Remodeling of nutrient homeostasis by unfolded protein response

メタデータ	言語: eng 出版者: 公開日: 2017-10-03 キーワード (Ja): キーワード (En): 作成者: メールアドレス: 所属:
URL	http://hdl.handle.net/2297/36892

Commentary

Remodeling of nutrient homeostasis by unfolded protein response

Toshinari Takamura

Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa, Ishikawa 920-8641, Japan

Tel: +81-76-265-2233

Fax: +81-76-234-4250

Corresponding author: Toshinari Takamura, ttakamura@m-kanazawa.jp

Word count; 1343

Number of figures; 1

The nature is unlikely to maintain systems that are detrimental for survival. Any pathway that was identified as a cause of illness must have its primary role. Endoplasmic reticulum (ER) stress, that was identified to mediate obesity-induced insulin resistance, is also no exception, and originally designed to keep nutrient homeostasis.

About one-third of all proteins is synthesized and folded into their native conformation in the ER (1). Unfortunately, as many as one-third of all newly synthesized proteins, especially those abundant in the cells, is misfolded, and should be fixed or cleared during the maturation processes (2). ER is also responsible for protein quality control (3). The burden of unfolded proteins in the ER lumen is identified as an ER stress by several ER stress sensors, known as ATF6, PERK and IRE-1. The ER stress sensors trigger cellular adaptation for unfolded protein accumulation to restore normal function of the cell, which is called as the unfolded protein response (UPR). The UPR initially 1) activates signaling pathway inducing a large number of ER chaperones that assist protein folding, 2) halts protein translation and transcription, and 3) ubiquitinates and

degrades unfolded proteins by 26S proteasome and through autophagy, the process called as ER-associated degradation (ERAD). If these adaptations fail to keep cell homeostasis, the UPR 4) commits the cell to a pathway of apoptosis or dedifferentiation (3).

Chronic UPRs are causally linked to the pathogenesis of human metabolic diseases such as obesity and type 2 diabetes. Accumulating evidence suggests that obesity promotes ER stress, which is detected as an enhanced UPR signaling, that activates c-jun N terminal kinase (JNK) and impairs insulin signaling at the level of IRSs in the liver and adipose tissue (4) (Figure). However, it still remains unknown what signals activate UPR under this condition. Defective autophagy (5) and proteasome dysfunction (6) have recently been proposed as molecular links between obesity and ER stress (Figure). In obesity scenario, ER stress in the liver and adipose tissue is assumed to cause insulin resistance and associated hyperinsulinemia (Figure). Conversely, it is possible to assume that hyperinsulinemia comorbid in obesity causes ER stress. Indeed, previous in vitro studies suggest that insulin upregulates UPR markers in

cultured murine peritoneal macrophages (7) and human neuroblastoma cells (8). In this issue of Diabetes (9), Boden et al. proved an in vivo role of insulin as the inducer of ER stress in human adipose tissue. Boden et al. performed 4 h and 8 h euglycemic (5.5 mmol/l) clamps with 3 different insulin concentrations (basal, medium postprandial and high postprandial, ranging from ~ 35 to ~ 1450 pmol/l) and examined biopsy samples of subcutaneous adipose tissue before and after the clamps in 16 healthy overweight~obese subjects. At least the high postprandial levels of insulin increased the UPR markers such as GRP78, Xbp-1s, ATF-4, nuclear ATF-6 and phospho-eIF2α at both time points in the adipose tissue samples, whereas acutely lowering insulin to below basal levels decreased the UPR markers. Insulin is an anabolic hormone and enhances global protein synthesis. Boden et al. hypothesized that insulin robustly increases protein synthesis large enough to exceed the ER folding capacity, and thereby produces ER stress via accumulation of misfolded/unfolded and ubiquitinated proteins. This hypothesis was supported by additional examinations as follows: 1) Among 25 proteins increased after 4 h of

