HIGHLIGHT

Mc3 and Mc4 receptors: complementary role in weight control

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Energy stores are maintained relatively constant in mammals, in spite of large variation in food availability and physical activity. This tight regulation is achieved by an endocrine feedback loop initiated by leptin. Leptin, produced by the adipocytes, signals nutritional status to the hypothalamus. Its concentration in plasma is correlated with adipose tissue mass and acutely decreases with fasting. Leptin signal triggers a neuroendocrine response involving neuropeptides that modulate appetite and energy expenditure. Some of them also influence pituitary secretions, thus mediating the adaptive hormonal responses associated with food deprivation: changes in circulating thyroid hormones levels, suppression of reproductive capacity and linear growth. Orexigenic peptides (neuropeptide Y, orexins, etc) are suppressed by leptin whereas anorexigenic signals are stimulated. Among them, the central melanocortin system plays a pivotal role in regulation of energy homeostasis (Fig. 1).

Proopiomelanocortin (POMC) expression in the hypothalamic arcuate nucleus is induced by leptin. The precursor is processed by the prohormone convertases PC1 and PC2 into alpha melanocyte stimulating hormone (αMSH), the principle agonist of the two melanocortin receptor isoforms Mc3 and Mc4. Another level of complexity is added by agouti-related protein (AgRP), a physiological antagonist of Mc3 and Mc4 receptors. Mc4r selective agonists cause anorexia and weight loss. These studies demonstrate the pivotal role of Mc4r in feeding behaviour. However, the physiological function of Mc3r has remained largely unknown.

Two recent reports analysing Mc3r knock out (KO) mice (4, 5) have addressed this question. Mutant mice were born at the expected frequency indicating that the KO was not associated with embryonic or neonatal lethality. All mice were viable and fertile through adulthood. Homozygous null Mc3r mice were not (or were only slightly) overweight, but fat mass of Mc3r−− mice was approximately double that of wild type or heterozygous mice, whereas lean body mass was reduced. Mc3r−− mice did not escape obesity when placed on a high fat diet, whereas Mc3r+/− mice may or may not gain weight in the same situation. Mc3r−− mice did not exhibit increased food intake, even being hypophagic in some groups (males on regular chow diet). Metabolic rate was normal in these animals. Thus, increased feed efficiency, not hyperphagia, contributed to increased fat mass in Mc3r−− mice (feed efficiency is defined as the ratio of weight gain to food intake). Decreased locomotor activity reached statistical significance in females (4) and in males (5). Thus, reduced energy expenditure could also contribute to the phenotype.

Mc3r−− mice were hyperleptinemic and developed mild hyperinsulinaemia but had normal corticosterone and total thyroxine (T4) levels. Their body length was significantly shorter than that of the wild-type littersmates, whereas Mc4r−− mice were longer than the controls.

These studies demonstrate that, in contrast to Mc4r which mainly controls food intake, Mc3r regulates fat stores by a peculiar metabolic pathway (Fig. 1).

Mc4r−− mice are not expected to be an independent risk factor for obesity due to absent Mc4r signalling. However, the role of the Mc3r receptor on obesity remains to be elucidated. It is possible that the Mc3r receptor might be involved in the regulation of other metabolic parameters such as glucose homeostasis and energy expenditure.
for obesity. Isolated disruption of Mc3r signalling in rodents results in increased fat mass, but not high body mass index, except when the animals are exposed to a high fat diet or when other alleles promoting fat storage are also present. Further investigation is required to determine the extent to which mutations in Mc3r may contribute to human obesity.

References


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