MINI-REVIEW

Possible involvement of endoplasmic reticulum stress in obesity associated with leptin resistance

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Abstract : Leptin is a hormone, which plays a central role in inhibiting food intake and body weight gain. Leptin is secreted from exocrine as well as endocrine cells. Circulating leptin activates JAK-STAT tyrosine kinases through Ob-Rb leptin receptor in the hypothalamus and brain stem. In recent years, "leptin resistance" has been considered to be one of the main causes of obesity. However, the detailed mechanisms of leptin resistance are not well understood. Recently, we hypothesized possibility that endoplasmic reticulum (ER) stress is involved in leptin resistance. In the present manuscript, we would like to mention possible mechanisms of ER stress-induced leptin resistance and possible implication in obesity. In addition, pathophysiological role of leptin's action in regulating endocrine as well as exocrine functions at the state of ER stress are discussed. J. Med. Invest. 56 Suppl. : 296-298, December, 2009

Keywords **:** *leptin, endoplasmic reticulum stress, obesity, STAT3*

INTRODUCTION

Obesity is associated with diseases such as Type 2 diabetes, cardiovascular disease, and hypertension. Thus, elucidation of the mechanisms of obesity is important subject. However, the molecular mechanism of obesity is not well understood. At such a circumstances, Friedman and colleagues identified the hormone "leptin" (1), which was found to be an important circulating signal for repressing food intake and body weight through its actions in the brain (hypothalamus) (2). Leptin activates JAK2-STAT3 tyrosine kinases through the Ob-Rb leptin receptor (3) in the hypothalamus and brain stem (4, 5). As leptin can repress food intake and enhances energy expenditure, it was initially expected that leptin is useful for treating obesity. However, it was found that increased levels of circulating leptin in obese mice and the animals did not show a decrease in food intake (6). In addition, the effect of leptin therapy in obese patients was reported to be modest (7). Overall, these results led to the idea that "leptin resistance" is involved in obesity (8).

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ER STRESS IN OBESITY ASSOCIATED WITH LEPTIN RESISTANCE

As noted above, elucidating the mechanisms of "leptin resistance" is important subject for treating obesity (9). In these circumstances, we recently found that one of the mechanisms of leptin resistance is mediated through endoplasmic reticulum (ER) stress (10). Stress signals, which impair ER function, will lead to an accumulation of unfolded proteins (which will result in ER stress). Accumulation of unfolded proteins is toxic to cells and we hypothesized possibility that ER stress would be

involved in leptin resistance. We found that ER stress-inducing reagents inhibited leptin-induced phosphorylation of STAT3 (10). Thus, it is suggested that ER stress would inhibit leptin's signal. As ER stress was reported to be increased in obesity (11), our results would provide basic mechanisms of obesity associated with leptin resistance (Fig 1). Considering the hypothesis, similar results were recently reported using mouse model of obesity (12-14), and it would be an interesting subject to further evaluate the mechanisms of obesity linking ER stress.

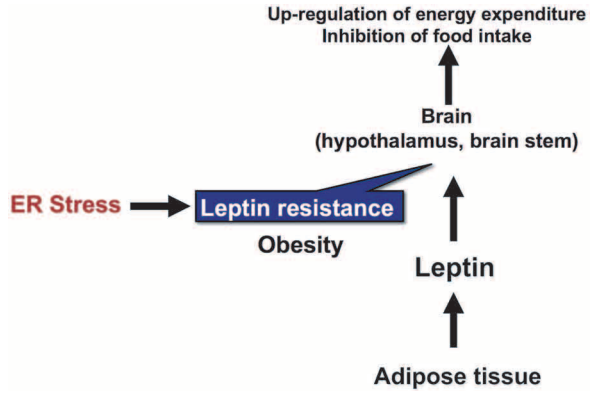

Figure 1 Possible involvement of ER stress in leptin resistance (obesity)
Leptin represses food intake and body weight through its actions in the brain. "leptin resistance" is a causative condition of obesity and we and other groups have recently suggested that ER stress would be involved in leptin resistance.

PERSPECTIVES

Further understanding of ER stress-induced leptin resistance may be critical subject for clarifying the molecular mechanism/appropriate pharmacological treatment of obesity. Interestingly, mice deficient in ER stress-related genes (XBP-1 and PERK) have been reported to result in abnormalities in exocrine pancreas and salivary gland (15, 16). Leptin is secreted from exocrine as well as endocrine cells such as gastric cells (17) or adipocyte (18). Moreover, leptin has been shown to modulate pancreatic functions (19, 20). Thus, it would be an interesting subject to clarify pathophysiological role of leptin's action in regulating endocrine as well as exocrine function in disease states involving ER stress in future studies.

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