

Does High Fat Diet have the Stress-Like Effect on Animals?

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Abstract

The increment of high fat ingestion appears to be one of the compensatory behaviors adopted by the contemporary society to reduce the social stress effects. The release of glucocorticoids, a common physiological response, was shown to contribute to the development of stress-associated diseases. So, this study aimed to verify the effect of high fat intake and social stress on metabolic profile and stress response. We also verify if high fat food and stress affect mitochondrial homeostasis. Rats were divided into: control (without social stress) (C) and experimental (with social stress) (ST) groups. Then, groups were subdivided into two: one group received common laboratory chow (NF), as the other had high-fat food added to the laboratory chow (HF). Food intake, corticosterone metabolites, mitochondria integrity, body and adrenal weight were assessed. The social isolation and high fat did not affect the adrenal and body weight, and mitochondria integrity; however, corticosterone metabolites and caloric intake were increased in ST-HF and C-HF when compared to C-NF and ST-NF groups. The present findings suggest that high fat administration increases caloric intake, corticosterone levels and that could have cumulative damaging effects along with changes in metabolic profile. Thus, high corticosterone levels, mainly associated with high fat and caloric intake, might also predict metabolic diseases development.

Introduction

Social interactions can trigger the stress response characterized by the activation of both the hypothalamic-pituitary-adrenal axis (HPA) and the sympathetic-adrenal system. This effect leads to increased levels of glucocorticoids, as cortisol and corticosterone [1–3]. These hormonal changes can trigger the reward-seeking behavior and increase the motivation for natural recompenses such as high-calorie and palatable foods intake. The hyperphagia seems to be the more predominant stress-response in the human population, but in a minority part of the population, reduced food intake and weight loss was also reported to be consequence of stress [4]. However, when comparing genders in stressful conditions, the overeating is predominant in females [5].

The tendency towards the highly palatable food ingestion can become an habit of self-medication, favoring body mass increment, abdominal fat deposition, and elevation of leptin and insulin levels [6–8]. Importantly these behaviors are considered risk factors for the metabolic syndrome [9, 10], cardiovascular diseases [11] and diabetes type 2 (DM2) [12,13].

Mitochondria dysfunction play a central role on the development of metabolic disease, such as DM2 [14] and its complications [15]. Levels of corticosterone could modulated mitochondria integrity whereas it was suggested that either to lower or higher amounts of this hormone diminish mitochondria metabolism [14].

In our previous study, we demonstrated that isolated females rats increase their intake of fat and that was associated to increase in corticosterone [3], such as in others studies [7,8,16]. In this study, therefore, we test the hypothesis that the increase in corticosterone may be due the increase in high fat food intake per se and not only due the methodology used to induce social stress and verify if high fat food and stress affect mitochondrial homeostasis.

Methods

Animals: Females Wistar rats (6 weeks old) were purchased from Charles River Laboratory. Housing and experimental treatment of

the animals were in accordance with the Guide for the Care and Use of Laboratory Animals from the Institute for Laboratory Animal Research [17].

Experimental groups: Animals were randomly divided in 2 groups, a control group (without social stress – N=12) (C) and an experimental group (with social stress – N=12) (ST). The animals from the social stress group were kept isolated (social stress) while the animals of the control group were paired (2 animals/cage) in the same cage. This is a validated methodology to induce stress as described by Brown et al. (1995) [18]. Subsequently, at same week, groups were divided for a second time according to food condition; whereas to the normal food group (NF) was offered pelletized laboratory chow, and to the high fat (HF) group was offered approximately 45g of fat food (bacon) added to pelletized laboratory chow daily. The conditions of C-NF (N=6), C-HF (N=6) or ST-NF (N=6) and ST-HF (N=6) were kept during 6 weeks. The fecal samples were collected three times: at beginning of experiment, after two and six weeks. The collection and the treatment was performed as described previously [3].

Caloric Intake: The alimentary intake was measured daily. To evaluate the food ingestion of the control group, the mean value of the ingestion between the paired females was calculated. The ingested calories were calculated by multiplying the quantity of food eaten for each animal (in grams of food consumed) by the specific calorific value of the chow (2.9Kcal/g) and of the bacon (5.4Kcal/g). Then, the calories ingested was divided by each animal body weight in the period as done by our group [3].

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Tissue analyses: At the end of experimental period, the animals were euthanized, and soleus muscle, adrenal and the abdominal fat were removed. Then, it was calculated the relationship between the abdominal fat (omental) and adrenal with body weight (g) as done previously [3].

