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AgRP neurons: a switch between peripheral carbohydrate and lipid utilization

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AgRP/NPY neurons are critical regulators of body weight and food intake. Concordant with their orexigenic effects, it is expected that AgRP ablation leads to the appearance of a lean phenotype. In the current issue of *The EMBO Journal*, Joly-Amado *et al* (2012) describe an obese phenotype in a model of AgRP-ablated mice, and link it to a shift in metabolic profile in efferent tissues such as the liver, muscle and pancreas.

Hypothalamic AgRP/NPY neurons are known to play a key role in the regulation of body weight and food intake. With the advent of 'toxin-receptor mediated cell knockout' technology, several reports have tried to address the physiological relevance of this set of neurons. The ablation of Agrp-expressing neurons has different consequences depending on the age of the mice. Thus, in the neonatal stage, temporal deletion of AgRP neurons by diphtheria toxin

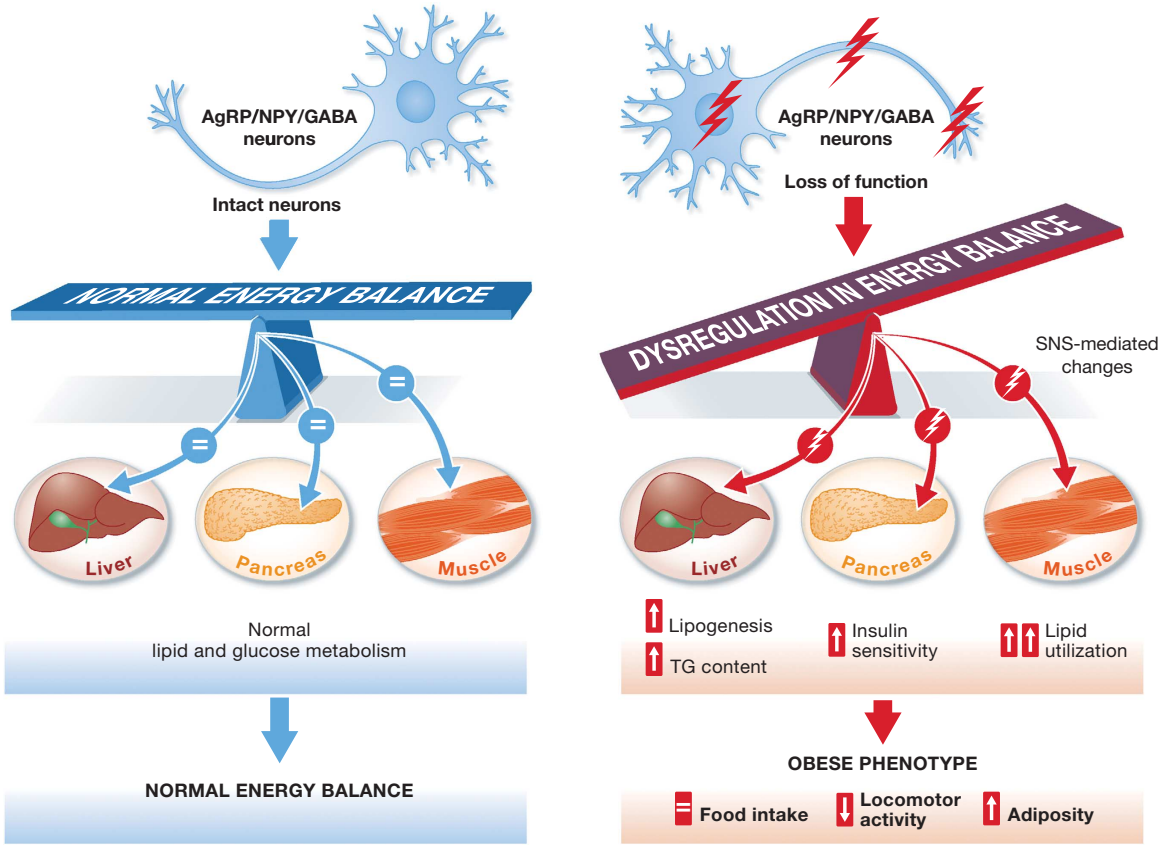

Figure 1 AgRP neurons are essential for normal energy homeostasis. AgRP neurons play a critical role in the regulation of energy balance. Manipulation of these hypothalamic neurons causes changes in the normal phenotype. Joly-Amado *et al* (2012) describe that AgRP deletion in the neonatal stage brings about the appearance of an obese phenotype in adulthood. AgRP ablation promotes changes in efferent tissues that lead to an increase in adiposity.

