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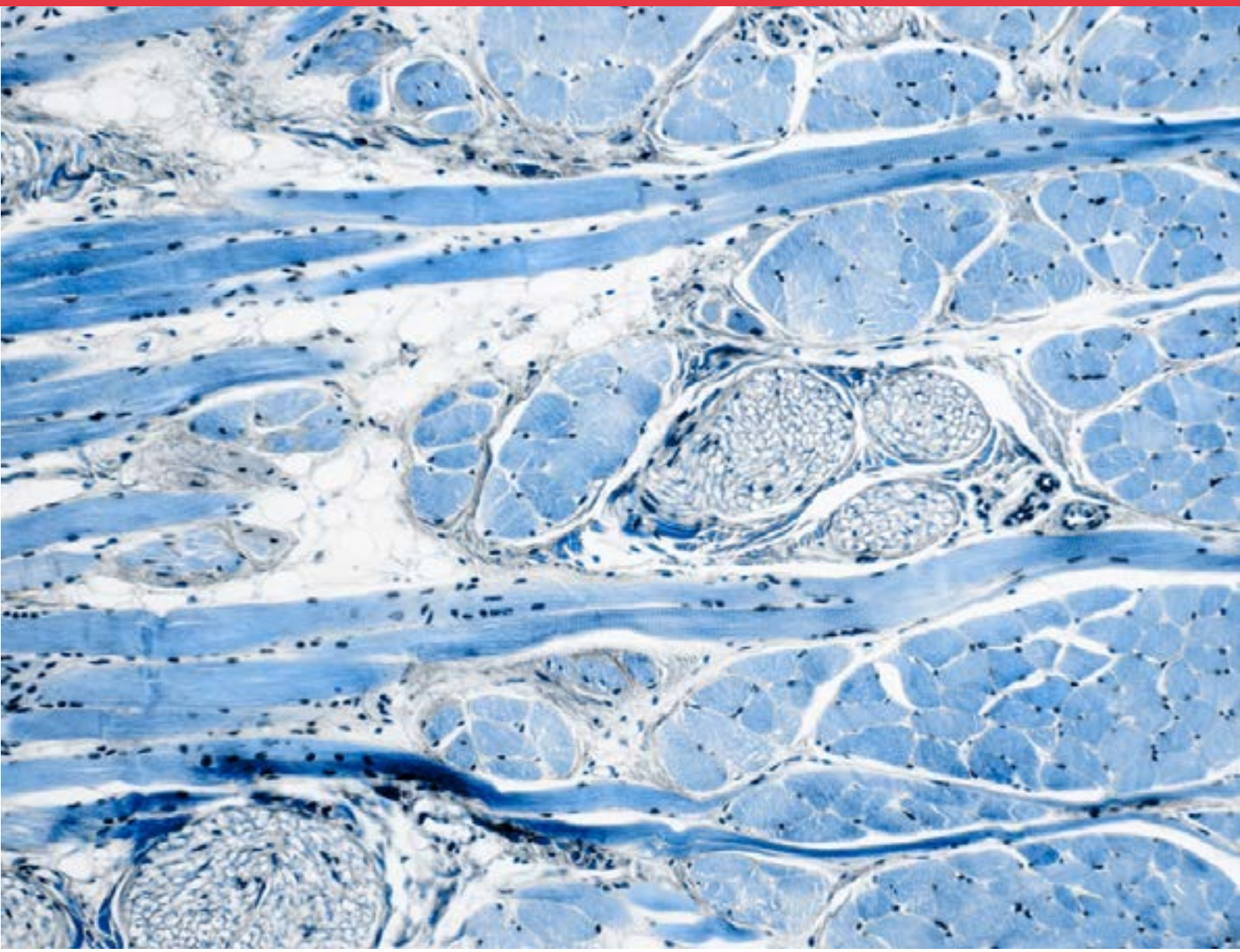