Biochemical analysis: The corticosterone metabolites extracted from feces (collected in metabolic cages during 12h) was measured using the Cayman Chemical Corticosterone Elisa Kit [3]. Mitochondrial integrity was assessed in soleus by measuring citrate synthase activity as described previously [15].

Statistical treatment: Statistical analyses were carried out using SigmaPlot 11.0 software and the Shapiro-Wilk normality test was performed. For variables with normal distribution ANOVA followed by Bonferroni test were applied, while Kruskal-Wallis test followed by Dunn's test were performed for data which did not present normal distribution. The levels of statistical significance were set at $P < 0.05$.

Results

Body weight, assessed every week, increased during the 6 weeks of experimental protocol, but no difference was found between groups. Animals feed with high fat food in control and stressed groups, acquired fewer calories from the laboratory chow than the animals feed only with chow (Figure 1a). The total calories intake, however, was higher in the groups feed with high fat diet (C-HF and ST-HF) (Figure 1b). Levels of corticosterone did not present any change between groups at the third week but at sixth week it was increased in ST-HF and C-HF when comparing to C-NF and ST-NF (Figure 1c). No differences in the relative weight of adrenal glands, in abdominal fat weight or citrate synthase activity were observed between groups (Table 1).

	AF (%)	AD (%)	CF (U/mg)
C-NF	5.28± 1.9	0.032±0.004	89.56±20.1
C-HF	4.81±1.0	0.037±0.003	74.45±9.3
ST-NF	4.81±1.0	0.03±0.007	75.45±9.3
ST-HF	4.92± 1.2	0.032±0.004	88.41±13.7

Table 1: Weigh of abdominal fat (AF), adrenal glands (AD) and activity of citrate synthase (CS) was measure at the end. Values are represented as mean ± SD obtained from more than 6 rats in each group. Control with normal (C-NF) and with high fat food (C-HF); stress treatment with normal (ST-NF) and high fat food (ST-HF).

Discussion

Social stressors are the unpleasant stimuli prevailing in westernized humans' lives [19]. Under stressful conditions, the HPA axis is over-activated; leading to disruption of the negative feedback control of glucocorticoids, which further damages the HPA axis. In chronic state, in which glucocorticoids concentrations are exacerbated, corporal energy resources are redirected inducing, in its majority, increase in high palatable food intake [20-22]. Here, we demonstrate that high fat diet per se exacerbates the HPA axis activity and increase the corticosterone levels, despite of the social stress situation, since individual housing for 6 weeks does not change faecal corticosterone levels under standard diet.

