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Research Article

Effects of 17β-Estradiol on the Activity of Dopamine D2 Receptors in the Selection of Carbohydrate, Lipid and Protein Macronutrients in Females Rats (Healthy Rats)

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Abstract: Overeating and obesity are the result of the malfunction of the normal appetite regulation loop. An imbalance appears between increased consumption and low energy expenditure, resulting in an accumulation of fat. Given the seriousness of obesity, we focused our study on the influences that 17-β-estradiol could have on the choice of different food categories (lipids, carbohydrates, proteins) through the dopaminergic system in rats. It appears that 17-β-estradiol modulates the activity of the two isoforms of dopamine D2 receptors, which have opposite effects. One of the isoforms would exclusively activate the consumption and metabolism of carbohydrates under the control of 17-β-estradiol, with a balance between energy production and expenditure and resulting in a stabilization of body weight. The other isoform, revealed by sulpiride blockade, would act mainly by hormonal induction of 17-β-estradiol, directing food consumption towards foods with high lipid, protein and carbohydrate potentials. This second isoform of dopamine D2 receptors produces hyperphagia and overweight, which can lead to long-term fat accumulation and obesity.
Keywords : 17β-estradiol, D2 receptors, bromocriptine, sulpiride, carbohydrates, lipids, proteins, obesity.

1. Introduction

Obesity constitutes a serious public health problem which affects millions of people throughout the world and tends to become a pandemic. Numerous studies have been carried out to understand the mechanisms underlying obesity and in particular weight gain. One of the main mechanisms underlying weight gain involves dopamine, which is well known for its role in food consumption and acts through the reward-related mesolimbic circuitry in various regions of the brain [1]. The dopaminergic reward system plays a major role in food consumption and weight gain. The appetite for tasty foods is mediated by dopamine pathways that form the reward system. Dopamine, in the central nervous system, is mainly produced in the substantia nigra and the ventral tegmental area (VTA). It is a predominant neurotransmitter in the mammalian brain, where it controls a wide variety of functions such as locomotor activity, cognition, emotion, motivation, food intake and endocrine regulation [2].

Expression of the motivational component of hunger requires dopamine to act on D1 and D2 receptors; thus the dopamine reward system plays a considerable role in the normal or disturbed eating behavior of individuals [3]. The areas of the brain associated with the reward circuit involved in the evaluation of pleasure generally have a large number of dopaminergic receptors [4]. Dopamine, a chemical neurotransmitter of reward signals, plays a key role in evaluating the appetitive value of food [5]. In obese people, dopaminergic receptors are generally less numerous, and/or dysfunctional in these areas of the brain. For the same amount of food, these people feel less pleasure when eating than people who are not obese [6]. Hyperphagia and obesity are the result of the dysfunction of the normal appetite regulation loop where an imbalance appears between an increase in consumption and a low energy expenditure, resulting in an accumulation of fat [7].

The central mechanisms that regulate weight gain involve the hypothalamus. Feeding behavior is also dependent on food availability, which is an environmental regulating factor. By exercising specific control over adipose tissue, the hypothalamus plays a major role in controlling body weight, which is the result of food intake and energy expenditure. The lateral nucleus of the hypothalamus is considered the "hunger"

center and its ventromedial nucleus the "satiety" center [8]. The hypothalamus is therefore seen as a long-term integrator of energy homeostasis, especially because of its sensitivity to leptin and insulin. At the peripheral level, the circulation of insulin, leptin and ghrelin, transmits information on the quantity of energy stored in the form of body fat, to the arcuate nucleus of the hypothalamus [9]. The neurons of the arcuate nucleus release neuropeptide Y, a powerful appetite inducer, which will activate the paraventricular nucleus and the lateral hypothalamus. Arcuate nucleus neurons containing neuropeptide Y are inhibited by peripheral leptin and insulin and become highly active again when levels of these hormones drop during undernutrition [10].

To date, ghrelin is the only known orexigenic factor secreted by the gastric mucosa. Its plasma concentration is at its highest before meals and decreases after them. Its effect precedes consumption and exceeds that of the feeling of hunger, it would be involved in motivation and the prospecting of food [11]. For example, ghrelin injections stimulate food intake by increasing appetitive eating behaviors and the number of meals [12]. The hypothalamus is involved in the regulation of food intake which can be done both on the quantity of food ingested, the duration and the frequency of ingestions during an episode of food intake. It triggers the process of satiety, determines the duration of the interval between two food intakes, and regulates the craving for food. The lateral hypothalamus areas have long been recognized as one of the areas of the brain involved in both rewarding and the intake of tasty foods. The orexin A and B neuropeptides are expressed exclusively in this brain area and play a key role in the rewarding aspects of food intake, through interactions with the classical reward pathways, i.e. the mesolimbic dopaminergic system [13]. The lateral hypothalamus plays a feedback role in the regulation of body weight. It belongs to the parasympathetic area of the hypothalamus and connects with all major regions of the brain and the main hypothalamic nuclei [14]. Tissue preparations from the lateral hypothalamus promote glucose utilization and insulin release [15]. Sugar consumption modifies the central metabolism of dopamine, and in particular causes the level of the most important metabolite of dopamine to vary in the hypothalamus [16].

The other mechanism that influences food consumption and body weight is through steroid hormones, notably 17-β-estradiol in females. We know, for example, that in women, the incidence of obesity increases significantly at menopause [17]. 17-β estradiol is a female hormone that plays a central role in body weight homeostasis. This hormone controls two different isoforms of dopamine D2 receptors to regulate sugar and alcohol consumption. It modulates these dopaminergic D2 receptors to increase appetite, reduce weight, but has no effect on water absorption [18]. Although there have been many works on the functioning of dopamine D2 receptors, our study will focus on their precise role in the choice of different types of food. That is to say, to understand the influence of dopaminergic D2 receptors in the consumption of different types of food. In other words, how does 17-β-estradiol control dopamine D2 receptors to direct food choice towards nutrient types (proteins, fats and carbohydrates) ? This is the question we will try to answer in this study. The aim of this study is to show whether 17-β-estradiol selects dopamine D2 receptor isoforms to direct food consumption towards food categories (carbohydrates, lipids or proteins). For this, we compared between healthy 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 the daily consumption of six (6) types of food. With a potentially high nutritional value per 100g in couples of macronutrients: carbohydrates-lipids, lipids-proteins, proteins-carbohydrates; either in a single dominant macronutrient: carbohydrates, lipids or proteins [19] [20] [21]. 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 conditions, at an ambient temperature of 30±2°C, with light/dark cycles of 12 hours each and relative humidity reaching 85±3%. Rats were housed individually in polypropylene cages (27 x 37 x 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 respectively as a selective agonist and antagonist at central dopamine D2 receptors [22] [23].

Thirty-six (36) Wistar rats weighing an average of 200±5 g were divided into healthy rats composed of six (6) groups which were simultaneously subjected to the following treatments: 17β-estradiol (5 µg/kg of body weight or bw ; [24]), bromocriptine mesylate (0.1 mg/kg bw ; [25]), sulpiride (20 mg/kg bw; [26]) and concomitant administration of "17β-estradiol + bromocriptine" or "17β-estradiol + sulpiride", and the DMSO vehicle (0.7%; [27]).

2.3. Methods

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) female 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 100g [19][20][21] is potentially high, either in pairs of macronutrients: carbohydrates-lipids (plantain banana chips: carbohydrates = 63.8g; lipids = 29.6g; proteins = 2.3g; 531 Kcal), lipids-proteins (salted roasted peanuts: carbohydrates = 11g lipids = 51.2g; proteins = 24.4g; 619 Kcal), protein-carbohydrates (white cornille bean: carbohydrates = 49g; lipids = 2.1g; proteins = 24g; 331 Kcal); either in a dominant macronutrient: carbohydrates (yellow corn: carbohydrates = 62g; lipids = 2.8g; proteins = 10g; 342 Kcal), lipids (coconut, dried almond: carbohydrates = 9.27g; lipids = 65.1g; proteins = 6.64g; 374 Kcal), proteins ("meat + fish" flour pellets: carbohydrates = 0g; lipids = 9g; proteins = 25g: 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, 4:30 p.m. and end around 7:00 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 = M0). After 24 hours, the remaining mass of each type of food is measured in all the cages (remaining mass of food = M24). The difference (M0 – M24) 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.

