adipose tissue. This visceral fat is associated with most health risks [78]. As adiposity increases, the risk of developing obesity, insulin resistance, diabetes, hypertension and cardiovascular disease also increases [79].

Our study shows that under normal physiological conditions, 17β-estradiol exerts a tonic inhibition on protein consumption in rats. The modulating effect of E2 on the SUL and BR receivers is almost nil. The functional absence of E2 caused by the ovariectomy lifts the tonic inhibition induced by E2 on the consumption of protein-rich food. The modulating activity of E2 on dopamine D2 receptors is nil on protein consumption, whereas this modulating activity appears weakly when E2 is administered to OVX rats. Thus, it appears that the activities of the SUL and BR receptors as well as the modulating effect of E2 on these D2 receptors are weakly involved in the regulation of protein consumption. Consequently, protein consumption would be regulated by another hormonal pathway different from E2. The protein-rich "meat + fish" flour pellets are similar to a meat diet for rats and therefore very caloric. Some authors argue that estrogen protects against adiposity, insulin resistance and type II diabetes, and regulates energy intake and expenditure [80]. Similarly other authors, have shown that bromocriptine restores the balance of energy intake according to energy status and body energy needs, which can be very important for the prevention of lipotoxicity and glucotoxicity, two hallmarks of insulin resistance and metabolic dysregulation [81]. These observations therefore show that E2 and BR

inhibit the consumption of high-calorie foods to avoid an imbalance between increased consumption and low energy expenditure, resulting in fat accumulation. According to Tounian, hyperphagia and obesity are the result of dysfunction of the normal appetite regulation loop [82]. Some studies have shown that body weight was unchanged in individuals with type II diabetes after administration of bromocriptine [83] [84]. Our results suggest that the factor contributing to the decrease in body weight in our animal model could be the decrease in caloric intake. Indeed, bromocriptine treatment has been shown to restore hypothalamic dopamine levels in rodents [85]. Similarly, Davis et al described higher levels of hypothalamic dopamine receptors after bromocriptine treatment in obese Zucker rats and associated such an increase with hyperphagia and reduced fat mass [86]. Ovariectomy removes the inhibition hated by E2 on the consumption of food with a high protein content and even the replacement of exogenous E2 does not completely prevent this protein consumption. These observations effectively indicate an alteration of estrogen receptors during ovariectomy. Interestingly, the consumption of this high protein food is not induced by sulpiride. Consumption of cornille white bean rich in pairs of carbohydrate-protein macronutrients, completely collapses at all treatment levels in rats after oophorectomy. These results suggest that under normal physiological conditions, a basal tone of 17β-estradiol is essential for the consumption of this type of food rich in pairs of carbohydrate-protein macronutrients. These results also show that in the absence of the basal tone of E2, the D2/SUL receptors no longer respond to the activation of E2 and that all the desires to increase the consumption of foods rich in couples of carbohydrate-protein macronutrients are triggered either by E2 alone or by its attempts to activate D2/BR receptors. In the control, the consumption of white beans, with a high carbohydrate-protein macronutrient couple content, requires the activation of sulpiride. These observations indicate that sulpiride is involved in the stimulation of protein consumption and more generally in the consumption of carbohydrates if it is induced by 17-β-oestradiol. This context brings us to the situation of eating tasty foods. Indeed, Martínez and collaboratros, report that the preference of animals for sweet or unsweetened food depends on its caloric content, the more the food is sweet and its caloric content is high, the tastier it seems [87]. Foods that are eaten during a binge episode are generally high in calories, fat and/or sugar, and are normally considered foods to be eaten in moderation [88] [89] [90]. Attention to appetizing foods is inhibited if the caloric value is not high enough. Moreover, conditioned place preference studies have provided more varied behavioral results [91] [92] [93]. In sterilized macaques, E2 increases the preference for a palatable diet over a chow diet [46]. These observations show that foods high in carbohydrates and protein would be tasty foods. These foods do not appear to be balanced and consumption of these foods appears to be regulated by basal E2 tone. Our results showed that E2 exerts a facilitating action of carbohydrate consumption; which explains the activation of the carbohydrate-protein macro-