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INTERRELATION OBESITY-STRESS IN THE DEVELOPMENT OF COGNITVE DEFICIT

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Abstract

Chronic exposure to stressful situations (CS) and consumption of high fat diets (HFD) are common conditions in modern society and have been identified as predisposing factors for different disorders. In this review, we focus on the effect CS and HFD have on cognition and the molecular pathways involved. In this context, our interest is to investigate the interaction between CS and HFD in the development of obesity and associated metabolic, behavioral and immune disturbances. Also, we search for peripheral markers as predictors of these disorders. For this purpose, C57Bl/6J mice were fed with control (CD) or HFD after weaning and exposed to CS in the adulthood. Taking into account the relevance of the inclusion of sex as a biological variable in research, our investigations were carried out in both males and females. Results indicate that males are more susceptible than females in modulating metabolic and cognitive functions under HFD and CS. Interestingly, males fed with HFD and exposed to CS showed a poorer cognitive performance correlated with a decrease in hippocampus and spleen BDNF mRNA expression. The emerging results of our research could promote the identification of new therapeutic interventions to prevent the progression of these disorders.

Keywords: obesity, stress, cognitive impairment; metabolic disorder.

Resumen

La exposición a estrés (CS) y el consumo de dietas hipercalóricas (HFD) típicos de la sociedad moderna, son identificadas como factores predisponentes a diferentes trastornos. En esta revisión, nos centramos en las evidencias de la literatura sobre el efecto del CS y la HFD en la cognición y las vías moleculares involucradas. Nuestro interés es investigar la interacción entre CS y HFD en el desarrollo de obesidad y las alteraciones metabólicas, conductuales e inmunológicas asociadas. Además, buscamos marcadores periféricos como predictores de estos trastornos. Para este propósito, ratones C57Bl/6J fueron alimentados con una dieta control (CD) o HFD después del destete y expuestos a CS en la edad adulta. Dada la relevancia de incluir al sexo como variable biológica, nuestras investigaciones se realizaron tanto en machos como en hembras. Los resultados indicaron que los machos son más susceptibles a la hora de modular las funciones metabólicas y cognitivas bajo HFD y CS. Los machos expuestos a HFD mostraron un peor rendimiento cognitivo relacionado con una disminución en la expresión del ARNm de BDNF del hipocampo y del bazo. Los resultados emergentes de nuestra investigación podrían promover la identificación de nuevas intervenciones terapéuticas para prevenir la progresión de estos trastornos.

Palabras claves: obesidad, estrés, déficit cognitivo, desorden metabólico.

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Introduction

Lifestyle - specifically dietary habits and stress exposure could play a detrimental role in health. According to a report broadcasted by the World Health Organization in 2024 [1], 1 in 8 people in the world are living with obesity. Worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled. In 2022, 2.5 billion adults (18 years and older) were overweight. In 2022, 37 million children under the age of 5 were overweight. Overweight and obesity are linked to more deaths worldwide than underweight. In fact, they are a major risk factor for non-communicable diseases such as: cardiovascular diseases (mainly heart disease and stroke), diabetes, musculoskeletal disorders (especially osteoarthritis) and some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon). In the last years, it was found that obesity may contributes to the development of neurodegeneration, cognitive impairment, and increased susceptibility to brain damage [2,3].

Likewise, the normal structure and function of the brain are altered by long-term stress [4]. Specifically, the hippocampus, a limbic area involved in learning and memory is particularly vulnerable to the effects of stress [4-5]. In addition, it was suggested that repeated exposure to stress confers a higher risk of developing neurodegenerative diseases [6-8].

Interestingly, a relation between CS and eating behavior has been described in humans (9, 10]. Similarly, several animal models showed an association between CS and obesity with divergent metabolic phenotypes [11, 12]. In general, it was found that CS raises the consumption of palatable foods resulting in obesity [13, 14].

In addition to review the literature on this subject I will present findings from our laboratory concerning to obesity, stress, cognitive impairment and their interaction. Moreover, peripheral markers as predictors of these disorders will also be postulated.