euglycemic-hyperinsulinemia, 5 ubiquitination pathway proteins increased by 1.8-3.0 folds; 2) ubiquitinated proteins were accumulated in the adipose tissue after 4 h of euglycemic-hyperinsulinemia; 3) the ER stress pathway and the ubiquitination pathway were upregulated in a canonical pathway analysis of mRNA and protein data; 4) insulin-induced posttranslational protein modifications, including acetylations, methylations, nitrosylations, succinylations and ubiquitinations, were identified in 8 proteins by mass spectrometry. Hyperinsulinemia increases glucose uptake and intracellular glucose metabolism, which lead to generation of reactive oxygen species (ROS) in mitochondria. Thus, Boden et al. ruled out the possible involvement of glucose metabolism-associated oxidative stress in the insulin-induced ER stress by clamp studies with identical degrees of hyperinsulinemia and different rates of glucose infusion, hyperglycemia and euglycemia. Under the same degree of hyperinsulinemic clamp, steady state glucose levels did not significantly affect the induction of mRNA for UPR markers. Increased rate of glucose infusion resulted in enhanced glucose uptake into the adipose tissue, but did not

upregulate oxidative stress markers, such as urinary excretion of 8-iso PGF2α as well as mRNA levels of Nrf2, HO1, VEGF, and inflammatory markers involved in NFκB and JNK pathways, and phosphorylation of JNK1 in the adipose tissue. Further complementary studies were conducted in vitro in cultured 3T3-L1 adipocytes: insulin at a dose of 10 nM induced mRNA and protein levels of the UPR markers.

Based on these findings, Boden et al. concluded that acute physiological increases in circulating insulin produces ER stress and UPR possibly via enhancement of protein biosynthesis and posttranslational protein modification, which leads to accumulation of unfolded/misfolded and ubiquitinated proteins, rather than via glucose uptake and subsequent oxidative stress (Figure). The most precious value of this paper is that Boden et al. proved this conclusion in a humans study. The observations in human study and biopsy samples are definitely of great value. Their hypothesis has clinical implications and may facilitate discussion that raises significance of both pathologic and physiologic ER stress to keep energy homeostasis.

However, limitation and difficulty in human-targeted experiments might have resulted in individual differences and small number of samples (data from only narrow part of the subjects). Therefore, some of their data could be further confirmed in large-scale clinical studies, and molecular bases also would better be addressed by additional cellular experiments to support their conclusion fully. Concerning the pathway involved in the insulin-induced ER stress, the observations of enhanced protein biosynthesis of several insulin-responsive proteins and protein modifications are not comprehensive proofs for burden of misfolded/unfolded proteins. More reliable proof of protein burden leading to ER stress may be western blotting of ubiquitinated proteins and an electron microscopic image of expansion and disorganization of ER membranes. Interestingly, insulin-induced accumulation of the ubiquitinated proteins in the adipose tissue seems marginal and variable in their study. This suggests that, beside unfolded protein accumulation, other pathways directly altering ER homeostasis also should be taken into account. These pathways may also be candidate pathologic conditions mediating ER stress in obesity, and may involve

oxidative stress (10), hypoxia (11) and toxic lipid (12).

To completely exclude involvement of glucose uptake in the insulin-induced ER stress, it should be confirmed that glucose transport inhibitors do not cancel the insulin-induced ER stress in 3T3-L1 adipocytes.

If the insulin-mediated UPR is dependent on enhanced protein biosynthesis, accumulation of ubiquitinated protein precedes the onset of UPR in the 3T3-L1 adipocytes cultured with insulin. Also, the insulin-induced ER stress must be canceled with protein biosynthesis inhibitors. In addition to enhanced protein biosynthesis, autophagy (5) and proteasome (6) are candidate targets of insulin to induce ER stress, because insulin impairs their function as observed in the state of obesity (Figure).

Concerning the significance of the present findings in the cellular and body homeostasis, Boden et al. postulate that insulin-induced UPR may relieve the ER stress and its associated insulin resistance. On the other hand, they pay caution to unrelieved ER stress and insulin resistance caused by long-lasting hyperinsulinemia owing to excessive calorie intake or in diabetic patients treated

with high-dose insulin (Figure). An important issue that should be proved is the net effects of insulin on the balance between UPR-mediated relief of ER stress and UPR-induced insulin resistance. Evaluation of some signs of UPR-induced insulin resistance, for example, JNK activation and decreased levels of insulin receptor substrates (6), might help understanding which direction the UPR remodels a cell toward either recovery or illness.