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(DT) injection has no major effects on energy balance (Luquet *et al*, 2005, 2007). However, in adult mice, as expected due to the potent orexigenic role of AgRP neurons, DT administration to these $AgRP^{DTR}$ mice promotes a huge reduction in body weight and food intake in a short time (Bewick *et al*, 2005; Gropp *et al*, 2005; Luquet *et al*, 2005), which can even lead to starvation (Luquet *et al*, 2005). It has been hypothesized that the absence of effect in the neonates could be due to 'compensatory mechanisms' developed during the neonatal stage, when the neurocircuitry is not fully formed (Luquet *et al*, 2005). It has been shown that DT injection to adult mice, which have been previously treated with DT during the neonatal stage, does not have the same drastic effect as seen in starvation-induced DT treatment (Luquet *et al*, 2005). In this issue of *The EMBO Journal*, Joly-Amado *et al* (2012) report an increase in feeding efficiency in 3-month-old $AgRP^{DTR}$ mice after DT injection during the neonatal stage. This change in feeding efficiency leads to an obese phenotype related to a decrease in locomotor activity. These results, contrary to those expected due to the orexigenic function of AgRP neurons, provide clues about the existence of a 'compensatory mechanism'. Furthermore, in this study, the development of obesity is concomitant with an increase in fat depot weight.

It is known that AgRP released from the AgRP/NPY neurons in the hypothalamus acts like an endogenous inhibitor of melanocortin receptors (MCRs) in the melanocortin system (Cone 2005). AgRP antagonizes the effects of POMC cleavage subproducts (e.g., α-msh) on these receptors to affect energy balance. It has been reported by Nogueiras *et al* (2007) that central manipulation of MCRs (using inhibitors or agonists) is able to control adiposity by modifying lipogenesis in WAT. Moreover, they found that hypothalamic MCRs act like a switch between carbohydrate and fat utilization: the blockade of MCRs decreases the percentage of fat utilized (Nogueiras *et al*, 2007). In the current issue, Joly-Amado *et al* (2012) describe changes in the same direction as found in this previous study; they report evidence of AgRP/NPY neuron involvement in the control of nutrient partitioning and lipid metabolism in peripheral tissues, in agreement with another report that demonstrated the importance of Sirt1 in AgRP neurons to modulate substrate utilization during fasting (Dietrich *et al*, 2010). The $AgRP^{DTR}$ mice used in this study show a shift in substrate utilization. AgRP deficiency stimulates lipid utilization, that is, these mice obtain energy from stored fat. Despite this shift in metabolic profile, adult $AgRP^{DTR}$ mice present more adiposity than controls. This can be explained by the fact that these mice show a potent increase in lipogenesis and triglyceride (TG) content in the liver. Post-pandrial plasma TG levels are raised, but they are normalized by fasting, providing evidence that the peripheral tissues of these AgRP-ablated mice obtain the energy required to maintain their functions from lipids. Furthermore, the authors describe a 'paradoxical benefit' in HFD-exposed mice. These animals are protected against the effects of HFD—their body weight and fat content are indistinguishable from wild-type mice, probably due to the fact that the mice utilize the excess fat found in the diet for energy.

To investigate the cause of this increase in fat utilization, the authors looked into the possibility that the muscles use TG as fuel. They uncovered different results between oxidative (soleus) and fast glycolytic (white gastrocnemius) muscles. The former showed an increase in lipid utilization correlated with a decrease in the maximal OXPHOS complex I respiration rate. No changes were found in the latter. Taken together, these results indicate that the ability to oxidize lipids to obtain energy is ameliorated in the oxidative muscles of adult AgRP-ablated mice.

Joly-Amado *et al* (2012) address the question about how the hypothalamic AgRP/NPY neurons can affect peripheral tissues. It is well known that the autonomic nervous system connects hypothalamic areas with different tissues (Nogueiras *et al*, 2007). Coinciding with previous studies that examined the sympathetic nervous system (SNS), the main mediator between the hypothalamus and WAT (Nogueiras *et al*, 2007), the current authors found that the SNS also mediates the response of the efferent tissues. They show that all of the effects described in liver, muscle and pancreas are dependent upon the SNS outflow from the hypothalamus.

