Research report

Hypothalamic expression of inflammatory mediators in an animal model of binge eating

Silvia Alboni\textsuperscript{a,\ast}, Maria Vittoria Micioni Di Bonaventura\textsuperscript{b}, Cristina Benatti\textsuperscript{a}, Maria Elena Giusepponi\textsuperscript{b}, Nicoletta Brunello\textsuperscript{a}, Carlo Cifani\textsuperscript{b}

\textsuperscript{a} Department of Life Sciences, University of Modena and Reggio Emilia, 41125 Modena, Italy
\textsuperscript{b} School of Pharmacy, Pharmacology Unit, University of Camerino, 62032, Camerino, Italy

HIGHLIGHTS

- Food-restricted rats stressed during non-estrus develop binge eating (BE) behavior.
- BE is associated with changes in mRNA levels of inflammatory markers in hypothalamus.
- iNOS mRNA increases in the anterior-tuberal hypothalamus of BE rats.
- IL-18/IL-18R system is down-regulated in hypothalamus of BE rats.

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ABSTRACT

Binge eating episodes are characterized by uncontrollable, distressing eating of a large amount of highly palatable food and represent a central feature of bingeing-related eating disorders. Research suggests that inflammation plays a role in the onset and maintenance of eating-related maladaptive behavior. Markers of inflammation can be selectively altered in discrete brain regions where they can directly or indirectly regulate food intake. In the present study, we measured expression levels of different components of cytokine systems (IL-1, IL-6, IL-18, TNF-\alpha and IFN-\gamma) and related molecules (iNOS and COX2) in the preoptic and anterior-tuberal parts of the hypothalamus of a validated animal model of binge eating. In this animal model, based on the exposure to both food restriction and frustration stress, binge-like eating behavior for highly palatable food is not shown when animals are exposed to the frustration stress during the estrus phase. We found a characteristic down-regulation of the IL-18/IL-18 receptor system (with increased expression of the inhibitor of the pro-inflammatory cytokine IL-18, IL-18BP, together with a decreased expression of the binding chain of the IL-18 receptor) and a three-fold increase in the expression of iNOS specifically in the anterior-tuberal region of the hypothalamus of animals that develop a binge-like eating behavior. Differently, when food restricted animals were stressed during the estrus phase, IL-18 expression increased, while iNOS expression was not significantly affected. Considering the role of this region of the hypothalamus in controlling feeding related behavior, this can be relevant in eating disorders and obesity. Our data suggest that by targeting centrally selected inflammatory markers, we may prevent that disordered eating turns into a full blown eating disorder.

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1. Introduction

Eating disorders are characterized by a persistent disturbance of eating and eating-related behavior that results in the altered consumption of food and significantly impairs physical health and/or psychosocial functioning [1]. Binge eating is a proto-typical eating-related maladaptive behavior that represents a central feature of bulimia nervosa, binge-eating disorder, and binge-purge anorexia nervosa [1] and it contributes to aggravate obesity and its associated pathologies [2–4].

A large body of evidence suggests that dieting, stress, and negative affective states represent triggers of binge eating in patients suffering from binge-eating disorder or bulimia nervosa [2]. Several studies have examined the linkage between stress response, inflammation and eating disorders [5,6]. Pro-
inflammatory cytokines (soluble factors which promote inflammation) can regulate hypothalamic–pituitary–adrenal (HPA) axis functionality and glucocorticoids secretion [7] while conversely stress can evoke the activation of pro-inflammatory cytokines such as interleukin (IL)–1, IL–6, IL–18, and tumor necrosis factor (TNF)–α causing general fatigue, sleep disturbance, and also appetite loss [8–10]. Indeed, cytokines can affect appetite and food intake both in a direct and an indirect way in animals as well as in humans [11]. Different cytokines [IL–1, IL–6, IL–18, TNF–α, and interferon (IFN)–γ] suppress food intake, by direct action in the central nervous system [12]. IL–1, IFN–γ, and TNF–α affect those hypothalamic neurons implicated in the regulation of eating behavior [13]. Moreover IL–1 and TNF–α alter the firing rate of glucose-sensitive neurons in the lateral hypothalamus possibly affecting peripheral signals to the feeding centers [14].

Corcos and colleagues [7] also described the indirect actions of cytokines, such as IL–1β, that increase plasma levels of catecholamines thereby yielding food intake suppression [15]. It has been suggested that an elevation of cytokines promotes the cascade of biochemical events culminating in a dysregulation of neurohormones, neuropeptides, and neurotransmitters which contributes to the development and persistence in either anorexia or bulimia nervosa [13].

However, while the role of cytokine systems in contributing to the development or perpetuation of eating disorders has been in some way explored [7], the involvement of these systems in the binge-eating behavior remains largely unknown. In particular no data are available so far on the regulation of cytokine systems in brain regions belonging to feeding circuits when binge-eating behavior is induced.