2.4. Statistical analyzes

One-way ANOVA analysis of variance was used to assess the effects of treatments (17-β-estradiol, bromocriptine, and sulpiride) on types of food eaten, overall food consumption, and body weight. The subsequent comparison of two means was performed by Fisher's post-hoc PLSD test [28]. 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 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on yellow maize consumption of healthy rats

A one-way ANOVA showed that the different treatments induced significant variations in mean daily consumption rates of yellow maize in healthy rats [$F(5,354)=217.448$, $p<0.001$] (**Figure 1**). Scheffé's post

hoc test (p's = 0.05) shows that compared to control rats (C: 0.816±0.023 g/rat/day), the daily consumption of yellow maize increases significantly in rats treated with bromocriptine (C+ BR: 1.116±0.052 g/rat/day) [$p < 0.001$], whereas it does not vary in rats treated with sulpiride (C+SUL: 0.85±0.036 g/rat/day), [$p = 0.131$], showing that bromocriptine receptors (D2/BR) specifically increase maize consumption because of its high sugar content. The treatment of rats with 17β-estradiol alone exacerbates the daily consumption of yellow maize (C+E2: 2.016±0.051 g/rat/day) compared to control females C, [$p < 0.001$]. The comparison of the C+SUL (0.850±0.036 g/rat/day) and C+E2+SUL (2.166±0.044 g/rat/day) groups, [$p < 0.001$], shows that 17β-estradiol activates the receptors of sulpiride (D2/SUL) to induce carbohydrate consumption. On the other hand, the C+E2+BR group (0.883±0.056 g/rat/day) reduced its consumption of yellow maize compared to the C+BR group (1.116±0.052 g/rat/day) [$p < 0.001$], showing that 17β-estradiol inhibits sugar consumption induced by bromocriptine receptors (D2/BR).

The nutritional value of yellow corn per 100 g is as follows: carbohydrates = 62 g; lipids = 2.8 g; protein = 10g; 342 Kcal per 100g. This food contains carbohydrates as the dominant macronutrient. Our results show that sulpiride receptors (D2/SUL) are not affected by sugar consumption and that estrogen and bromocriptine receptors (D2/BR) can induce sugar consumption according to homeostatic needs. E2 controls D2/BR receptors in this activity.

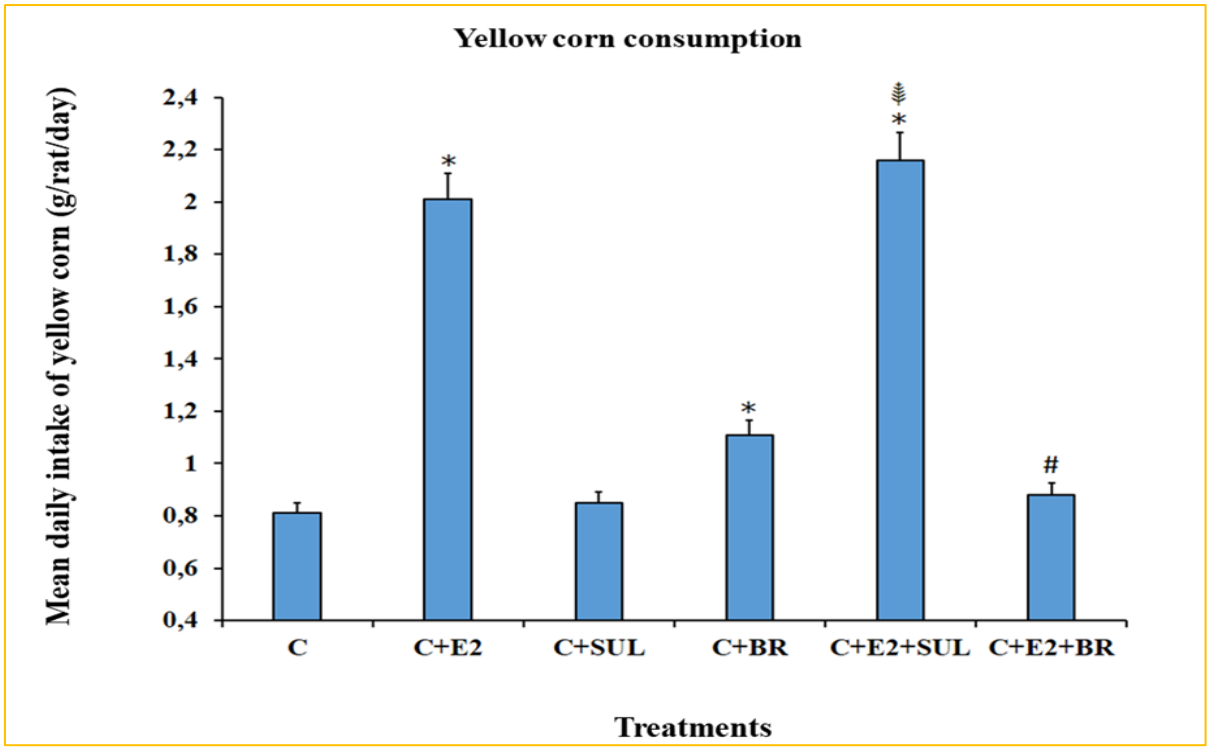

Figure 1: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on consumption of yellow maize (carbohydrates = 62 g; lipids = 2.8 g; proteins = 10 g; 342 Kcal per 100 g) healthy rat rats.

The mean quantity over 10 consecutive days of treatment (g/rat/day±SEM) of the consumption of yellow maize within each experimental group (N=6 rats) is represented in the healthy rats subjected to the various treatments. The effects of the hormone (E2), the D2/SUL and D2/BR receptors and their respective interactions on variations in the daily consumption of yellow maize are evaluated. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, $p < 0.05$; "⁑" Represents a significant difference between the direct stimulating effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), $p < 0.001$; "#" 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), $p < 0.001$. N=6 rats in each of the six (6) treated groups.

3.2. Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of dried coconut kernels in healthy rats

The one-way ANOVA shows that the different treatments have significant effects on the variations in the average daily consumption of dry coconut kernels in healthy rats [$F(5, 354) = 16.96$, $p < 0.001$], (**Figure 2**).

