Endoplasmic Reticulum Stress: Another Link Between Obesity and Insulin Resistance/Inflammation?

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Obesity, which has reached epidemic proportions in the U.S. and is increasing worldwide, is closely associated with insulin resistance (peripheral and hepatic) and with a state of low-grade inflammation, the latter characterized by elevated levels of proinflammatory cytokines in blood and tissues (1). Insulin resistance and inflammation in turn are associated with type 2 diabetes, hypertension, atherogenic dyslipidemias, and disorders of blood coagulation and fibrinolysis, all of which are independent risk factors for the development of atherosclerotic vascular disease, including heart attacks, strokes, and peripheral arterial disease (1).

WHAT IS THE CONNECTION BETWEEN OBESITY AND INSULIN RESISTANCE AND INFLAMMATION?

The reason why obesity is so closely associated with insulin resistance and inflammation is not completely understood. On one hand, there is evidence to show that blood levels of free fatty acids (FFAs) play an important role in the development of obesity-related insulin resistance and inflammation (rev. in 2). Plasma FFA levels are increased in most obese people, and acutely raising plasma FFA levels increases insulin resistance as well as the expression of proinflammatory cytokines, whereas lowering plasma FFA levels reduces insulin resistance. Mechanisms involved in FFA-induced insulin resistance include accumulation (in muscle and liver) of lipids and lipid intermediates such as diacylglycerol, activation of several protein kinase C isoforms, reduction in tyrosine phosphorylation of the insulin receptor substrates 1 and 2 (2), and activation of the proinflammatory nuclear factor-κB pathway (3,4). On the other hand, not all obese insulin-resistant subjects have elevated plasma FFA levels, and normalizing the elevated plasma FFA levels in insulin-resistant obese patients with type 2 diabetes improves but does not normalize insulin sensitivity (5). This suggests that there are probably other causes for obesity-related insulin resistance and inflammation. One of these appears to be endoplasmic reticulum (ER) stress.

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WHAT IS ER STRESS AND WHY IS IT SUSPECTED TO PLAY A ROLE IN OBESITY-ASSOCIATED INSULIN RESISTANCE AND INFLAMMATION?

The ER is a major site for protein as well as for lipid and sterol synthesis (6). Ribosomes attached to the ER membranes release newly synthesized peptides into the ER lumen, where chaperones and foldases assist in the proper posttranslational modification and folding of these peptides (6). The properly folded proteins are then released to the Golgi complex for further modification before they are transported to their final destination. If the influx of misfolded or unfolded peptides exceeds the ER folding and/or processing capacity, ER stress ensues. Three proximal ER stress sensors have been identified. They are inositol-requiring enzyme (IRE)-1, PKR-like ER-regulating kinase (PERK), and activating transcription factor (ATF)-6. These sensors trigger activation of pathways that alleviate ER stress, termed the unfolded protein response. The unfolded protein response can achieve this by slowing protein synthesis and/or by turning up the production of protein chaperones needed for proper protein folding or, if unsuccessful, by degrading the unfolded proteins (6).

Excess nutrient intake is the main cause for obesity, and several recent studies have implicated ER stress as an early consequence of nutrient excess and a cause for the development of insulin resistance and inflammation. For instance, chronic excess nutrient intake has been shown to cause ER stress as well as insulin resistance and inflammation in adipose tissue of *ob/ob* mice and in mice fed high-fat diets, whereas overexpression of some chaperone genes or administration of chaperone proteins reduced ER stress, insulin resistance, and inflammation in rodents (rev. in 7). Furthermore, it has been recently shown that ER stress is increased in subcutaneous fat of obese human subjects (8).

The cause for increased ER stress in fat is not known, but based on animal data, excess nutrient intake appears to be a likely possibility. The adipose tissue has to take up and store excess calories as fat and, hence, needs to synthesize many proteins to meet this challenge. In addition, the massive expansion of adipose tissue requires synthesis of structural proteins. Fatty acids, which are an important part of overnutrition and which have been shown to induce ER stress in cultured hepatocytes and pancreatic β-cells (9), are likely to be among the agents causing ER stress.

HOW CAN ER STRESS CAUSE INSULIN RESISTANCE AND INFLAMMATION?

ER stress has been demonstrated to trigger activation of several serine/threonine kinases, including c-jun NH$_2$-terminal kinase (JNK) and IκB-α kinase (IKK). For instance, ER stress leads to formation of the IRE-1α-TRAF 2 complex, which results in phosphorylation and activation of

IKK. IKK phosphorylates and inactivates IκB-α, resulting in activation and nuclear translocation of nuclear factor κB, which is a key promoter of inflammation (10). The IRE-1α-TRAF 2 complex also phosphorylates and activates JNK, which induces the expression of proinflammatory cytokines and induces insulin resistance via serine phosphorylation of insulin receptor substrates 1 and 2 (11).

ER stress is also a major source for the production of reactive oxygen species (ROS). This can occur via activation of protein disulfide isomerase (PDI), an enzyme which catalyzes disulfide bridge formation and in the process generates ROS. ROS are known to promote insulin resistance and inflammation (6,10). Thus, the ER may be a proximal site that senses nutritional excess and translates it into metabolic and inflammatory responses.

ER STRESS IN HUMAN ADIPOSE TISSUE

Several recent reports support the concept of a close dynamic relationship between obesity and ER stress in human subjects. Thus, ER stress has been demonstrated in adipose tissue of obese insulin-resistant nondiabetic subjects (8,12), and in this issue of *Diabetes* Gregor et al. describe the effects of bariatric surgery on ER stress (13). These authors studied 11 obese men and women before and again 1 year after gastric bypass (Roux-en-Y) surgery. They found that several markers of ER stress including GRP78 and XBP1s mRNA and the phosphorylated forms of eIF2α and JNK-1 proteins all had decreased significantly 1 year after surgery, while liver biopsies from a subset of four patients showed reduced staining for GRP78 and eIF2α proteins (13).

As is often the case, these interesting findings raise new questions. Most importantly, it would be important to know what was responsible for the decrease in ER stress in these obese individuals after surgery. Was it the decrease in nutrient intake resulting in reduced oxidative stress and reduced need to synthesize proteins to metabolize and store excess calories? Early measurements, before significant weight loss occurred, would have been helpful to answer this question. Or was it the loss of adipose tissue and an associated decrease in the release of adipokines and FFAs? Supporting that possibility was the finding that ER stress, albeit reduced, was still present 1 year after surgery even though caloric intake was presumably below normal. Or, what seems likely, was it a combination of both? Also, did the decrease in ER stress contribute to the decrease in insulin resistance and, if so, by what mechanism? Thus, there remain many unanswered questions. However, this is a new field of research, which is attracting much attention, and therefore it can be expected that many of these questions will soon be addressed in other studies.

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