OBESITY

**HSP60 INTEGRATES
CENTRAL CROSSTALK**

Obesity is associated with mitochondrial dysfunction in the hypothalamus resulting from decreased levels of the mitochondrial chaperone Hsp60, a new study by Kleinridders *et al.* reports. The alterations in mitochondrial function further increase insulin and leptin resistance, thereby potentially worsening the metabolic consequences of obesity.

Insulin and leptin interact synergistically in the hypothalamus to control appetite and energy expenditure, and both insulin and leptin resistance have been associated with mitochondrial dysfunction.

“The mitochondrial chaperone Hsp60 is a crucial protein for the maintenance of mitochondrial integrity and cell viability,” says senior investigator C. Ronald Kahn (Harvard Medical School). “Leptin has been shown to modulate the expression of Hsp60 *in vitro*, so we decided to look at whether Hsp60 might be modulated in the hypothalamus of obese and diabetic, obese mice and its regulation by leptin.”

Using various mouse models, the investigators could demonstrate decreased Hsp60 expression in diabetic brains in the presence of mitochondrial dysfunction and insulin resistance. The decreased levels of Hsp60 in obese, diabetic mice resulted from disrupted leptin signalling and were restored by leptin treatment. Of note, gene expression analysis of dissected human brain samples showed that patients with type 2 diabetes mellitus also exhibit decreased central expression of HSP60. “More importantly, we show that Hsp60 dysregulation plays a causal role in hypothalamic insulin resistance by inducing mitochondrial dysfunction and oxidative stress,” explains lead author André Kleinridders. “We think that leptin signalling, by modulating mitochondrial activity via Hsp60, impacts hypothalamic insulin signalling. Ultimately, our findings point to a novel role for Hsp60 as an integrator of leptin and insulin crosstalk in the hypothalamus.”

“As we cannot directly study hypothalamic metabolism in humans *in vivo*, our hypothesis will be hard to test in man,” reflects Kahn. “However, agents that increase HSP60 expression might overcome this difficulty and could prove useful in the treatment of the metabolic syndrome.”

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