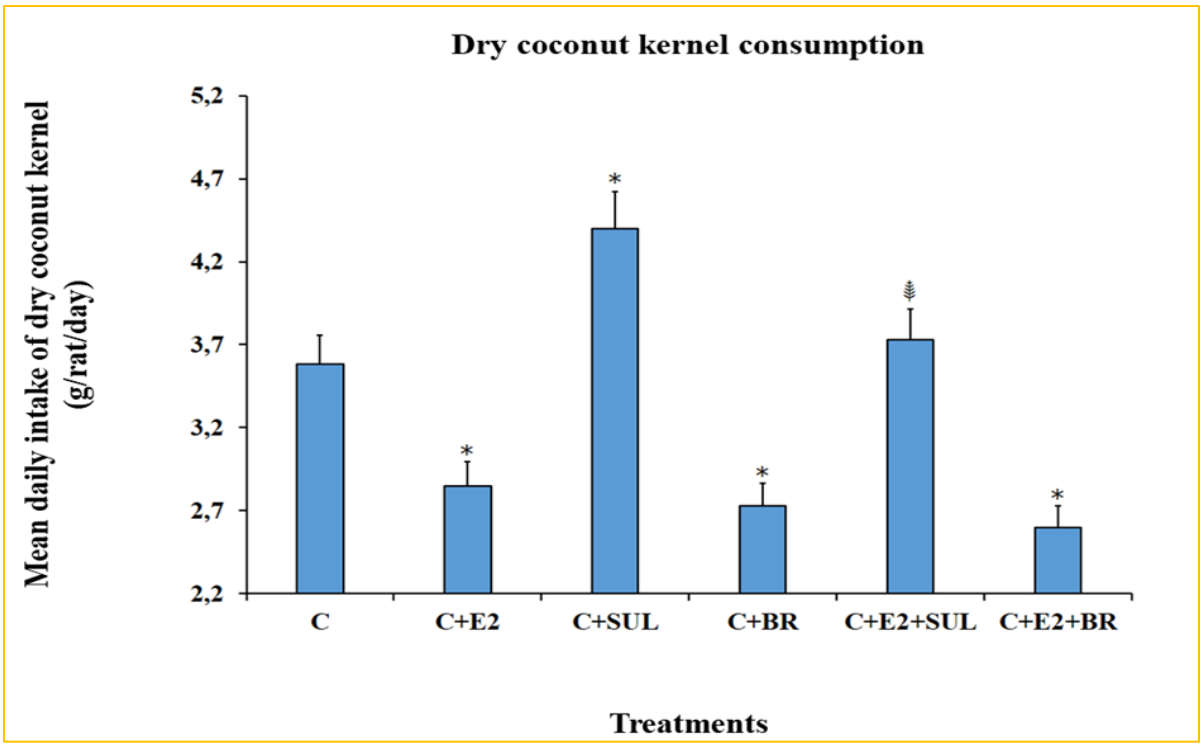

Figure 2: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of dried coconut kernels (carbohydrates = 9.27 g; lipids = 65.1 g; proteins = 6.64 g; 374 Kcal per 100 g) of healthy rats.

The average rates over 10 consecutive days of treatment (g/rat/day±SEM) of the consumption of dried coconut kernels in each experimental group (N=6 rats) were represented in healthy rats subjected to the 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. "∗" Corresponds to a difference in significance: between the treated groups of control C and the untreated group of control C, $p < 0.001$; "⁜" Represents a significant difference between the direct stimulating effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), $p < 0.001$; "#" Corresponds to a significant difference between the direct stimulation effect of the D2 receptor/BR (BR) and the effect of association of the receptor and the hormone (E2+BR), $p < 0.05$. N=6 rats in each of the six treated groups.

The post-hoc comparison of the means, using the Scheffé F test shows that the treatment of rats with 17β-estradiol decreases the daily consumption of dry coconut kernels (C+E2: 2.85±0.073 g/rat/day) compared to control rats (C: 3.583±0.105 g/rat/day), [$p < 0.001$]. Compared to the control group, the consumption of dried coconut kernels increases significantly in the group treated with sulpiride (C+SUL: 4.400±0.090 g/rat/day), [$p < 0.001$], while it is very reduced in the group treated with bromocriptine (C+BR: 2.733 ± 0.059 g/rat/day), [$p < 0.001$]. The rats treated with 17β-estradiol + sulpiride (C+E2+SUL: 3.733±0.063 g/rat/day) significantly reduced their daily consumption of dried coconut kernels compared to the sulpiride group (C+SUL: 4.400±0.090 g/rat/day), [$p < 0.001$], thus showing that 17β-estradiol inhibits the consumption of food rich in lipid activated by sulpiride receptors (D2/SUL). On the other hand, the C+BR group (2.733±0.059 g/rat/day) is not significantly different from the C+E2+BR group (2.6±0.068 g/rat/day), [$p = 0.14$], showing that the inhibition of bromocriptine receptors (D2/BR) on lipid consumption is independent of 17β-estradiol. The dry coconut kernel having for 100 g a nutritional value of 9.27 g in carbohydrates, 65.1 g in lipids and 6.64 g in proteins is a food rich in lipids. It appears that under physiological conditions, the consumption of highly lipid-rich energy foods is inhibited independently by E2 and BR with synergistic effects between E2 and BR. On the other hand, the consumption of foods rich in lipids is strongly stimulated by SUL, whose action is blocked by E2.

3.3. Effects of 17β-estradiol (E2), sulpiride (SUL), and bromocriptine (BR), on "meat + fish" meal pellet consumption of healthy rats.

The one-way ANOVA shows that the different treatments have significant effects on the variations in the average daily consumption rates of "meat + fish" meal pellets [$F(5, 354) = 53.104$, $p < 0.001$]. The consumption of "meat + fish" meal pellets is strongly inhibited in all the treatments carried out in the control

females (**Figure 3**). Indeed, the Scheffé post hoc test (p's = 0.05) shows that compared to the control (C: 1.583±0.044 g/rat/day), sulpiride (C+SUL: 1.016±0.036 g/rat/day) and bromocriptine (C+BR: 0.883± 0.043 g/rat/day), significantly reduce the daily consumption of "meat + fish" meal pellets [p < 0.001]. Compared to the control (C), 17β-estradiol (C+E2: 0.816±0.027 g/rat/day) further reduces this consumption of "meat + fish" meal pellets [p < 0.001]. Treatment of rats with sulpiride alone (C+SUL) had no effect on the consumption of "meat + fish" meal pellets compared to rats treated simultaneously with sulpiride +17β-estradiol (C+E2+SUL: 1.083±0.041 g/rat/day) [p = 0.229]. Similarly, females treated with bromocriptine alone (C+BR) did not modify the daily consumption of "meat + fish" meal pellets compared to female rats treated concomitantly with bromocriptine + 17β-estradiol (C+E2+BR: 0.891±0.035 g/rat/day) [p = 0.883]. These results show 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.

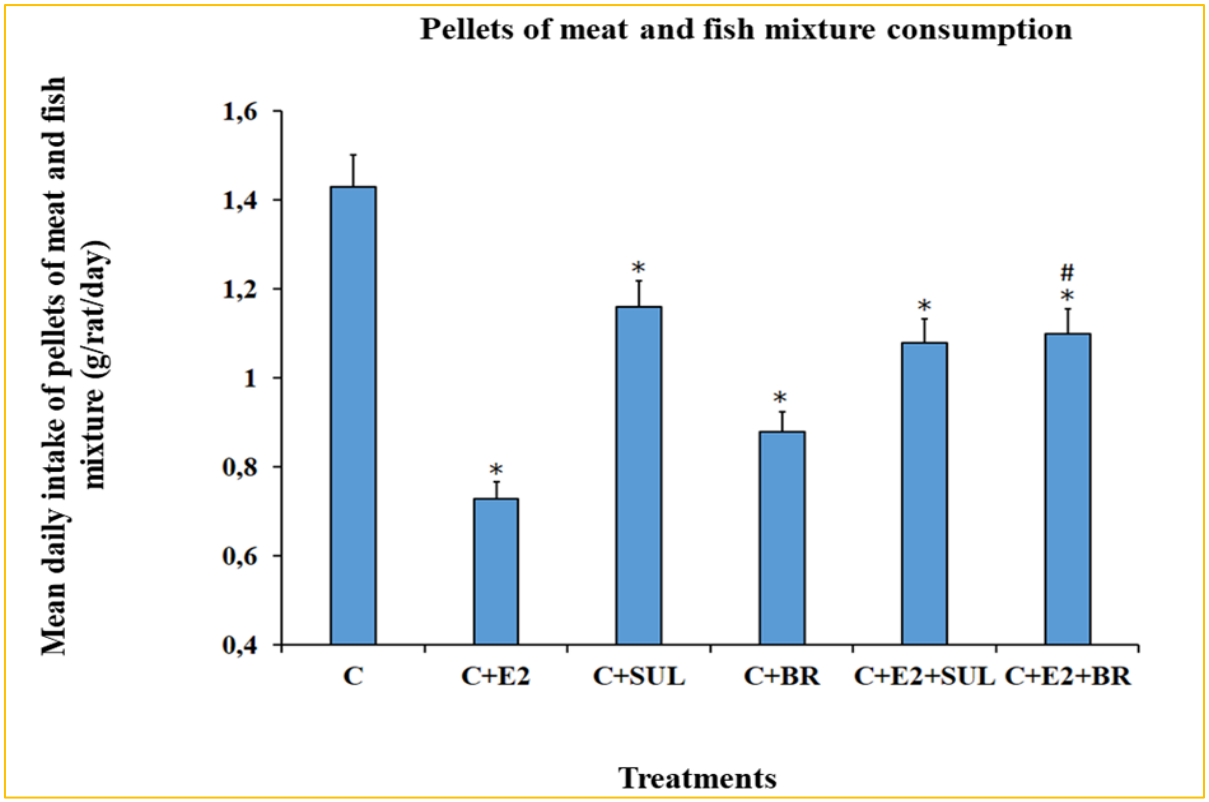

Figure 3: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of "meat + fish" meal pellets (carbohydrates = 0 g; lipids = 10 g; proteins = 30 g; 120 Kcal per 100 g) of healthy rats.

