

COMMENTARY



Hypothalamic GRP78, a new target against obesity?

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ABSTRACT

The chaperone GRP78 (glucose related protein 78), also called BiP (binding immunoglobulin protein) is a key regulator of endoplasmic reticulum (ER) stress. We recently described that over-expression of GRP78 specifically in the ventromedial nucleus of the hypothalamus (VMH) releases hypothalamic ER stress in rodent obese models leading to weight loss, reduced hepatic steatosis and improved insulin and leptin sensitivity. The action of GRP78 is mediated by a feeding-independent mechanism involving increased sympathetic tone, augmented brown adipose tissue (BAT) thermogenesis and induction browning of white adipose tissue (WAT).

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Obesity is the consequence of elevated energy intake relative to energy expenditure. In the developed world, the prevalence of obesity and its related pathologies has increased over the last 30 years and has now reached pandemic proportions [1,2]. Thus, improving our understanding of the physiological mechanisms that regulate body weight and energy balance has become a great challenge for the scientific community.

Over last years, accumulating evidence has demonstrated that energy balance can be regulated by peripheral signals acting on the central nervous system (CNS), including the hypothalamus [3-5]. The number of studies on this topic is continuously increasing to identify new therapeutic approaches against obesity, but the precise molecular mechanisms involved remain still uncertain. Increased energy expenditure could be a target to reduce body weight [6,7], and in recent years there has been an increasing interest in the activation of the thermogenic process, especially the central control of brown adipose tissue (BAT) activity [8,9], but also in the activation of beige/brite adipocytes in the white adipose tissue (WAT), a process known as browning [7,10-12]. Theoretically, activation BAT and/or browning may represent a therapeutic strategy to combat obesity, therefore both tissues have been widely studied as promising targets against obesity and related disorders.

The hypothalamus is one of the main regulators of BAT and browning. Particularly, the ventromedial nucleus of the hypothalamus (VMH) has been shown to

be widely involved in the regulation of both processes in response several peripheral signals [12-21]. Although recent data have demonstrated that AMP-activated protein kinase (AMPK) is a key regulator of thermogenesis in the VMH [5,22], there is still a black hole in the understanding of the molecular mechanism operating in this nucleus.

The endoplasmic reticulum (ER) is a cellular place where proteins are matured, assembled and folded, and any alteration in ER homeostasis disturbs this protein processing, leading to accumulation of unfolded proteins, which triggers the unfolding protein response (UPR) [23-26]. Increasing evidence has shown a strong interaction between ER stress and the pathology of obesity. ER stress is closely related with obesity-associated insulin resistance in peripheral tissues, such as pancreas and liver [27-33]. Current evidence also indicates that obesity and overnutrition-induced inflammation causes ER stress in the hypothalamus, inducing insulin and leptin resistance and, ultimately, weight gain [18,21,34-39]. Of note, improving protein folding (i.e. chemical chaperones) recovers leptin and insulin signaling, normalizing body weight [34-37,39]. Current evidence has also shown that central ceramide-induced lipotoxicity induces ER stress leading to weight gain, glucose intolerance and decreased sympathetic tone and BAT thermogenesis [18,40]. Of note the central action of ceramides can be reversed by decreasing ER stress, specifically into the VMH [18].

