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Getting a "GRiP" on Hypothalamic Endoplasmic Reticulum Stress to Combat Obesity

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The endoplasmic reticulum (ER) coordinates the synthesis, folding, and sorting of proteins for retention in the cell or for entry into the secretory pathway. Certain conditions (e.g., calcium dyshomeostasis, lipotoxicity, abnormally elevated protein synthesis) may result in protein misfolding and aberrant accumulation in the ER. This process, known as ER stress, activates the adaptive unfolded protein response (UPR), a conserved set of molecular pathways that leads to decreased protein synthesis and misfolding and to increased protein degradation and autophagy, overall aiming to restore cellular homeostasis (1,2). However, persistent activation of the UPR triggers cell death pathways. ER stress and the UPR thus play crucial roles in protein folding and cell survival. Several studies further indicate that they have broader functions in the regulation of cell physiology, including growth, differentiation, and cellular metabolism.

ER stress can have internal cellular causes (e.g., increased protein synthesis, inefficient protein folding linked to mutations) or may be triggered by factors external to cells. In particular, inflammation caused by chronic overnutrition/unhealthy diet has been proposed to be an inducer of ER stress (3–5). ER stress triggered by such external factors is currently thought to contribute to the etiology of several human diseases. For example, ER stress has emerged as a key mechanism involved in the development of obesity and type 2 diabetes (T2D), as well as in aging and age-related neurodegenerative diseases, including Alzheimer disease (3,6,7).

In obesity and T2D, chronic ER stress in peripheral tissues contributes to insulin resistance (3). Recent evidence further implicates ER stress and abnormal activation of the UPR in the hypothalamus in central leptin/insulin resistance in obesity and T2D (8–12). Hypothalamic ER stress and inflammation are intimately connected. An interesting study reported that, unlike inflammation in peripheral tissues, which progressively develops as a consequence of obesity (3), administration of a high-fat diet (HFD) to rats rapidly triggers inflammatory signaling in the hypothalamus, evident within 1–3 days of HFD and prior to substantial weight gain (13). This indicates that the central nervous system rapidly senses the effects of diet. Importantly, hypothalamic inflammation was detected in the brains of obese humans, providing clinical relevance to the findings in rodent models and further implicating hypothalamic dysfunction in the pathogenesis of obesity (13,14).

Because the hypothalamus controls various aspects of peripheral metabolism, including appetite control, energy expenditure, carbohydrate/lipid metabolism, and blood pressure, recent studies aimed to investigate whether alleviating hypothalamic ER stress and inflammation could have a beneficial impact on whole-body metabolic control, e.g., regulating peripheral glucose homeostasis (15). Indeed, transient hypothalamic ER stress induces peripheral glucose intolerance and increases plasma levels of noradrenaline in mice, whereas central inhibition of brain ER stress by a chemical chaperone, tauroursodeoxycholic acid (TUDCA), partially reversed obesity-associated metabolic and blood pressure deregulation (16).

In this issue of *Diabetes*, Contreras et al. (17) demonstrate that viral-mediated expression of the ER resident chaperone glucose-regulated protein 78 kDa (GRP78), also known as binding immunoglobulin protein (BiP), decreases hypothalamic ER stress in mice fed an HFD, causes white adipose tissue browning, and increases brown adipose tissue thermogenesis. ER stress leads to activation of three major signaling branches of the UPR, namely the PKR-like ER kinase (PERK), inositol-requiring enzyme 1 (IRE1), and

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activating transcription factor 6 (ATF6) pathways. GRP78 is a key regulator of ER homeostasis. When protein folding proceeds normally in the ER lumen, GRP78 is bound to PERK, ATF6, and IRE1 and keeps them in inactive states (Fig. 1). However, when misfolded proteins accumulate in the ER lumen, GRP78 binds misfolded proteins, thereby releasing the brake on PERK, IRE1, and ATF6 (18). Although the UPR is an adaptive process aimed to give cells the chance to recover from stress by attenuating translation and enhancing folding-related mechanisms, persistent activation of the UPR is maladaptive and blocks global protein synthesis, stimulates cell death pathways, and leads to degeneration (2). Remarkably, Contreras et al. (17) found that region-specific alleviation of ER stress in the ventromedial nucleus of the hypothalamus, a region centrally involved in regulation of brown adipose tissue thermogenesis, by GRP78 overexpression (as well as by central administration of TUDCA) was accompanied by reversion of the obese and metabolic phenotype in mice (Fig. 1). They further showed that this effect was mediated by the activation of sympathetic β3 adrenergic receptor signaling (17).