The association among neuro-inflammation, eating disorders and stress exposure

The brain is a highly energy-demanding organ that depends on the accurate regulation of energy metabolism for the best neuronal function and total brain health. Disruptions in this delicate balance can lead to neuro-vulnerability and promote the development of various neurological disorder. A recent and interesting review written by Clement-Suarez et al [17] provides an exhaustive analysis of the neuro-vulnerability associated with energy metabolism dysregulation. The neuro-vulnerability, characterized by dysfunction and dysregulation within these neural pathways, has emerged as a key factor contributing to the development of metabolic disorders, including obesity, diabetes, and eating disorders. In this comprehensive narrative review, the authors examined the neurobiological basis of energy metabolism, neuroendocrine interactions, neural control of food intake and energy expenditure, and the role of neuro-inflammation emphasizing the importance of bidirectional relationship between metabolic dysregulation and neuroinflammatory processes. Additionally, they also evaluate the use of neuroimaging techniques in studying neuro-vulnerability and their potential applications in clinical settings. The evidence showed in this review highlight the essential role of neural circuits and systems in maintaining metabolic homeostasis. On the other hand, the emerging data highlight the essential role of energy metabolism dysregulation and its impact on neuro-vulnerability.

In the context of obesity-induced cognitive decline, the neuro-inflammation generated in the hippocampus has been associated with changes in the integrity of the blood-brain barrier is of particular interest [18]. Local and systemic inflammation induced by obesity can cause BBB breakdown, reduced removal of waste, and elevated infiltration of immune cells [18]. Cytokines such as IL-1 beta, IL-6, IFN-gamma, TNF-alpha and MCP1, have been involved in the generation of neuroinflammation and the increase in oxidative stress, leading to cognitive decline [19]. Severe obesity is indeed associated with an inflammatory profile characterized by increased concentrations of circulating cytokines [20,21]. The effect of inflammation, mediated by glucocorticoids on microglia, on

brain function and behavior has been reported in many other chronic inflammatory conditions such as chronic stress exposure [22] It was suggested that repeated exposure to stress confers a higher risk of developing neurodegenerative diseases [6,22].

Neurotrophins are a family of secreted proteins that control neuron survival and development, and regulate neuronal plasticity [23]. The members of this family are brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 (NT3) and neurotrophin NT4/5. Particularly, BDNF has been implicated in learning and memory formation [24]. Interestingly, it has been proposed that serum levels of BDNF could be correlated to cognitive function, but conflicting data were found in patients with Alzheimer's disease and individuals with mild cognitive impairment [25]. Additionally, it was found that BDNF mRNA expression in leukocytes is related to Frontal Assessment Battery scores in crack-cocaine and alcohol use disorder patients [26].

Obesity-Chronic Stress interaction in males and females

The interest of our laboratory is to study the effect of chronic stress exposure on cognitive performance and the correlation with metabolic changes induced by a HFD. In addition, we investigate neurotrophins and cytokine levels in the hippocampus. Moreover, we analyze if the molecular changes in the hippocampus are also found in the spleen which would allow us to propose lymphocytes as peripheral marker of susceptibility to behavioral alterations induced by HFD and/or stress exposure. For this purpose, one month old male and female C57Bl/6J mice were fed with HFD for 28 weeks being then exposed to stressful conditions from the 3 months of age until the end of the experiment. Our aim was to investigate the effects that ~~of~~ an obesogenic diet during infancy and adolescence would have on metabolism and cognitive behavior outcomes following stressors exposure during adulthood (see experimental scheme in figure 1).

The relevance of the inclusion of sex as a biological variable in research, to improve the understanding of disease mechanisms was heavily emphasized [15; 16]. However, despite evidence supporting a link between diet and stress, as well as memory impairment and metabolic changes, few studies investigate the interplay of these factors on the metabolic and cognitive outcomes in both, females and males.