nutrient couple. In the absence of E2 consumption of the carbohydrate-protein macronutrient couple is inhibited. On the other hand, 17β-estradiol reinforces the inhibitory action induced by bromocriptine receptors (D2/BR) on the consumption of foods rich in pairs of carbohydrate-lipid macronutrients such as plantain banana chips. In effect, E2 inhibits the consumption of foods rich in carbohydrate-lipid macronutrient pairs induced by D2/SUL receptors. Under physiological conditions, the consumption of high-energy foods rich in carbohydrate-lipid macronutrient couples is inhibited by E2 and BR alone, with synergistic effects between E2 and BR. On the other hand, the consumption of these foods is strongly stimulated by SUL, the action of which is blocked by E2. Our results show that the consumption of foods with a codominance in carbohydrate-lipid nutrient pairs requires a basal tone of E2. Disappearance of basal estrogen tone caused by ovariectomy is not established by replacement of exogenous E2, resulting in E2 dysfunctions in the regulation of D2 receptors to control consumption of carbohydrate-rich macronutrient pair foods lipids. Mention may be made, for example, of the inversion of the effect of D2/BR receptors and its synergistic control by E2 in the consumption of this type of food in OVX rats. Similarly, 17β-estradiol inhibits the consumption of foods rich in lipid-protein macronutrient couples, such as roasted and salted peanuts. Our results show that D2/BR receptors are not involved in the consumption of this type of food. On the other hand, sulpiride is involved in the consumption of this type of food under the control of E2. 17β-estradiol has no influence on D2/BR receptors in the consumption of foods high in lipid-protein macronutrient couples; confirming the non-involvement of D2/BR receptors in the consumption of this type of food. We also observe in this experiment that the absence of estrogenic tone created by ovariectomy leads to dysfunctions of E2 in the regulation of D2 receptors to control the consumption of foods rich in couples of lipid-protein macronutrients. In this case, we also note the inversion of the effect of the D2/BR receptors and its synergistic control by E2 in the sense of an increase in the consumption of this type of complex food in the OVX rats. Overall, our results show that 17β-estradiol and BR inhibit food consumption independently and with no synergistic effect between E2 and BR. Consequently, D2/BR receptors would not be involved in the regulation of appetite and food intake. They would moderately undergo the regulatory influence of 17β-oestradiol on appetite, but could be solicited on the contrary by the factors triggering satiation. On the other hand, SUL greatly increases food consumption alone or under the hormonal influence of 17β-estradiol, which can increase or inhibit the activity of D2/SUL receptors depending on homeostatic needs. However, the functioning of D2/SUL receptors would require basal estrogen tone, given the involvement of these receptors in the choice of consumption of complex foods. D2/SUL receptors are thought to be involved in the regulation of appetite and food intake. Indeed, our study shows an inhibition of food consumption during ovariectomy, therefore a decrease in the total amount of all food types consumed per day. On the other

hand, this elimination of the ovaries promotes an increase in body weight. These results are in agreement with the work of certain authors who report that the obese and dysmetabolic phenotype induced by the interruption of the estrogen signal (estrogen deficiency), results mainly from a reduction in energy expenditure and not from an increase in food intake [94] [95] [96]. Wohlers and Spangenburg report that estrogen deficiency setting in at menopause promotes the accumulation of fat mass, mainly at the visceral level, reflecting an increase in weight [97]. After menopause, when estrogen levels decline, women experience a general increase in weight [98] [99]. It is important to note that the increase in abdominal fat in postmenopausal women tends to be visceral and not subcutaneous [100]. Estrogen receptors (ERα and ERβ) are present in adipose tissue, potentially indicating regulation of adipocyte function by estrogen [101] [102] [103]. ERα and ERβ can differentially mediate the effects of estrogen on adipose tissue, with ERα primarily regulating adipose homeostasis via adipocyte growth and proliferation, and ERβ regulating the gender-specific distribution of adipose tissue [102]. Previous studies have demonstrated that ERα-mediated estrogen signaling pathways upregulate α2A-adrenergic receptor expression in subcutaneous but not visceral adipose tissue [104]. The α2A-adrenergic receptor controls the anti-lipolytic pathways, promoting the accumulation of adipose tissue. Thus, E2 signaling may bias fat distribution towards subcutaneous fat deposits versus visceral fat deposits [102]. Heine *et al.* showed the differential effects of estrogen receptors (ERα and ERβ) on adiposity using ERα knockout (αERKO) mice, which develop severe intra-abdominal obesity [105]. This gives proof that the estrogen ERα receptor positively regulates adipose homeostasis and metabolism, whereas at menopause (ovariectomized rats) the functional absence of estrogen, *i.e.* the absence of ERα causes unregulated signaling through ERβ, which promotes fatty accumulation at the visceral level [106]. Our study shows that replacement of E2 by administration of exogenous 17β-estradiol to ovariectomized rats reduces their food consumption and body weight. Loss of ovarian hormones induces increased body weight as well as increased blood glucose and decreased plasma insulin response to glucose, which can be reversed by estrogen therapy after oophorectomy [107] [108]. In the control rats, 17β-estradiol activates the D2/SUL receptors which direct the food choice towards a consumption of foods rich in lipids and nutrient coulpe, favoring an increase in food consumption and then in body weight. On the other hand, the administration of 17β-estradiol to ovariectomized rats treated with sulpiride inhibits the D2/SUL receptors, favoring a reduction in the quantity of food consumed and maintaining the increase in body weight. These observations highlight a direct involvement of 17β-estradiol in the homeostatic regulation of body weight, either by controlling carbohydrate consumption by D2/BR receptors for energy expenditure, or by modulating the intake of foods with high energy potential by D2/SUL receptors for body weight gain. The increase in weight in OVX rats is thought to be caused by a dietary imbalance oriented towards massive consumption of