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 shown in healthy rats subjected 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 "meat + fish" meal pellets are compared. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, p < 0.01; "⸸" Represents a significant difference between the direct stimulating effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), 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), p < 0.01. N=6 rats in each of the six treated groups.

3.4. Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of white cornille (black-eyed) bean in healthy rats

A one-way ANOVA test shows that the treatments exerted significantly different effects on the average daily white bean consumption rates (**Figure 4**), [F (5, 354) = 564.81, p < 0.001]. The post-hoc comparison of the means, using the Scheffé F test shows that the treatment of the rats with sulpiride (C+SUL: 5.816 ± 0.121 g/rat/day) increases the daily consumption of white beans compared to the controls (C: 3.016±0.073 g/rat/day), [p < 0.001]; whereas bromocriptine (C+BR: 2.983±0.071 g/rat/day) has no effect on this consumption [p = 0.745].

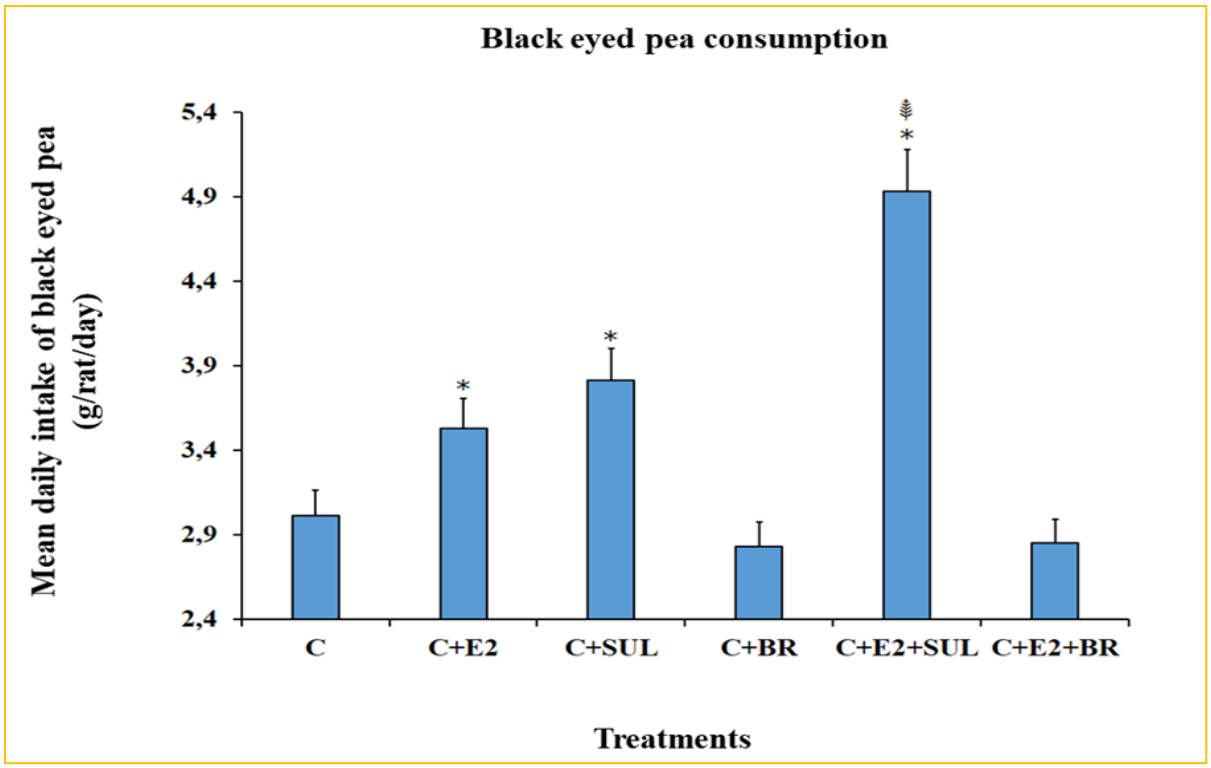

Figure 4: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of the dry mature seed of the white cornille (black-eyed) bean, (carbohydrates = 49 g; lipids = 2.1 g; protein = 24 g; 331 Kcal per 100 g) in healthy rats.

The average daily rates over 10 consecutive days of treatment (g/rat/day±SEM) of white bean consumption in each experimental group (N=6 rats) are represented in the healthy rats subjected 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. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, $p < 0.01$; "⁑" Represents a significant difference between the direct stimulating effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), $p < 0.001$; "#" Corresponds to a significant difference between the direct stimulation effect of the D2 receptor/BR (BR) and the effect of association of the receptor and the hormone (E2+BR), $p < 0.05$. N=6 rats in each of the six (6) treated groups.

Treatment of rats with 17β-estradiol (C+E2: 5.533±0.1 g/rat/day) increases the daily consumption of white bean compared to controls [$p < 0.001$]. It is important to point out the reversal of the role of E2 with regard to the consumption of this type of food. In addition, the co-treatment of rats with 17β-estradiol + bromocriptine (C+E2+BR: 2.883±0.091 g/rat/day) shows no significant difference compared to the treatment of rats with bromocriptine alone (C+BR) on the daily consumption of white beans [$p = 0.39$]. These observations show that the BR receptors are not involved in the control of white bean consumption even under hormonal activation. On the other hand, the simultaneous administration of 17β-estradiol + sulpiride (C+E2+SUL: 8.283±0.083 g/rat/day), very significantly increases the daily consumption of white cornille bean compared to sulpiride alone (C+SUL), [$p < 0.001$], indicating that 17β-oestradiol activates sulpiride receptors (D2/SUL) to induce white bean consumption. Consequently, 17β-estradiol would direct D2/SUL receptors towards the consumption of foods with carbohydrate-protein codominance.

3.5. Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of plantain banana chips in healthy rats.

The one-way ANOVA shows that the different treatments induced significant variations in the average daily consumption rates of plantain chips [$F(5, 354) = 58.185$, $p < 0.001$] (Figure 5). Scheffé's post hoc test (p's = 0.05) shows that compared to control rats (C: 1.95±0.073 g/rat/day), the administration of sulpiride to rats (C+SUL: 2.316±0.062 g/day) significantly increases the daily consumption of plantain chips [$p < 0.001$], whereas treatment with bromocriptine (C+BR: 1.616±0.081 g/ratte/day) decreases this consumption [$p = 0.003$]. The group treated with 17β-estradiol (C+E2: 1.183±0.051 g/rat/day) compared to the control group (C) significantly reduced its daily consumption of plantain chips [$p < 0.001$]. The C+E2+BR group

(1.166±0.041 g/rat/day) reduced their consumption of plantain chips compared to the C+BR group [p < 0.001], showing that 17β-estradiol reinforces the inhibitory action induced by bromocriptine receptors (D2/BR) on the consumption of foods rich in carbohydrate-lipid macronutrient couples. Similarly, the C+E2+SUL group (2.016±0.047 g/rat/day) reduced its consumption of plantain banana chips compared to the C+SUL group [p < 0.001] showing that E2 inhibits the consumption of foods rich in couples of carbohydrate-lipid macronutrients 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.

