Nardilysin in hepatocyte regulates adaptive thermogenesis in brown adipose tissue through the control of skin blood flow.

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Adaptive thermogenesis is enhanced not only by cold exposure but also by feeding, which is considered as a partial defense mechanism against obesity. We have previously demonstrated that whole-body knockout mice of a metallopeptidase nardilysin (NRDC) show hypothermia and cold intolerance. Despite these phenotypes, NRDC-deficient mice (NRDC-KO) show enhanced adaptive thermogenesis in brown adipose tissue (BAT), which is due to the increased heat dissipation. Here we found that NRDC expression in the liver is increased by fasting and decreased by re-feeding in wild-type mice. To elucidate the liver-specific role of NRDC in energy metabolism, we established hepatocyte-specific NRDC deficient mice (LKO). Unexpectedly, LKO showed an enhanced BAT thermogenesis and whole-body energy expenditure, indicating the role of NRDC in inter-organ network of liver and BAT. Notably, the phenotypic difference between control and LKO was eliminated by hepatic vagotomy or the elevation of ambient temperature to thermoneutrality (30℃), suggesting that hepatic NRDC regulates BAT thermogenesis via the nervous control of heat dissipation. Indeed, LKO showed a significant increase in skin blood flow of the plantar at room temperature (23℃). Together, diet controls NRDC expression in liver, which in turn regulates adaptive thermogenesis in BAT through the control of skin blood flow.