

## Predictive behaviors for anxiety and depression in female Wistar rats subjected to cafeteria diet and stress



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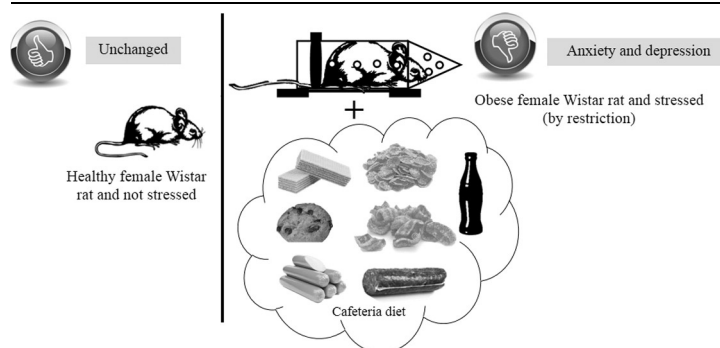
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### HIGHLIGHTS

- Cafeteria diet used in this study is effective in inducing obesity in female Wistar rats.
- Chronic stress induced in the animals does not increase obesity in females of the chosen rodent lineage.
- Obese and stressed female rats presented a higher anxiety index and predictive behavior for depression.

### GRAPHICAL ABSTRACT



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### ABSTRACT

Obesity and chronic stress have been considered important public health problems that affect millions of people worldwide. Our aim was to analyze the effect of obesity associated with chronic stress on neurobehavioral parameters in female rats, considering that the association of these syndromes can enhance the negative effects on homeostasis. The animals were distributed into standard diet (Std), standard diet + stress (Std + stress), cafeteria diet (Cafe), and cafeteria diet + stress (Cafe + stress) groups. The animals of groups Std and Std + stress were fed with rodent standard feed. Groups Cafe and Cafe + stress, additionally to the standard feed, were offered palatable and calorie-rich processed food and cola-type soft drink ad libitum. From the eighth experimental week, groups Std + stress and Cafe + stress were subjected to restraint chronic stress model (50 days). After the stress protocol, predictive anxiety (open-field and elevated plus-maze tests) and depression (forced swim) were applied. The cafeteria diet was effective in inducing obesity. The ratio locomotion in the central quadrants/total locomotion evaluated during the open field test was not indicative of anxiogenic or anxiolytic effect in the

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animal's behavior. However, the elevated plus maze test showed that obese and stressed animals were prone to higher anxiety levels. In addition, the obese and stressed animals display less climbing behavior than all the other groups, which can be considered an indicator of depression-like behavior. Nevertheless, it is suggested that the mechanisms involved in effects of obesity associated with chronic stress be better investigated in female rats, considering the organic complexity related to these modern illnesses.

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## 1. Introduction

Obesity is considered epidemic and one of the main public health problems of the world [26,40,98]. It is defined as the accumulation of excess body fat to the extent that it results in other health complications, thus reducing life expectancy [3,30,31,48]. In humans, co-morbidities associated with obesity include psychological distress, osteoarthritis, type 2 diabetes mellitus, hypertension, hyperlipidemia, fatty liver (steatosis), cardiovascular disease and certain types of cancer [39,83]. The steady increase in life expectancy due to advanced medical treatment may be reversed by negative impacts of obesity on youth today in Westernized countries [66].

In clinical practice, body fat is most commonly and simply estimated by using a formula that combines weight and height [45]. The underlying assumption is that most variation in weight for persons of the same height is due to fat mass, and the formula most frequently used in epidemiological studies is the body-mass index (BMI). A graded classification of overweight and obesity using BMI values provides valuable information about increasing body fatness. It allows meaningful comparisons of weight status within and between populations and the identification of individuals and groups at risk of morbidity and mortality. It also permits identification of priorities for intervention at an individual or community level and for evaluating the effectiveness of such interventions. It is important to appreciate that, owing to differences in body proportions; BMI may not correspond to the same degree of fatness across different populations. Nor does it account for the wide variation in the nature of obesity between different individuals and populations. A World Health Organization (WHO) expert committee has proposed the classification of overweight and obesity that applies to both men and women and to all adult age groups ( $\text{BMI (kg m}^{-2}\text{)} = 25.0\text{--}29.9$ , overweight;  $30.0\text{--}39.9$ , obesity and  $\geq 40.0$ , morbid obesity [99]. However, it is important to emphasize that data presented reflect knowledge acquired largely from epidemiological studies in developed countries.