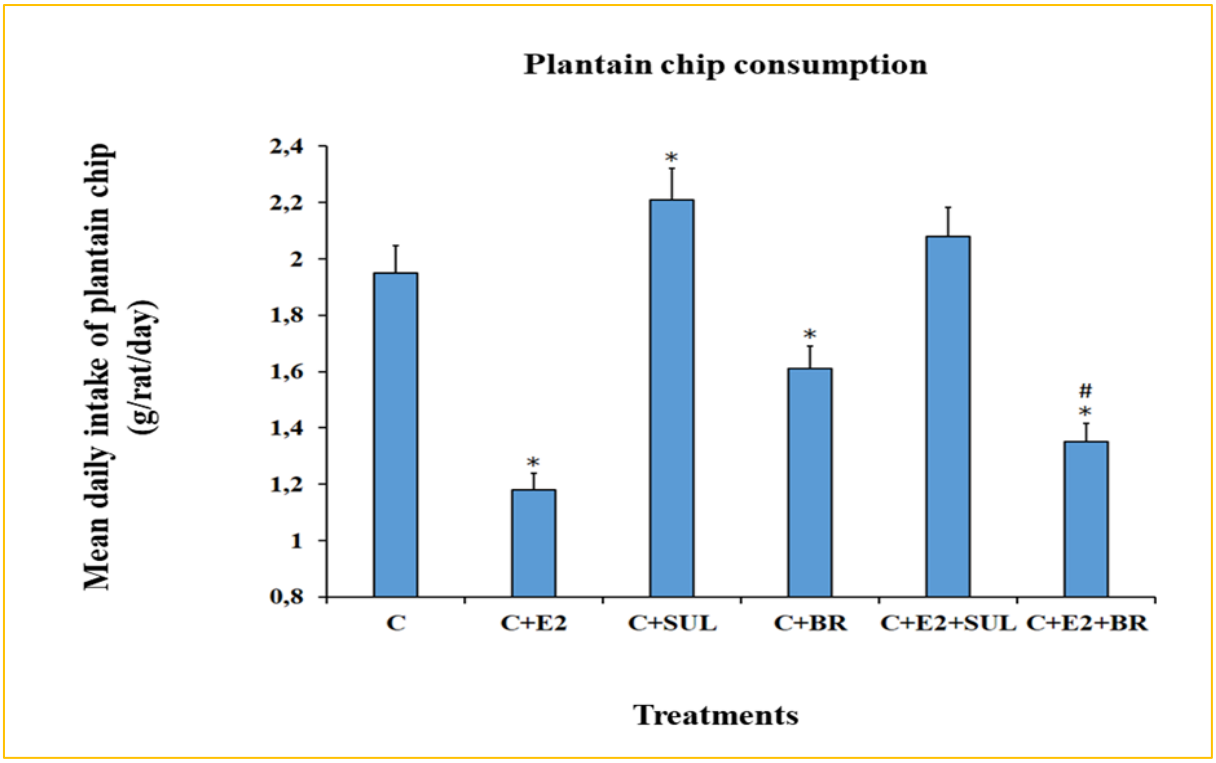

Figure 5: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on consumption of plantain chips (carbohydrate = 63.8 g; fat = 29.6 g; protein = 2 .3 g; 531 Kcal per 100 g) of healthy rats.

The average 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) were represented in healthy rats subjected to the 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 plantain banana chips are evaluated. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, p < 0.01; "⋕" Represents a significant difference between the direct stimulation effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), 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), p < 0.01. N=6 rats in each of the six (6) treated groups.

3.6. Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of roasted and salted peanuts in healthy rats.

One-way ANOVA showed that the different treatments induced significant variations in the mean consumption rates of roasted and salted peanuts [F(5,354)=84.224, p<0.001], (**Figure 6**). Scheffé's post hoc test (p's = 0.05) shows that compared to control rats (C: 1.083±0.047 g/rat/day), the administration of bromocriptine (C+BR: 1.016±0.045 g/rat /day) does not modify the daily consumption of roasted and salted peanuts [p = 0.317], whereas the treatment of rat rats with sulpiride significantly increases the consumption of this food (C+SUL: 1.883±0.062 g/rat/day), [p < 0.001]. Rats treated with 17β-estradiol (C+E2: 0.5±0.036 g/rat/day) significantly reduce the daily consumption of roasted and salted peanuts compared to control

rats (C), [p < 0.001], showing as well as 17β-estradiol inhibits the consumption of foods rich in couples of lipid-protein macronutrients.

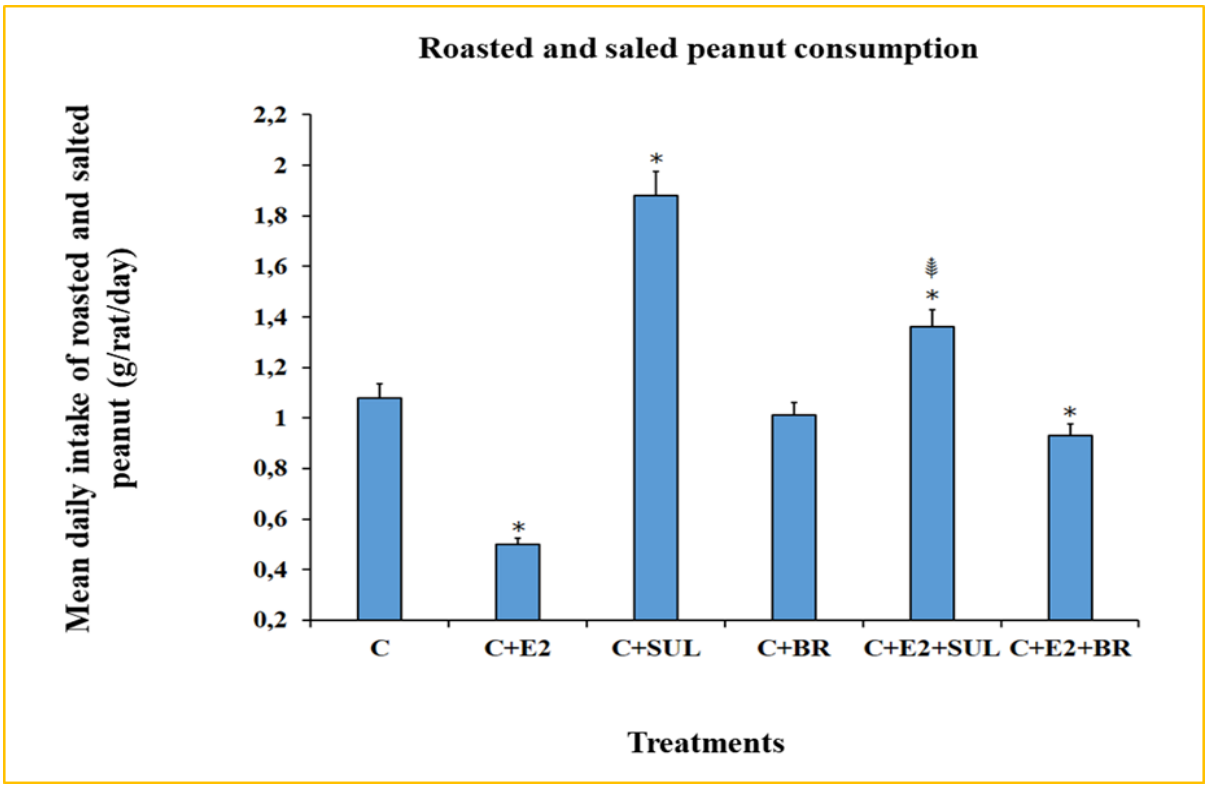

Figure 6: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the consumption of roasted and salted peanuts (carbohydrates = 11 g; lipids = 51.2 g; proteins = 24.4 g; 619 Kcal per 100 g) of healthy rats.

The average daily rates over 10 consecutive days of treatment (g/rat/day±SEM) of the consumption of roasted and salted peanuts in each experimental group (N=6 rats) were represented in the healthy rats subjected to the 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 roasted and salted peanuts are compared. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, p < 0.05; "⁑" Represents a significant difference between the direct stimulating effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), p<0.001; "#" Corresponds to a significant difference between the direct stimulation effect of the D2 receptor/BR (BR) and the effect of association of the receptor and the hormone (E2+BR), p<0.05. N=6 rats in each of the six (6) treated groups.