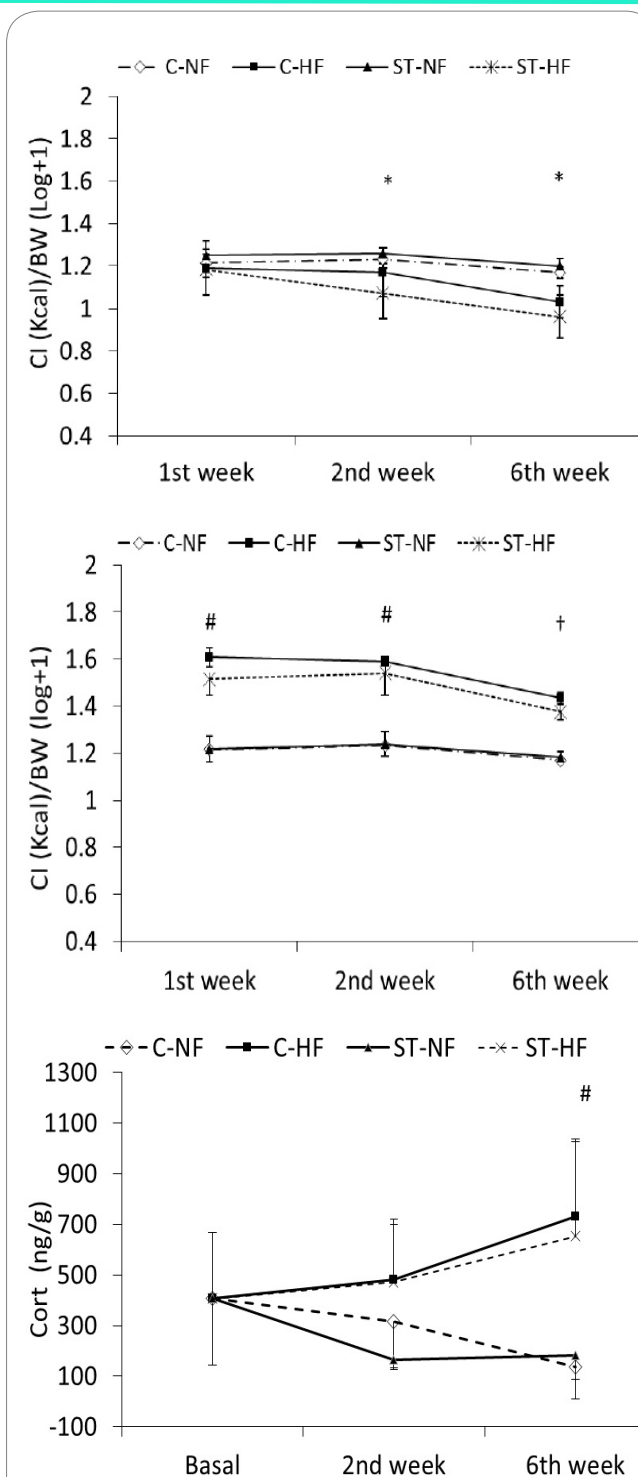


Figure 1: The effect of social-stress and high-fat diet on stress response markers. Caloric intake of standard laboratory chow (a) Standard Laboratory Chow + fat food (bacon) (b) normalized by body weight (CI/BW) assessed at first, second and sixth weeks of experiment. (c) Fecal corticosterone metabolites (CORT) were measured before experimental protocol, and the follow second and sixth weeks. Values are represented as mean ± SD obtained from 6 rats in each group. Control with normal (C-NF) and with high fat food (C-HF); stress treatment with normal (ST-NF) and high fat food (ST-HF). * $P < 0.05$ ST-HF vs. C-NF and ST-NF # $P < 0.05$ ST-HF and C-HF vs. C-NF and ST-NF, † C-HF vs. C-NF and ST-NF.

Changes in food intake triggered by stressful situation still a matter of debate as both hyperphagia and hypophagia was described as outcome of this situations [3,23]. An issue that might explain the resultant change in food intake pattern and the differences in these studies could be the type of stressor (physical or psychological) or with its extent [24–26]. When genders are compared, overeating is a stress related outcome predominant in females [16]. Here, as in our previous study [3], the caloric intake increased in animal submitted to social stress. However, in opposite to what was reported by other authors, the exacerbated caloric intake did not promote augment of abdominal fat [7,27], perhaps because of the high fat constitution in the present study or by the duration of experimental procedure. During the daily monitoring of the food amount and quality, it was noted that the animals fed mostly on the bacon's fat instead of the meat and chow. Once the chow used in the experiment was specific for rats, being composed by balanced nutrients, animals that fed on chow instead of bacon must have reached a more favourable nutritional state, showing a better caloric efficiency, also observed in Pecoraro et al [28]. Therefore, according to our results we suggest that high fat intake had a similar effect of stress response. This idea is corroborated by our results showing that corticosterone level were elevated only due high fat intake. In agreement, it was demonstrated that high-fat feeding resulted in the impairment on the ability to restore basal corticosterone following stress [29].

Related to mitochondrial integrity, here we demonstrated that levels of corticosterone induced by six weeks of high fat diet was not harmful for mitochondrial integrity, as demonstrated by the activity of citrate synthase. Therefore we suggest that mitochondria dysfunction induced by high levels of corticosterone could be a slow process.

Since DM2 have become the epidemic of the human's contemporary life, and overeating is recognized as one of the main factor this disease [12,30,31], researchers have been using different methodologies to study DM2. The offer of high fat food to rodents is a common methodology to induce DM2 characteristics, as abdominal fat accumulation, changes in the lipid profile and levels of insulin [3,32–34]. The results here suggest that if high fat diet is used to induce DM2, the increase of corticosterone may also be an element to be considered since this hormone influence insulin secretion and function [35,36], such as glycogen synthase [37] and glucose transport system [38]. Indeed, our previous report showed that regular exercise, a DM2 prevention strategy, attenuated corticosterone levels [3]. Therefore, it is possible to propose that the increase in corticosterone induced by the high fat food could also contribute to disease development, such as DM2.

Conclusion

Concluding, long-term high fat intake per se activates the HPA axis and that contribute to the increase in levels of corticosterone. Therefore, we propose that the protocol of DM2 induction through high fat offers to laboratory rodents could elevate the corticosterone levels. The elevated corticosterone together with high glucose or triglycerides might also induce metabolic diseases development.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

All the authors substantially contributed to the study conception and design as well as the acquisition and interpretation of the data and drafting the manuscript.

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