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## Differential pre-mRNA splicing regulates Nnat isoforms in the hypothalamus after gastric bypass surgery in mice.

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### Abstract

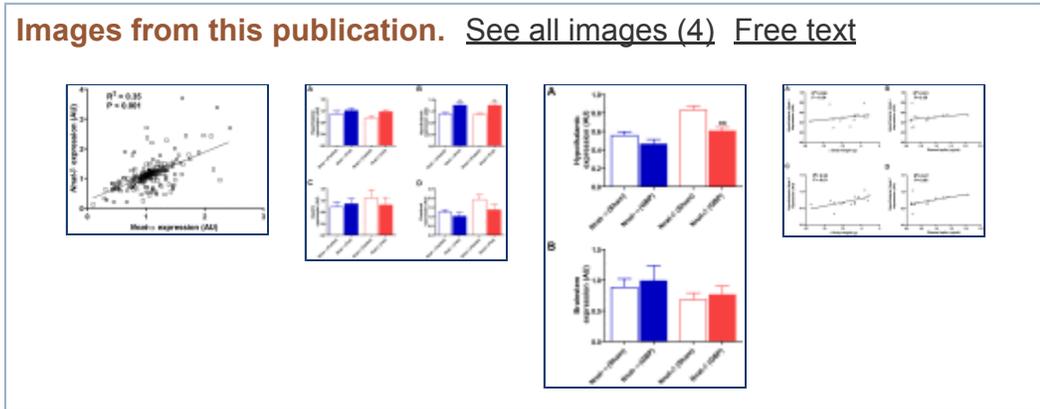
**BACKGROUND:** Neuronatin (NNAT) is an endoplasmic reticulum proteolipid implicated in intracellular signalling. Nnat is highly-expressed in the hypothalamus, where it is acutely regulated by nutrients and leptin. Nnat pre-mRNA is differentially spliced to create Nnat- $\alpha$  and - $\beta$  isoforms. Genetic variation of NNAT is associated with severe obesity. Currently, little is known about the long-term regulation of Nnat.

**METHODS:** Expression of Nnat isoforms were examined in the hypothalamus of mice in response to acute fast/feed, chronic caloric restriction, diet-induced obesity and modified gastric bypass surgery. Nnat expression was assessed in the central nervous system and gastrointestinal tissues. RTqPCR was used to determine isoform-specific expression of Nnat mRNA.

**RESULTS:** Hypothalamic expression of both Nnat isoforms was comparably decreased by overnight and 24-h fasting. Nnat expression was unaltered in diet-induced obesity, or subsequent switch to a calorie restricted diet. Nnat isoforms showed differential expression in the hypothalamus but not brainstem after bypass surgery. Hypothalamic Nnat- $\beta$  expression was significantly reduced after bypass compared with sham surgery ( $P=0.003$ ), and was positively correlated with post-operative weight-loss ( $R(2)=0.38$ ,  $P=0.01$ ). In contrast, Nnat- $\alpha$  expression was not suppressed after bypass surgery ( $P=0.19$ ), and expression did not correlate with reduction in weight after surgery ( $R(2)=0.06$ ,  $P=0.34$ ). Hypothalamic expression of Nnat- $\beta$  correlated weakly with circulating leptin, but neither isoform correlated with fasting gut hormone levels post- surgery. Nnat expression was detected in brainstem, brown-adipose tissue, stomach and small intestine.

**CONCLUSIONS:** Nnat expression in hypothalamus is regulated by short-term nutrient availability, but unaltered by diet-induced obesity or calorie restriction. While Nnat isoforms in the hypothalamus are co-ordinately regulated by acute nutrient supply, after modified gastric bypass surgery Nnat isoforms show differential expression. These results raise the possibility that in the radically altered nutrient and hormonal milieu created by bypass surgery, resultant differential splicing of Nnat pre-mRNA may contribute to weight-loss.

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