The consumption of roasted and salted peanuts is not modified in the C+E2+BR group (1±0.047 g/ratte/day) compared to the C+BR group [p = 0.801], indicating that the D2/BR receptors are not involved in the consumption of this type of food. On the other hand, rats co-treated with 17β-estradiol + sulpiride (C+E2+SUL: 1.366±0.055 g/rat/day) reduced their consumption of roasted and salted peanuts compared to rats treated with sulpiride alone (C+ SUL) [p < 0.001], indicating that 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.

3.7. Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the food consumption of healthy rats.

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 one-way ANOVA showed that the different treatments induced significant variations in average daily food consumption rates (**Figure 7**), [F(5,354)=100.82, p<0.001]. Scheffé's post hoc comparison (p's = 0.05) shows that the bromocriptine group (C+BR: 10.116±0.116 g/rat/day) reduced the amount of food consumed daily

compared to the control group (C: 12.133±0.16 g/rat/day), [p < 0.001], whereas the sulpiride group (C+SUL: 13.033±0.131 g/rat/day) increased its daily food consumption [p < 0.001]. The E2 group reduced the quantity of food consumed daily compared to the control group (C+E2: 10.733±0.121 g/rat/day), [p < 0.001]. The C+E2+BR group (09.816±0.122 g/rat/day) did not modify its daily food consumption compared to the C+BR group, [p = 0.077]. The C+E2+SUL group (12.116±0.11 g/rat/day) compared to the C+SUL group shows a reduction in its daily food consumption [p < 0.001].

3.8. Effects of 17β-Estradiol (E2), Sulpiride (Sul) and Bromocriptine (BR), on the body weight of healthy rats.

The ANOVA test for a way shows that the treatments exert significantly different effects on body weight variations **(Figure 8),** [F (5, 354) = 9, p <0.001]. The Post Hoc of Scheffé test (P's = 0.05) shows that unlike witnesses (C: 201.426±0.25 g/rat/day), weight reduction is caused by the administration of bromocriptine (C+BR: 200.301±0.309 g/rat/day), [p = 0.005], while sulpiride (C+Sul: 202.483±0.225 g/rat/day) causes weight increase [p = 0.002]. The rats treated with 17β-Estradiol (C+E2: 200.701±0.169 g/rat/day) have a reduced body weight compared to control rats [p = 0.017]. The co-treatment of 17β-Estradiol+Sulpiride (C+E2+Sul: 201.7±0.305 g/rat/day) reduced the body weight of the rats compared to the rats treated with the sulpiride alone (C+Sul), [p = 0.041]. On the other hand, the simultaneous treatment of the rats with the 17β-Estradiol+Bromocriptine (C+E2+BR: 200.416±0.363 g/rat/Day) has no effect on the weight compared to the Bromocriptine group (C+BR), [p = 0.809].

These results indicate that the increases in food consumption and weight are induced by the D2/Sul receptors controlled by 17β-Estradiol, while the D2/BR receptors cause a specific inhibition of the independent weight of the control of 17β-Estradiol.

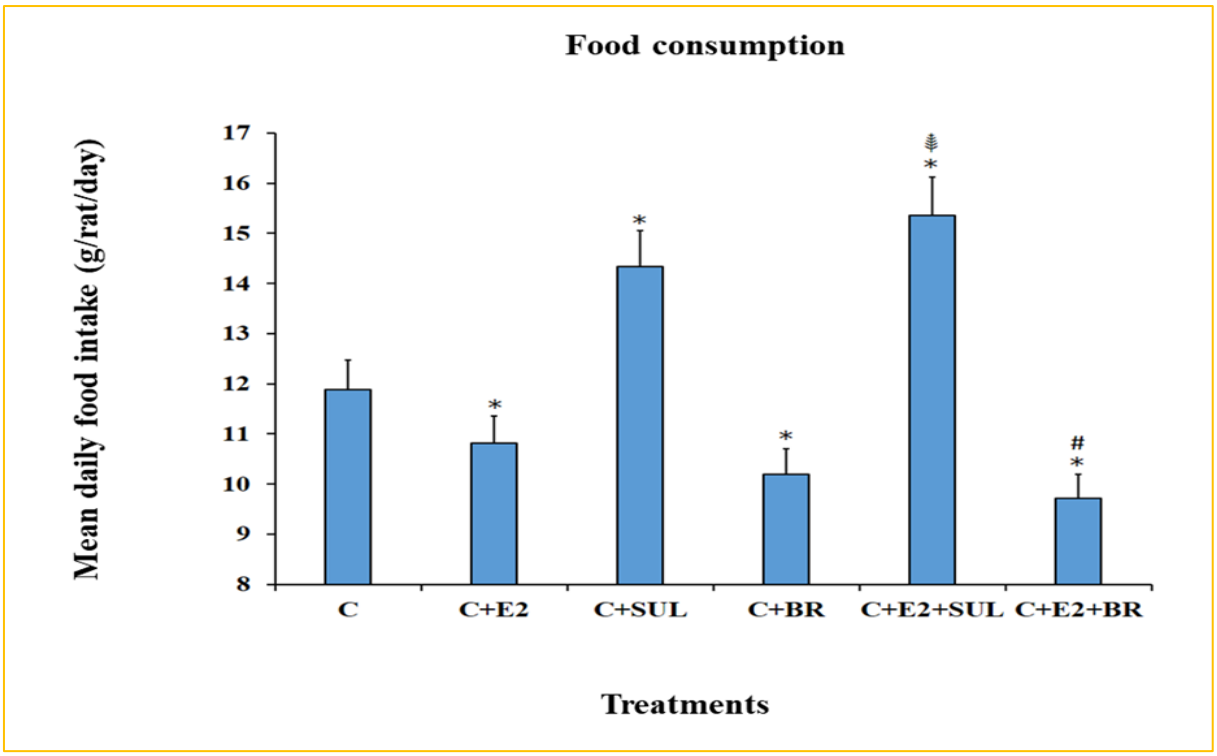

Figure 7: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the food consumption of healthy rats.

The average daily amounts of food consumption (g/rat/day±SEM) over 10 consecutive days of treatment within each experimental group (N=6 rats) were represented in the healthy rats subjected 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 evaluated. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, p < 0.01; "⁑" Represents a significant difference between the direct stimulating effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), p < 0.001; "#" Corresponds to a significant difference between the direct stimulation effect of the D2 receptor/BR (BR) and the effect of association of the receptor and the hormone (E2+BR), p < 0.05. N=6 rats in each of the six (6) treated groups.

