# 論　文　内　容　要　旨

HOMOCYSTEINE CAUSES NEURONAL LEPTIN RESISTANCE AND ENDOPLASMIC RETICULUM STRESS

（ホモシステインは神経細胞におけるレプチン抵抗性と小胞体ストレスを誘導する）

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# ABSTRACT

This research is mainly based on our previous findings about the relation between homocysteine and leptin resistance in order to develop a novel compound for obesity treatment.

Leptin is a 16-kDa hormone secreted from the adipose tissue and has important role as energy and appetite regulator. Leptin works by binding to its receptor and then through JAK-STAT signalling pathway. When this JAK-STAT pathway is disrupted, leptin signal cannot transmit optimally, and there should be a condition called “leptin resistance”. This condition is mentioned as one of the factors causing obesity. Nevertheless, the mechanisms of leptin resistance remain unknown. In the previous study, our group reported that Endoplasmic Reticulum (ER) stress induced leptin resistance (Hosoi T., et al. 2008). ER stress occurs because of the accumulation of the unfolded proteins in the ER membrane. When this happens, the unfolded protein response (UPR) will take over in order to normalize the function of the ER. The activation of leptin signal was evaluated by Western blot analysis using a phospho (Tyr705) signal transducer and the activator of transcription factor (STAT3) antibody. ER stress blatantly inhibited leptin-induced STAT3 phosphorylation.

In the previous study, our group also reported that homocysteine might induce ER stress and caused leptin resistance. Homocysteine activates UPR in neuronal cells leading to increase the expression of GRP78/BiP as well as HERP, the ER stress response gene. We also examined whether homocysteine has a toxicity effect on the neuronal cells by CCK8 and LDH assay. We hypothesized that homocysteine caused cell death and then inhibited the JAK-STAT signaling pathway of leptin.

Together, these findings suggest that the mechanism of leptin resistance is gained from inducing ER stress.