Here we measured expression levels of immune targets (including pro-inflammatory cytokines and related molecules) in the hypothalamus of an animal model of binge eating and relative controls. In this animal model, binge eating for a familiar highly palatable food is evoked in female rats by exposure to cyclic food restrictions combined with frustration stress [16,17] according to the hypothesis that dieting and stress are key etiological determinants of binge eating.

Although several brain areas (such as bed nucleus of the stria terminalis–BNST, lateral habenula, or ventral tegmental area) are involved in regulating feeding, appetite, motivational behavior, and are they sensitive to changes in cytokine systems [18,19], here we have focused our attention on the hypothalamus. This area represents indeed the neuro-endocrine interface in the brain and it is a key station for central circuits to orchestrate the maintenance of body homeostasis or allostatic also because of its high responsiveness to immune signals. Among the basic life functions controlled by the hypothalamus there are feeding, energy metabolism, and stress response [20]. The hypothalamus includes a number of nuclei that can be grouped along the antero-posterior axis in the preoptic, anterior, tuberal, and posterior (mammillary) regions. While the preoptic area contains nuclei participating in fluid homeostasis and electrolyte metabolism, reproduction and maternal behavior, and in the regulation of sleep and wakefulness, the anterior and tuberal regions contain centers controlling feeding, appetite and ingestive behavior, and stress responses (autonomic and endocrine responses) [21,22].

First, we evaluated changes in the transcription of inflammatory genes in both the anterior–tuberal and in the preoptic hypothalamus of animals exposed to cyclic food restrictions and frustration stress developing a binge-like eating behavior to look for the region specificity of the effects with respect to feeding and related behavior.

Secondly, the effect of the estrus phase was investigated in the same experimental conditions, given that food-restricted animals experiencing the frustration stress during estrus failed to develop binge-like eating behavior [23].

2. Material and methods

2.1. Subjects and diet composition

Female Sprague-Dawley rats (Charles River, Calco, Italy), weighing 200–225 g at the beginning of the experiments were used. Rats were housed under a 12-h light/dark cycle (lights on at 08:00 am) with free access to food and water for 2 weeks prior to the experiments. They were kept in a room at constant temperature (20–22 °C) and humidity (45–55%). Rats were housed individually in metal cages (30 × 30 × 30 cm). All experiments were carried out in accordance with the EC guidelines governing animal welfare and protection (EEC Council Directive 2010/63/UE), Italian legislation on animal experimentation (Decreto Legislativo n. 116, 27 January 1992) with the guidelines of the National Institutes of Health on the use and care of laboratory animals, and had the approval of the local Ethical Committee. All efforts were made to minimize animal suffering and to reduce the number of animals used in this study.

Rats were given standard food pellets and, during habituation and feeding test, highly palatable food as previously described [24,25]. The highly palatable food (3.63 kcal/g) was a paste prepared by mixing Nutella (Ferrero, Alba, Torino, Italy) chocolate cream (5.33 kcal/g; 56%, 31% and 7% from carbohydrate, fat and protein, respectively), grounded food pellets (4RF18), and water in the following weight/weight percent ratio: 52% Nutella, 33% food pellets, 15% water.

2.2. Binge eating experimental procedure

In the experiments described below (Fig. 1A) female rats were exposed (or not exposed) for 24 days to three 8-day cycles of food restriction (66% of Chow intake on days 1–4 and free-feeding on days 5–8 of each cycle) during which they were given access to palatable food for 2 h during the light cycle between 10:00 am and 12:00 pm (2 h after the onset of the light cycle) on days 5–6 and 13–14 of the first two cycles (total of 4 exposures). According to our previous experiments, where we also demonstrated that restricted and non-stressed or non-restricted and stressed animals do not show binge eating, in order to induce the impaired feeding behavior, food-restricted animals were also exposed to a frustration stress manipulation (at 10:00 am) consisting of 15 min exposure to the coffee cup containing the palatable food that was placed inside a metallic grid container and hung up on the anterior wall of the cage. Rats could see and smell the palatable food but could not access it. During this 15 min period, the rats engaged in repeated movements of the forepaws, head, and trunk, suggesting that they were attempting to reach the palatable food. Thirty-six rats (n = 18 each group) were used for behavioral test (experiment 1). Twenty-six rats were used for molecular biology studies selected from a cohort of forty animals to obtain 13 animals in estrus and 13 in non-estrus (n = 6–7) (experiment 2).

2.2.1. Experiment 1: effect of history of food restriction and frustration stress on highly palatable food intake in female rats

On the test day, we assessed palatable food intake for 2 h immediately after exposure to frustration stress. After 15 min, the palatable food cup was placed inside the cage and food intake was determined for 2 h. During the test session, we measured food intake for 15 and 120 min in stressed animals and relative controls (Fig. 1A) [24,26].
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