Finally, insulin is one of the key players in accelerating aging (13). In this regard, it would be possible to assume that insulin resistance itself can be a compensatory adaptation to avoid cellular aging caused by excessive insulin signaling. The study by Boden et al. posed several important ‘black boxes’ worth being unraveled in order to understand both pathological and physiological ER stresses to remodel nutrient homeostasis.

ACKNOWLEDGMENTS

T.T. was supported by Grants-in-Aid from the Ministry of Education, Culture,

Sports, Science, and Technology of Japan, and research grants from Novo Nordisk, Eli Lilly, and Sanofi-Aventis.

References

1. Ghaemmaghami S, Huh WK, Bower K, Howson RW, Belle A, Dephoure N, O'Shea EK, Weissman JS: Global analysis of protein expression in yeast. Nature 2003;425:737-741

2. Schubert U, Anton LC, Gibbs J, Norbury CC, Yewdell JW, Bennink JR: Rapid degradation of a large fraction of newly synthesized proteins by proteasomes. Nature 2000;404:770-774

3. Walter P, Ron D: The unfolded protein response: from stress pathway to homeostatic regulation. Science 2011;334:1081-1086

4. Yalcin A, Hotamisligil GS: Impact of ER protein homeostasis on metabolism. Diabetes 2013;62:691-693

5. Yang L, Li P, Fu S, Calay ES, Hotamisligil GS: Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. Cell Metab 2010;11:467-478

6. Otoda T, Takamura T, Misu H, Ota T, Murata S, Hayashi H, Takayama H, Kikuchi A, Kanamori T, Shima KR, Lan F, Takeda T, Kurita S, Ishikura K, Kita Y,

Iwayama K, Kato K, Uno M, Takeshita Y, Yamamoto M, Tokuyama K, Iseki S, Tanaka K, Kaneko S: Proteasome dysfunction mediates obesity-induced endoplasmic reticulum stress and insulin resistance in the liver. Diabetes 2013;62:811-824

7. Misra UK, Pizzo SV: Up-regulation of GRP78 and antiapoptotic signaling in murine peritoneal macrophages exposed to insulin. Journal of leukocyte biology 2005;78:187-194

8. Inageda K: Insulin modulates induction of glucose-regulated protein 78 during endoplasmic reticulum stress via augmentation of ATF4 expression in human neuroblastoma cells. FEBS letters 2010;584:3649-3654

9. Boden G, Cheung P, Salehi S, Homko C, Loveland-Jones C, Jayarajan S, Stein TP, Williams KJ, Liu ML, Barrero CA, Merali S: Insulin regulates the unfolded protein response (UPR) in human adipose tissue. Diabetes 2013;

10. Malhotra JD, Kaufman RJ: Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxidants & redox signaling 2007;9:2277-2293

11. Hosogai N, Fukuhara A, Oshima K, Miyata Y, Tanaka S, Segawa K, Furukawa S, Tochino Y, Komuro R, Matsuda M, Shimomura I: Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. Diabetes 2007;56:901-911

12. Wei Y, Wang D, Topczewski F, Pagliassotti MJ: Saturated fatty acids induce endoplasmic reticulum stress and apoptosis independently of ceramide in liver cells. American journal of physiology Endocrinology and metabolism 2006;291:E275-281

