The central role of the endoplasmic reticulum (ER) stress on the development of obesity and type 2 diabetes

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Abstract

The obesity epidemic becomes serious threat to public health in the 21st century. Obesity creates significant health risks for a variety of metabolic disorders including type 2 diabetes and cardiovascular diseases. The endoplasmic reticulum (ER) is a central organelle for protein biosynthesis, folding, and traffic. Perturbations in ER homeostasis (ER stress) and associated signaling cascades (the unfolded protein response, UPR) have been implicated in a variety of metabolic disorders, such as obesity and type 2 diabetes. X-box binding protein 1 (XBP1s) is one of key signaling molecules in the UPR and plays a crucial role in hepatic glucose homeostasis via multiple "cross-talk" with other signaling molecules such as p38 MAPK, IKKβ, PI3K, Brd7 and FoxO1. Obesity is characterized by central leptin resistance. In an attempt to identify compounds that could reverse leptin resistance, two natural compounds, celastrol and withaferin A, have been discovered to suppress food intake and lead to healthy body weight loss in leptin-resistant obese mice by reducing hypothalamic ER stress and increasing leptin sensitivity. Therefore, intervening in ER stress and modulating signaling components of the UPR would provide promising therapeutics for the treatment of human metabolic diseases.