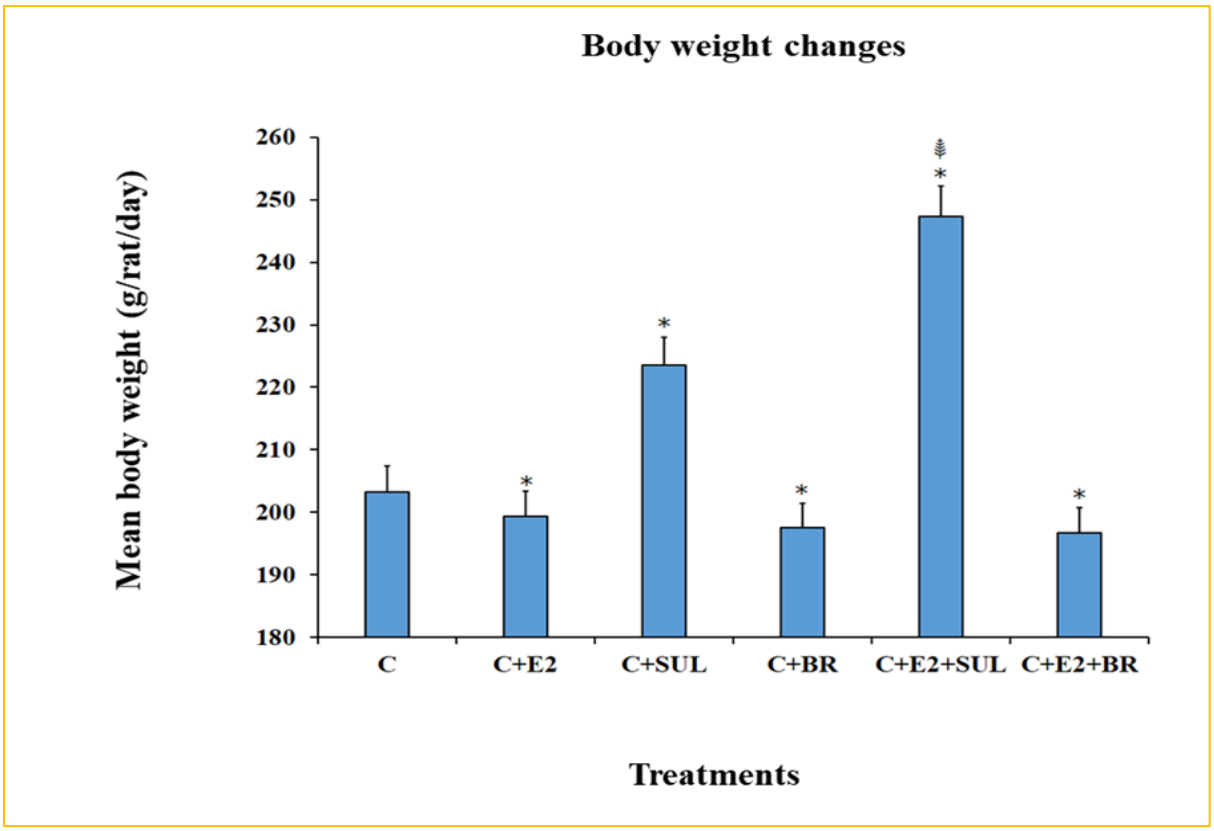

Figure 8: Effects of 17β-estradiol (E2), sulpiride (SUL) and bromocriptine (BR) on the body weight of healthy rats.

The daily variations in mean body weight over 10 consecutive days of treatment (g/rat/day±SEM) within each experimental group (N=6 rats) are represented in the healthy rats subjected to the various treatments. The effects of the hormone (E2), D2/SUL and D2/BR receptors and their respective interactions on changes in mean body weight are assessed. "∗" Differences in significance: between the treated groups of control C and the untreated group of control C, $p < 0.01$; "⁑" Represents a significant difference between the direct stimulation effect of the D2 receptor/SUL (SUL) and that of the combination of the receptor and the hormone (E2+SUL), $p < 0.05$; "#" Corresponds to a significant difference between the direct stimulation effect of the D2 receptor/BR (BR) and the effect of association of the receptor and the hormone (E2+BR), $p < 0.05$. N=6 rats in each of the six (6) treated groups.

4. Discussion

In our study, the use of agonist (bromocriptine) and antagonist (sulpiride) of dopaminergic D2 receptors, made it possible to show that the isoforms of dopaminergic D2 receptors direct food consumption towards different types of macronutrients (carbohydrates, lipids and proteins). This dietary orientation takes place under the hormonal influence of 17-β-estradiol, which modulates the activity of the two isoforms of dopaminergic D2 receptors, which have opposite effects.

Our results show that the consumption of foods exclusively high in carbohydrates, such as yellow maize (carbohydrates = 62 g; lipids = 2.8 g; proteins = 10 g; 342 Kcal per 100 g), is triggered either directly by 17-β-estradiol or bromocriptine, or by sulpiride under hormonal induction of 17-β-estradiol. Under these conditions, there is no synergistic effect between 17-β-estradiol and bromocriptine in the stimulation of sugar consumption. Boswell and collaborators report that, when Sprague-Dawley rats are given the opportunity to eat a mixture of chocolate and cake, they absorb a large quantity 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 chocolate mixed with the cake than the control animals [29]. These observations show that 17β-estradiol does indeed induce sugar consumption. But the effect of 17β-estradiol on sugar consumption is dose dependent. Indeed, Boswell and collaborators showed that the consumption of a 0.25% sucrose solution was higher than the consumption of 2% sucrose. These authors suggest that when the solution is pleasant for the animal to consume, it increases its consumption [29]. Our study also showed that 17β-estradiol promotes carbohydrate consumption depending on its caloric content in food, so the effect of 17β-estradiol on carbohydrate consumption is a function of its content. Concordant results show that 17β-

estradiol induces carbohydrate consumption, when the animal is in the context of a diet considered pleasant [29]. This supports the hypotheses of some authors who report that 17β-estradiol encourages the consumption of tasty foods (rich in carbohydrates) [30]. These observations show that foods with a high carbohydrate content would be tasty foods and that 17β-estradiol effectively induces the consumption of foods rich in carbohydrates. Previous studies have shown that estrogens and their receptors play a key role in the regulation of carbohydrate homeostasis and they have established a positive correlation between the estrogen pathway and the main features of the metabolic syndrome (obesity, insulin resistance and hyperglycaemia) [31] [32]. Our results show that sulpiride receptors (D2/SUL) are not affected by sugar consumption and that estrogen and bromocriptine receptors (D2/BR) can induce sugar consumption according to homeostatic needs. E2 controls D2/BR receptors in this activity.

The dry coconut kernel having for 100 g a nutritional value of 9.27 g in carbohydrates, 65.1 g in lipids and 6.64 g in proteins is a food rich in lipids. It appears that under physiological conditions, the consumption of highly lipid-rich energy foods is inhibited independently by E2 and BR with synergistic effects between E2 and BR. On the other hand, the consumption of foods rich in lipids is strongly stimulated by SUL, whose action is blocked by E2. Our work shows that, unlike bromocriptine, sulpiride induces the consumption of high-energy foods that are particularly rich in lipids (dry coconut fines). Previous results indicate that the systemic injection of dopamine D2 receptor antagonists increases the consumption of foods rich in lipids [33]. These observations show that sulpiride-sensitive receptors direct consumption towards foods rich in lipids. Jaber and associates, examined the chronic effects of the administration of sulpiride 100 mg/kg, for 14 days. They observed that sulpiride increased dopaminergic D2 receptor mRNAs by more than 125% in general and more than 72% in the striatum in particular [34]. 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 (lipids). This D2 receptor subclass would be revealed in the presence of sulpiride blockade. Moreover, Martes et al. demonstrated that treatment with a dopamine antagonist preferentially increases the shorter D2S isoform in the brain or pituitary [35]. By analogy, the D2S isoform would correspond to D2/SUL and the other D2L isoform would be the equivalent of D2/BR in our study [18].

It is interesting to note that all the treatments inhibit the consumption of exclusively protein-rich foods ("meat + fish" flour pellets: carbohydrates = 0 g; lipids = 10 g; proteins = 30 g; 120 Kcal per 100 g), even the hormonal activation of 17-βestradiol maintains this inhibition of protein consumption. Indeed, the work of Tews and collaborators indicates that a drop in intake is caused by high protein diets. According to these authors, in addition to partial anorexia, rats, when given the choice, avoid high protein diets and prefer diets with lower protein content [36]. Adrian and his collaborators have defined the nutritional needs of adult rats in protein between 9-18% or 36 to 72 kcal [37]. According to Smith and Johnson for the adult rat, the lower limit of a balanced protein content would be 4%. Below this threshold, a diet would be classified in the category of diets devoid of an amino acid and/or in that of diets without protein [38]. These observations show that the "meat + fish" flour pellets is a high protein diet (30% protein). Some authors have demonstrated that food preferences are also influenced by the protein content of the diet. When rats have to choose between two diets, one containing a normal content and the other containing an excess of protein, they choose the normal protein diet. In other words, they avoid the high protein diet [36] [39].