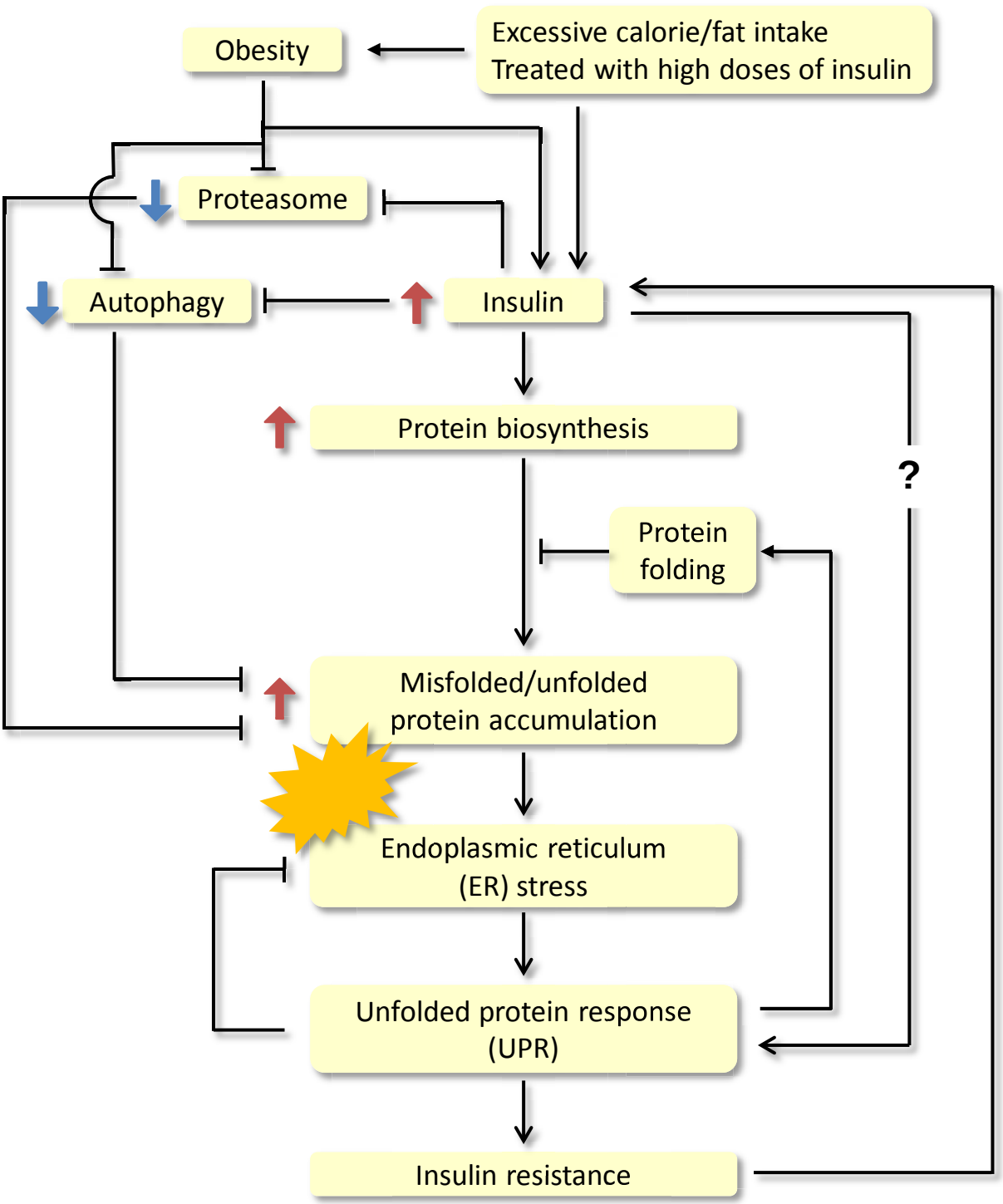
13. Russell SJ, Kahn CR: Endocrine regulation of ageing. Nature reviews Molecular cell biology 2007;8:681-691

Figure legend

Figure 1

Impact of hyperinsulinemia as a consequence and cause of obesity-associated ER stress on nutrient homeostasis

Hyperinsulinemia caused by obesity and overnutrition produces ER stress and UPR, by way of enhanced protein biosynthesis and subsequent accumulation of misfolded/unfolded proteins. In addition to enhanced protein biosynthesis, proteasome and autophagy are candidate targets of insulin to induce ER stress because insulin could impair their function as observed in the state of obesity. Also, other yet unrecognized pathways, independent of misfolded/unfolded protein accumulation, might be involved in the insulin-induced UPR. It is an open question for future study whether UPR causes insulin resistance or relieves ER stress.


Obesity
Excessive calorie/fat intake
Treated with high doses of insulin
Proteasome
Autophagy
Insulin
Protein biosynthesis
?
Protein folding
Misfolded/unfolded protein accumulation
Endoplasmic reticulum (ER) stress
Unfolded protein response (UPR)
Insulin resistance