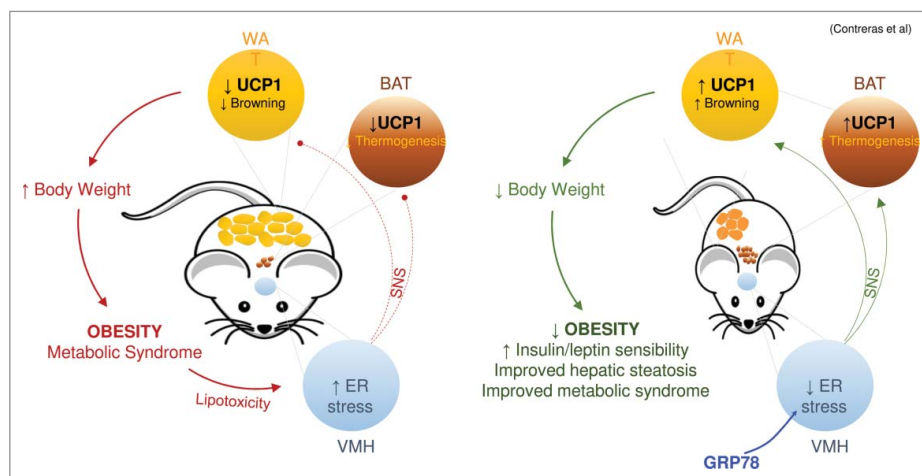


Figure 1. GRP78 in the VMH modulates BAT and WAT. Over-expression of GRP78 specifically in the VMH ameliorates hypothalamic ER stress in rodent obese models leading to weight loss, reduced hepatic steatosis and improved insulin and leptin sensitivity. The action of GRP78 in the VMH is mediated by a feeding-independent mechanism involving increased tone of the sympathetic nervous system (SNS), increased BAT thermogenesis and stimulation browning of WAT.

Despite the evidence linking hypothalamic ER stress to several metabolic actions, its potential role in the control of white fat browning and its physiological relevance remains unknown. Recent data from our group have helped to better understand the link between hypothalamic ER stress, BAT thermogenesis and WAT browning [21]. Specifically, we show that the chaperone GRP78 (glucose related protein 78), also called BiP (binding immunoglobulin protein), which is located upstream of the UPR pathway [23,25,26], acts within the VMH to exert a beneficial effect on obesity. Notably, this fact was confirmed in several types of models, such as short-term (2 months) and long-term (6 months) high fat diet (HFD)-induced obese rats, as well as in a genetic model, namely obese Zucker rats (OZR) [21]. In all these paradigms, the mechanism was common, showing feeding-independency and sympathetic control. Moreover, the fact that it also operates in OZR suggest independency of leptin signaling [21]. These results reveal that, like BAT activation, white fat browning is regulated by ER stress within the VMH and fit with the idea that stimulation of this process protects from diet induced obesity [21]. The relevance of this result is interesting because, besides decreased body weight, targeting of GRP78 elicited a marked overall improvement of the metabolic phenotype of HFD obese rats, as demonstrated by decreased adiposity, improved leptin signaling and increased insulin sensitivity (Figure 1) [21].

Despite the initial enthusiasm following the identification of BAT in adult humans [41-45], further data demonstrated that human BAT is mainly composed by beige/brite adipocytes cells rather than brown cells [46,47]. Browning of white fat has therapeutic potential to promote body fat reduction. Although several mechanisms have been

proposed [12,48,49], the neuronal pathways within the CNS controlling WAT browning have remained largely unknown. Our study provides novel evidence that amelioration of ER stress in the VMH by GRP78 is a central mechanism regulating WAT browning. Overall, these data suggest that targeting the hypothalamic control of WAT browning may be a potential strategy against obesity and associated comorbidities. In this sense, chemical chaperones, which are a common agent for mitigating ER stress [21], have the potential to improve leptin resistance in over-nutrition and overweight. For example, tauroursodeoxycholic acid (TUDCA) or 4-phenyl butyric acid (4-PBA), which ameliorate ER stress and enhances leptin sensitivity in vitro and in vivo [21,35,36], can strengthen weight loss and anorectic effects when co-administered with exogenous leptin [36]. Furthermore, 4-PBA and TUDCA have been approved by the U.S. Food and Drug Administration (FDA) and have high safety profiles in humans [50,51], thus providing an emerging therapeutic approach for metabolic diseases. Considering that our data also demonstrate that TUDCA induces BAT and browning in our HFD obese rats [21], therefore it is tempting to speculate that similar effects could be found in humans, a hypothesis that deserves further investigation.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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