Another health problem that has affected millions of people is stress exposure, which is related to modern world dynamics [61]. As discussed by Lazarus [49] and Taylor and Stanton [85], stress can result from a certain condition and/or lifestyle and lead to an ample series of behavioral alterations. Among them, there are changes in eating habits, which reflect an interaction between the organism's physiological state and environmental conditions [67,79,90]. Chronic stress is associated with metabolic disorders and changes in energy homeostasis [5], which can induce to compensatory pleasant and compulsive behaviors, such as the intake of palatable and calorie-rich foods, and consequently lead to obesity [9,15,37].

Although the importance of the analysis of the joint effects of obesity and stress is recognized [21–23,25,56–58,86,96], studies involving the association of these conditions in neurobehavioral aspects are lacking. In addition, some studies have pointed to different results when males and females are evaluated in studies involving obesity [2] and stress [4,32,42,52]. Especially on stress, various stressor agents and protocols have been used. According to Franceschelli et al. [32], the chronic mild stress model is one of the most extensively investigated animal models of chronic stress. However, only a limited number of studies have been conducted in female rodents. In relation to obesity, although some work has been conducted using female rats [71,17,38,81,82], the neurobehavioral aspects that can indicate neuropsychiatric disorders, such as

locomotor alterations, anxiety and depression have not been the focus of these studies.

Obesity is considered an “extreme” linked to nutrition, whose effects can be enhanced when in association with chronic stress. Obesity (induced in murine models by introducing cafeteria diets) has caused damage to several organic functions [92,27,84,93]. However, there is still the necessity of specific investigations on the factor stress linked to obesity, once stress alone is an impacting factor to the organism. The objective of our study is to analyze the effect of obesity associated with chronic stress on neurobehavioral parameters in rats, considering that the association of these diseases can increase the negative effects on homeostasis. Our hypothesis is that obesity associated with chronic stress by restraint induces anxiety-like and depression-like behaviors in female Wistar rats.

## 2. Material and methods

### 2.1. Animals and experimental groups

Female Wistar rats from the matrices obtained from the *Biotério Central* (Animal Facility) of the Federal University of Goiás (Goiás, Brazil) were kept in the animal facility of the Laboratory for Biological Research of the *Instituto Federal Goiano*, Urutaí, Goiás, Brazil. The animals were subjected to a natural photoperiod (approximately 12:12 h), and offered food and liquids ad libitum. Forty-five day old animals were used (age corresponding to the final stage of puberty, according to Andrade et al. [1], distributed in the following experimental groups: standard diet (Std); standard diet + stress (Std + stress); cafeteria diet (Cafe) and cafeteria diet + stress (Cafe + stress). We emphasize that the diet started at this age (forty-five days old) and then subsequent manipulations were performed when the animals were young adults. Each experimental group was composed of six animals, and two experiments were conducted independently, totalizing twelve animals per group. The animals were maintained individually in separate cages. All procedures were approved by the Institutional Committee for Animal Care and Use of the *Instituto Federal Goiano*, Goiás, Brazil (protocol n. 003/2014) in accordance with the Guide for the Care and Use of Laboratory Animals, 8th edition (2011). Animal handling and all experiments were performed in accordance with the International Guidelines for Animal Welfare.

### 2.2. Experimental design

Standard diet groups (stress or no stress) were fed with rodent standard feed (Nuvilab – CR1®) (Table 1). Cafeteria diet groups (stress or no stress) were fed with cafeteria diet, which consisted of palatable foods with expressive levels of lipids. This food composition is nowadays prevalent in urban societies and associated with the pandemic of obesity. Cafe and Cafe + stress groups (in separate feeders) were offered daily three varieties of palatable foods ad libitum (randomly selected from the foods listed in Table 2 – all values were expressed by the amount (in grams) informed on the food package), besides rodent standard feed. Cafe and Cafe + stress groups received the same variety of palatable food, in addition to standard diet (Fig. 1). Std and Std + stress groups received standard diet only.

The cafeteria and standard diets were weighed before and after consumption. The daily consumption was calculated by subtracting the

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