foods with a single dominant macronutrient or a coulpe of mecronutrients. The abolition of basal estrogen tone would also lead to a dysfunction of the D2/BR receptors, or even a reversal of their role, all of which would trigger an increase in body weight. Replacement of E2 reduces body weight and this action would induce inhibition of D2/SUL receptor activity and enhancement of D2/BR activities. Overall, these observations show that 17β-estradiol may play an important role in the stability of body weight in women by regulating the fixed set point of body weight by modulating the activities of dopamine D2 receptors. Richard et al state that removal of the ovaries causes a very strong and long-lasting induction of food reward and eating behavior, suggesting that ovarian sex steroids are essential for the maintenance of normal eating behavior [109]. The two isoforms of D2 receptors (D2S and D2L) have opposite effects. The D2L isoform revealed by the administration of bromocriptine would exclusively activate the consumption and metabolism of carbohydrates under the control of 17-β-oestradiol, with a balance between energy production and expenditure and resulting in weight stabilization. This could be the non-genomic action of 17-β-estradiol [77] [110]. The other D2S isoform, revealed by blocking sulpiride, which promotes food selection with high lipid, protein and carbohydrate potentials; produces overeating and overweight, which can lead to fat accumulation and obesity in the long term. Therefore, D2/SUL receptors could play a crucial role in the etiology of obesity. Indeed, our studies show that 17β-estradiol globally reduces food consumption without affecting body weight, which shows its direct role in stabilizing the balance: between energy production and expenditure and consequently weight stabilization [111]. These observations show that 17β-estradiol is in fact a specific modulator of the two isoforms of dopamine D2 receptors. Our work shows that ovariectomy alters the functionality of estrogen receptors, D2/BR and D2/SUL. By modulating the D2/SUL receptors, 17β-estradiol would be involved in the regulation and biosynthesis of these receptors (D2S, *i.e.* D2/SUL). According to Wu and collaborators the 17β-estradiol acts to modulate the ratio of the two dopamine D2 receptor isoforms (D2L/D2S), by transcription of their respective genes, following the induction of nuclear estrogen receptors [112]. Our work on ovariectomy confirms that D2/SUL receptors are specific inducers of the consumption of foods rich in lipids or carbohydrate-lipid, lipid-protein and carbohydrate-protein macronutrient couples, causing an increase in body weight. The activities of these receptors occur under hormonal induction of 17β-estradiol. On the other hand, D2/BR receptors, such as 17β-estradiol, generally exert a direct and effective inhibitory action on the consumption of foods with a high lipid and/or protein content, on the quantity of food and on weight gain. However, these receptors effectively activate the consumption of carbohydrate-rich foods for the maintenance of homeostasis.

5. Conclusions

The regulation of body weight by 17β-estradiol involves the control of several

major functions, such as the consumption of different types of food (carbohydrates, lipids and proteins). Under normal physiological conditions, 17β-estradiol activates D2/SUL receptors that direct dietary choice toward consumption of foods high in fat and nutrient content, promoting increased food intake and body weight. On the other hand, the administration of 17β-estradiol to ovariectomized rats treated with sulpiride inhibits the D2/SUL receptors, favoring a reduction in the quantity of food consumed and maintaining the increase in body weight. 17β-estradiol is directly involved in the homeostatic regulation of body weight, either by controlling carbohydrate consumption by D2/BR receptors for energy expenditure, or by modulating the intake of foods with high energy potential by D2/SUL receptors for body weight gain. The increase in weight in ovariectomized rats is thought to be caused by a dietary imbalance oriented towards massive consumption of foods with a single dominant macronutrient (lipid) or in pairs of macronutrients (lipid-carbohydrate, lipid-protein or carbohydrate-protein).

This review will help to better understand the relationships between 17β-estradiol and D2 receptors in the selection of carbohydrate, fat and protein macronutrients, as well as their consequences on body weight gain in postmenopausal women. Although significant efforts have been devoted to research on homeostatic and hedonic eating, further studies on food type selection and orientation need to be conducted. By identifying a possible existence of interference of other essential nutrients (such as vitamins) with estrogen receptor complexes and D2 receptors, on the influence of E2 in behavior and food selection. Together, the behavioral and physiological techniques will help us better understand the underlying mechanisms that may increase the risk of obesity in the absence of E2 (menopause) and develop therapeutic strategies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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