AgRP/NPY neurons also release γ-aminobutyric acid (GABA; Horvath *et al*, 1997). It has been demonstrated that GABA is necessary for the normal regulation of body weight (Tong *et al*, 2008). Constitutive inactivation of *Vgat* in AgRP neurons provokes body weight loss associated with an increase in locomotor activity (Tong *et al*, 2008). It has been reported that bretazenil (GABA agonist) replacement in adult $AgRP^{DTR}$ mice after DT injection rescues the anorexic phenotype and minimizes changes in body weight and food intake (Wu *et al*, 2009). Furthermore, that study showed that bretazenil administration solely into the parabrachial nucleus is enough to prevent the anorexia. Joly-Amado *et al* (2012), following the same strategy as in previous reports, investigated the role of GABA in the phenotype reported. They found that subcutaneous bretazenil treatment rescues the obese phenotype in adult $AgRP^{DTR}$ mice, increasing the RQ, which means an increase in carbohydrate utilization, and significantly decreasing the body fat content, thus emphasizing the importance of GABA release by the AgRP/NPY neurons to modulate energy balance.

In summary (see Figure 1), Joly-Amado *et al* (2012) in a series of elegant experiments describe a novel phenotype observed in a mouse model of neonatal depletion of AgRP neurons. They link the obese phenotype observed in these mice with an increase in lipogenesis in the liver and an increase in lipid utilization by oxidative muscles. Furthermore, the authors show that these changes in the lipid profile of the peripheral tissues are due to AgRP ablation and are mediated by the SNS, and are not a consequence of adiposity in these mice. This study provides more clues about the existence of a 'compensatory mechanism' developed during the postnatal period. In spite of this, the mice are still sensitive to AgRP and GABA treatment. It is apparent that more effort is required to completely and comprehensively elucidate and understand the exact mechanism by which this model of AgRP-ablated mice become obese in adulthood.

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Conflict of interest

The authors declare that they have no conflict of interest.

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References

Bewick GA, Gardiner JV, Dhillo WS, Kent AS, White NE, Webster Z, Ghatei MA, Bloom SR (2005) Post-embryonic ablation of AgRP neurons in mice leads to a lean, hypophagic phenotype. *FASEB J* **19:** 1680–1682

Cone RD (2005) Anatomy and regulation of the central melanocortin system. *Nat Neurosci* **8:** 571–578

Dietrich MO, Antunes C, Geliang G, Liu ZW, Borok E, Nie Y, Xu AW, Souza DO, Gao Q, Diano S, Gao XB, Horvath TL (2010) Agrp neurons mediate Sirt1's action on the melanocortin system and energy balance: roles for Sirt1 in neuronal firing and synaptic plasticity. *J Neurosci* **30:** 11815–11825

Gropp E, Shanabrough M, Borok E, Xu AW, Janoschek R, Buch T, Plum L, Balthasar N, Hampel B, Waisman A, Barsh GS, Horvath TL, Brüning JC (2005) Agouti-related peptide-expressing neurons are mandatory for feeding. *Nat Neurosci* **8:** 1289–1291

Horvath TL, Bechmann I, Naftolin F, Kalra SP, Leranth C (1997) Heterogeneity in the neuropeptide Y-containing neurons of the rat arcuate nucleus: GABAergic and non-GABAergic subpopulations. *Brain Res* **756:** 283–286

Joly-Amado A, Denis RGP, Castel J, Lacombe A, Cansell C, Rouch C, Kassis N, Dairou J, Cani PD, Ventura-Clapier R, Prola A, Flamment M, Foufelle F, Magnan C, Luquet S (2012) Hypothalamic AgRP-neurons control peripheral substrate utilization and nutrient partitioning. *EMBO J* **31:** 4276–4288

Luquet S, Perez FA, Hnasko TS, Palmiter RD (2005) NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. *Science* **310:** 683–685

Luquet S, Phillips CT, Palmiter RD (2007) NPY/AgRP neurons are not essential for feeding responses to glucoprivation. *Peptides* **28:** 214–225

Nogueiras R, Wiedmer P, Perez-Tilve D, Veyrat-Durebex C, Keogh JM, Sutton GM, Pfluger PT, Castaneda TR, Neschen S, Hofmann SM, Howles PN, Morgan DA, Benoit SC, Szanto I, Schrott B, Schürmann A, Joost HG, Hammond C, Hui DY, Woods SC *et al* (2007) The central melanocortin system directly controls peripheral lipid metabolism. *J Clin Invest* **117:** 3475–3488

Tong Q, Ye CP, Jones JE, Elmquist JK, Lowell BB (2008) Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance. *Nat Neurosci* **11:** 998–1000

Wu Q, Boyle MP, Palmiter RD (2009) Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. *Cell* **137:** 1225–1234

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