Previous studies have established GRP78 as an important player in peripheral ER stress. An elegant study demonstrated that GRP78 overexpression reduces ER stress markers in the livers of obese *ob/ob* mice (19). Moreover, GRP78 improves glucose-stimulated insulin secretion in a pancreatic cell line (20). Additionally, HFD-induced obesity and insulin resistance were found to be attenuated by adaptive activation of the UPR in *Grp78*$^{+/-}$ mice compared with wild-type littermates (21). Those studies demonstrate that GRP78 plays a key role in regulation of peripheral ER stress and glucose homeostasis. The new study by Contreras et al. (17) adds to this growing field by demonstrating

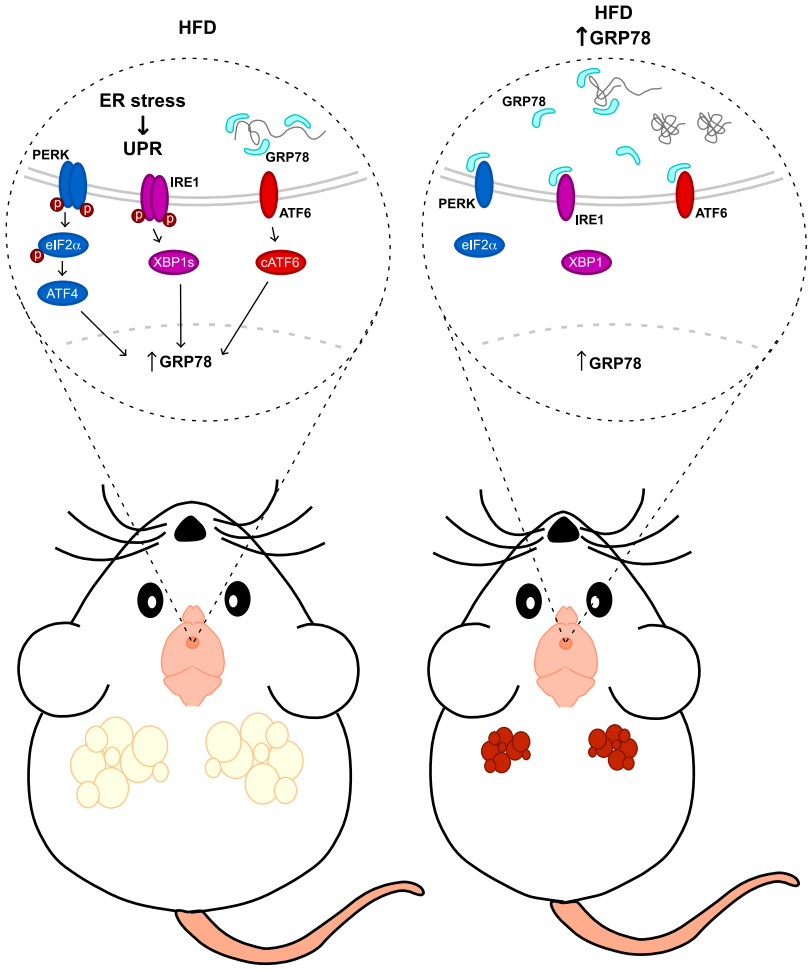

Figure 1—GRP78 alleviates hypothalamic ER stress in HFD-fed mice. In HFD-fed mice (left), ER stress causes the release of GRP78 from PERK, IRE1, and ATF6 and its binding to misfolded proteins that abnormally accumulate in the ER lumen. This leads to the UPR comprising the activation of one or more of the pathways mediated by PERK, IRE1, and ATF6. This protective process, reversible during the adaptive phase of the UPR, becomes maladaptive and detrimental to cell functions in the long term. Overexpression of GRP78 (right) in the ventromedial nucleus of the hypothalamus helps to regulate ER function via its role as a chaperone in protein folding and assembly by targeting misfolded protein for degradation and by binding of GRP78 to PERK, IRE1, and ATF6, holding them in an inactive state and alleviating the activation of the UPR.

that GRP78 plays a key regulatory role in hypothalamic ER stress in the context of obesity and other metabolic diseases.

Interestingly, hypothalamic ER stress was recently described in mouse and nonhuman primate models of Alzheimer disease (22). In mice, glucose intolerance caused by induction of experimental Alzheimer disease features was rescued when central ER stress was reduced by treatment with TUDCA (22). Alzheimer disease and other degenerative metabolic disorders are commonly associated with the accumulation of misfolded and aggregated proteins, and the identification of chaperones, such as GRP78/BiP, that play a crucial role in ER homeostasis will advance our knowledge on how to control aberrant stress signaling associated with such diseases. Hypothalamic ER stress suppression could thus represent a potential strategy to combat obesity and metabolic and other degenerative diseases.

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