The nature of the depression induced by the ingestion of a high protein diet would be due to the low palatability of the high protein diet [40], combined or not, with the induction of a conditioned taste aversion [36] [39] [41] or with the induction of enhanced satiety [42] [43]. Currently, it is considered that among the three macronutrients, proteins have the highest satiety power in rats and in humans [43-49]. However, the relative differences in the effects of macronutrients have been explained by the physiological or physiopathological state of the subjects or by the differences in methodology, such as the duration of the load or its route of administration, intragastric or intraduodenal or intravenous [42, 43] [50-53]. Thus our results show that the consumption of foods excessively rich in protein ("meat + fish" flour pellets: 30% protein) is inhibited by all the treatments. Therefore, under normal physiological conditions, 17β-estradiol exerts a tonic inhibition on protein consumption in rats. The modulating effect of E2 on the D2/SUL and D2/BR receptors is almost nil in the consumption of protein-rich foods. 17β-estradiol blocks all food consumption when the dominant macronutrients are lipids (dried coconut kernel) or proteins (meat + fish flour granules) exclusively, or the pairs of dominant macronutrients formed by carbohydrates-lipids (crisps plantain) or lipids-proteins (roasted and salted peanuts). According to our results, estrogens play a key role in controlling food intake and energy expenditure. These results are confirmed by some authors who report 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 stabilizing weight [54]. It has long been established that estrogens are likely to promote a reduction in food intake, both in humans and in primates [55]. Ogawa and collaborators have shown that obesity and type 2 diabetes are associated with dysregulation of neuro-hormonal and tissue functions that control the feeling of hunger, nutritional intake, body mass, metabolism of glucose and lipids. However, the α estrogen receptor plays an essential role in the regulation of food intake and energy expenditure by estrogens [56]. Bromocriptine has similar actions to 17β-estradiol. Indeed, bromocriptine activates the consumption of foods with a high carbohydrate content, while it inhibits the consumption of foods with a high lipid or protein content or foods with dominant carbohydrate-lipid macronutrient pairs. Our study shows that 17-βestradiol and bromocriptine reduce the amount of food consumed by stabilizing body weight. According to Eckel, 17β-estradiol reduces body weight and adipose tissue [57].

On the other hand, our work indicates that bromocriptine has no effect on foods with dominant lipid-protein or carbohydrate-protein macronutrient pairs. The majority of D2/BR receptor actions are independent of the modulating effects of 17β-estradiol. According to Roepke and collaborators, this modulation of appetite seems to be linked to a combination of membrane and genomic effects, since 17β-estradiol regulates the expression of genes involved in the control of food intake [58]. Accordingly, like 17β-estradiol, D2/BR receptors inhibit food intake and thus reduce body weight. Unlike bromocriptine, sulpiride induces the consumption of foods high in energy and particularly rich in lipids (dried coconut kernels) or foods rich in couples of lipid-protein macronutrients (salted roasted peanuts), or carbohydrate-lipid pairs (banana chips plantain), while it has no effective action on sugars and proteins. However, under hormonal induction of 17β-estradiol, sulpiride effectively activates the consumption of foods exclusively rich in sugar (corn) or foods rich in couples of carbohydrate-protein macronutrients (white beans); as being in search of glucose to ensure homeostasis [18]. At the same time, 17β-estradiol blocks the primary activities of D2/SUL receptors, by inhibiting the consumption of foods rich in lipids, or couples of lipid-protein or carbohydrate-lipid macronutrients, which sulpiride activates alone.

Direct activation of dopamine D2 receptors by bromocriptine slightly increases carbohydrate consumption (yellow corn), whereas blockade by sulpiride shows no difference in consumption with control rats. According to Hodge and associates, blockade of D2 type dopaminergic receptors reduces the consumption of palatable (sweet) foods in rats [59]. However, under hormonal induction of 17β-oestradiol, sulpiride effectively activates the consumption of foods exclusively rich in carbohydrates or carbohydrate-protein macronutrient pairs (white beans). These observations indicate that sulpiride is involved in the activation of protein consumption in association with carbohydrates and more generally in the consumption of carbohydrate-rich foods if induced by 17β-estradiol. This context brings us to the situation of eating tasty foods. Indeed, Martínez and collaborators 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. [60]. These observations show the existence of a synergy of action between 17-βestradiol and sulpiride in the activation of the consumption of foods rich in carbohydrates and proteins such as white beans. Thus, 17β-estradiol can divert the activity of D2/SUL receptors towards the consumption of sugar-rich compounds, which is not the normal function of D2/SUL receptors. As a result, D2/SUL receptors would simultaneously activate food consumption leading to an increase in body weight. These two factors would be positively regulated under hormonal induction of 17β-estradiol.

Furthermore, our results show that the D2/SUL isoform decreases the consumption of foods very rich in carbohydrates and rather amplifies the consumption of foods containing couples of macronutrients with a high content of carbohydrates-lipids, lipids-proteins and carbohydrates-proteins. Conversely, the D2/BR isoform stimulates carbohydrate consumption. These observations highlight the opposite nature of the activities of the two (2) dopamine D2 receptor isoforms. Our results show the direct involvement of dopaminergic D2 receptors in the choice of consumption of food types. This choice would be made according to the two (2) isoforms of dopaminergic D2 receptors. According to Wu and collaborators, 17β-estradiol acts to modulate the ratio of the two isoforms of D2 dopamine receptors, by transcription of their respective gene, induced by the nuclear estrogen receptor [61]. The first D2L isoform, directly activated by bromocriptine, a specific central agonist of D2 dopamine receptors, and the second D2S isoform, activated by sulpiride blockade, a specific central antagonist of D2 receptors, would direct the food choice directly, or under induction of 17-β- estradiol. It appears from our work that bromocriptine orients the food choice towards a high carbohydrate consumption, but inhibits the consumption of foods rich in lipids, proteins or a couple of macronutrients, without causing a gain in body weight or an increase in the amount of food consumed. As for sulpiride, it directs the food choice, on the one hand towards a high lipid consumption with

simple dominance or co-dominance with carbohydrates and proteins in food, on the other hand towards a high consumption of sugar with simple dominance or co-dominant with proteins (carbohydrate-proteins), under hormonal induction of 17-β-estradiol. This food orientation of sulpiride causes a gain in body weight and an increase in the amount of food consumed. These observations are supported by the work of Baptia and collaborators, who demonstrated that sulpiride considerably increases body weight and fat mass in rats [62, 63]. Thanos and associates, report that in obese subjects, the availability of dopaminergic D2 receptors in the striatum is decreased, which can encourage them to seek food (glucose and high fat content) such as a means of temporarily compensating for the under-stimulation of reward circuits controlled by dopamine [63]. Previous studies show that intra-hypothalamic injections of sulpiride increase food consumption, even in satiated rats [64]. Our studies show that 17β-oestradiol 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 [65]. These observations show that 17β-estradiol is in fact a specific modulator of the two isoforms of dopamine D2 receptors.

5. Conclusion

The combined actions of 17-β-estradiol and dopaminergic D2 receptors guarantee weight stability, playing a key role in adipost (a mechanism for regulating fat mass whose center is the hypothalamus). The regulation of body weight by 17-β-estradiol involves the control of several major functions, such as the consumption of different types of food (carbohydrates, proteins and lipids). This hormone modulates the activity of two isoforms of dopamine D2 receptors, which have opposite effects. One of the D2 isoforms exclusively activates carbohydrate consumption under the control of 17-β-estradiol. The other isoform D2, acts by hormonal induction by directing food consumption towards foods containing macronutrient couples with potentially high content: carbohydrates-lipids (crisps), lipids-proteins (peanuts), proteins-carbohydrates (white beans), which leads to overeating and overweight.

6. Outlook

Our future research will be directed towards studying the relationship between thiamine and 17-β-estradiol for the selection of food types. Indeed, it would be interesting to evaluate the effects of thiamine deficiency (partly linked to alcohol consumption) on the activities of 17-β-estradiol and dopaminergic D2 receptors. Subsequently, the interferences that exist between thiamine, 17-β-estradiol and dopaminergic D2 receptors will also be studied in the case of ovariectomy performed in rats.

Declarations

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Conflict of Interest: The authors have explicitly declared that there is no conflict of interest in relation to this article.

Ethics Approval: A week before the start of the tests, the animals 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.

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