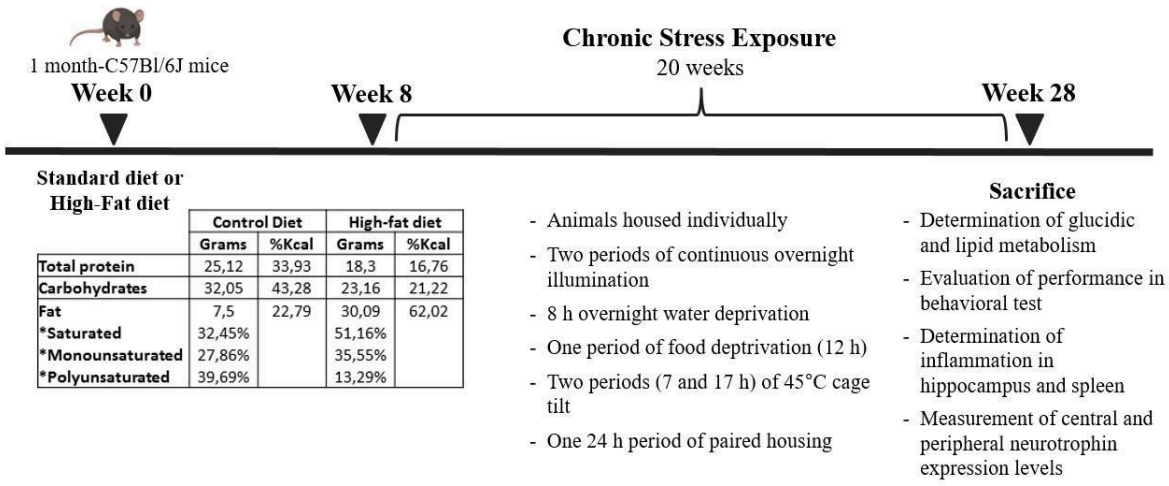

Figure 1. Scheme diagram showing the experimental design. One-month-old male and female C57Bl/6J mice were randomly assigned initially to two groups: control diet (CD) or high-fat diet (HFD). Subsequently, mice from each group were divided into two subgroups: one was exposed to chronic stress (CD+ CS and HFD +CS) and the other was left

undisturbed (CD and HFD) for the remaining 20 weeks. Table insert in the figure shows macronutrient and fat composition of the standard (CD) and high-fat diets (HFD).

The main results of this study, showed in Table 1, indicate that males are more susceptible than the females in modulating metabolic and cognitive functions under HFD and CS. In both sexes HFD induced weight gain, fat accumulation, insulin resistance~~,~~ and high cholesterol. However, results indicated that males are more sensitive to the deleterious effects of diet and stress, producing more detrimental effects in both metabolic and spatial working memory [27]. An outstanding finding in this study is the presence of a sexual dimorphism in modulating metabolic and cognitive functions under HFD and CS being males more susceptible than females. In addition, poorer cognitive performance was related to a decrease in hippocampal BDNF mRNA expression. Interestingly, these changes were observed in the spleen as well [27].

Table I. Key findings about the effect of HDF and/or CS in males and females.
1- HFD-feeding increased body weight and fat content associated to caloric intake in males and females. CS stress exposure resulted in a decrease in body weight not related to caloric intake.
2- HFD and/or stress altered glucose and lipid metabolism with a worse profile in males than in females.
3- HFD feeding and CS exposure impaired cognitive performance in males.
4- HFD feeding and CS exposure induce a reduction in brain derived neurotrophic factor mRNA expression and an increase of IFN-gamma in hippocampus only in male.
5- Impaired cognitive performance in males correlated with a reduction in brain derived neurotrophic factor mRNA expression in spleen.

Future perspectives

Taking in consideration the results concerning the interaction between HFD feeding and CS exposure, it is our interest:

1) Evaluate if peripheral BDNF mRNA expression could predict the level of cognitive performance in individuals with diet-induced obesity and ~~to~~ be a factor that suggest neurovulnerability under stress situations. The emerging results of this research could promote the identification of new therapeutic interventions to prevent the progression of these disorders.

2) Examine the pharmacological response to drugs used for the treatment of anxiety and depression induced by CS exposure, such as Fluoxetine. Preliminary results indicated that behavioral alterations improved in animals fed with control diet but not in HFD-fed mice [28]. These results point to the need for further studies to evaluate the usefulness of treating anxiety with fluoxetine in patients with obesity and exposed to stressful events.

3) Investigate the effect of HFD on cognitive performance in animals expose to Prenatal Stress (PS) It is proposed that PS insults during fetal development result in increased likelihood of developing chronic disease, such us attachment difficulties, affective disorders, stress hyper-responsiveness, neurological and cardio-metabolic disorders, asthma and allergies [29].

Previously, we observed that females were more resilient to PS consequences, but when they were fed a HFD, they showed significant metabolic impairment [30]. These findings encourage the analysis of the effects of PS and HDF interaction on cognitive performance.

4) Explorate the participation of the gut-brain axis cross talk in HFD-CS interaction. Nowadays, this is a topic of great interest. Several studies have suggested that alterations in gut microbiota induce an impairment in cognitive abilities in several pathological conditions [31].

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