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Obesity has been linked to endoplasmic reticulum (ER) stress, which contributes to the development of obesity-associated diseases such as type 2 diabetes. However, the mechanisms underlying this were unclear. Hotamisligil and colleagues now show that changes in lipid metabolism in obesity cause ER stress by interfering with protein folding through a mechanism involving lipids.

The authors first purified ER from mouse livers and analysed protein expression. Many proteins were differentially regulated in lean and obese mice; for example, enzymes involved in lipid metabolism were upregulated in obese mice, as were genes encoding lipid synthesis proteins. Unexpectedly, overall protein synthesis was not upregulated. Furthermore, the ER from liver cells of lean and obese mice differed in fatty acid composition and in the ratio of phosphatidylcholine (PtdCho) to phosphatidylethanolamine (PtdEtn). The increased conversion of PtdEtn to PtdCho in obese mice, leading to a high PtdCho/PtdEtn ratio, was not caused by high lipid consumption but instead by increased PtdCho synthesis.

Previous studies had suggested that PtdCho can interfere with the activity of Ca^{2+} pumps, and a recent report also linked changes in sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA) levels to ER stress. As Ca^{2+} is important for chaperone function and thus protein folding, these changes in lipid metabolism could compromise protein folding, leading to ER stress. Indeed, adding PtdCho to liver-derived microsomes *in vitro*, or overexpressing PtdEtn *N*-methyltransferase (*Pemt*; which converts PtdCho to PtdEtn) *in vitro*, significantly inhibited SERCA function and, consequently, Ca^{2+} transport into the ER.

To confirm this *in vivo*, the authors depleted *Pemt* in the livers of obese mice. The consequent reduction of PtdCho/PtdEtn led to increased Ca^{2+} transport in the ER, decreased expression of hepatic ER stress indicators, suppression of genes involved in hepatic lipogenesis and improved glucose homeostasis (a phenotype associated with decreased ER stress in obese mice). Similar findings were obtained by overexpression of *Serca* in obese mice.

These observations provide surprising insights into the mechanisms that give rise to ER stress in obesity, suggest that specific alterations in lipid metabolism are crucial in pathogenesis and offer new therapeutic targets for obesity-associated diseases.

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ORIGINAL RESEARCH PAPER Fu, S. *et al.* Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. *Nature* 1 May 2011 (doi:10.1038/nature09968)
FURTHER READING Park, S. W. *et al.* Sarco(endo)plasmic reticulum Ca^{2+}-ATPase 2b is a major regulator of endoplasmic reticulum stress and glucose homeostasis in obesity. *Proc. Natl Acad. Sci. USA* **107**, 19320–19325 (2010)