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Coordinated activation of central amygdala–arcuate nucleus NPY circuits are required for the development of stress-induced obesity



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Neuropeptide Y (NPY) is one of the most powerful orexigenic peptides, exerting critical feeding related functions in the hypothalamus. However, NPY is also present in extra-hypothalamic nuclei where it is modulated in response to metabolic and other physiological perturbations, but far less is known about these NPY populations and their influence on energy homeostasis. Under conditions of high-fat-diet (HFD) feeding in combination with chronic stress (HFDS), the expression of NPY is robustly upregulated in the central amygdala (CeM) as well as in the arcuate nucleus (Arc), accompanied by an increase in HFD consumption resulting in a significant increase in body fat mass, and a decrease in energy expenditure (EE). To delineate the functional role of CeM-NPY under HFDS condition, we overexpressed NPY specifically in NPY neurons of the CeM in mice. This resulted in increase in food intake and diet-induced EE, subsequently leading to an increase in body fat mass. Importantly, specific ablation of NPY in the neurons of the CeM significantly reduced the obesity-associated phenotype, confirming the importance of NPY in the CeM for the regulation of stress-induced obesity (SIO). Not surprisingly, HFDS-treated mice are also less insulin sensitive with strongly reduced glucose tolerance. Under unstressed situation, insulin reduces the level of NPY in the CeM, which leads to the reduction in food intake in mice, exhibiting an anorectic action. However, our results show that this anorectic action of insulin on the CeM-NPY neurons is impaired under HFDS condition, exaggerating the development of diet-induced obesity. In summary, our data provide important new insights to the contribution of CeM-derived NPY in stress-induced feeding and also identifies the underlying mechanism for the development of obesity under combined high caloric food intake and stressful conditions.

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Development of biomarkers for protein malabsorption and *in vivo* inhibition of B⁰AT1(SLC6A19)



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Recent studies have established that dietary protein restriction has beneficial impacts on the metabolic health and it promotes

improved glucose homeostasis by increasing the induction of FGF21 from liver. B⁰AT1 (SLC6A19) is the major neutral amino acid transporter in the intestine that carries out the bulk of amino acid absorption from the diet. It also reabsorbs neutral amino acids in the proximal tubule of the kidney. Mice lacking B⁰AT1 show signs of protein restriction such as elevated levels of FGF21 and reduced mTORC1 activity. Moreover they have improved glucose homeostasis and are protected from diet induced obesity. Pharmacological blockage of this transporter is expected to replicate this phenotype and it could be employed to treat metabolic diseases such as type 2 diabetes. To evaluate the efficacy of inhibitors of B⁰AT1, we aimed to develop biomarkers that can reliably detect successful inhibition of B⁰AT1 in mice *in vivo*. B⁰AT1 wildtype and knockout mice served as surrogates for control and fully inhibited B⁰AT1 activity. Lack of B⁰AT1 was confirmed by delayed plasma appearance rates of [¹⁴C]-labelled neutral amino acids compared to wildtype mice after intragastric administration of a mixture of amino acids. A GC-MS based non targeted metabolomics approach was used to discriminate metabolites profiles in plasma, urine and faecal samples. Lack of B⁰AT1 was readily detected by significantly increased abundance of neutral amino acids in urine and faecal samples. Metabolites of bacterial protein fermentation such as cresol, 3-indole-propionic acid, 3 hydroxyphenylacetate were more abundant in B⁰AT1 knockout mice, indicating protein malabsorption of dietary amino acids. ROC curve analysis was used to validate the use of these metabolites as biomarkers. These findings provide putative metabolite biomarkers that can be used to detect protein malabsorption and the inhibition of this transporter in intestine and kidney.

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The role of Nox5 in diabetic complications



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Adiposity and spatial memory impairments are determined by the pattern of access to high-fat, high-sugar ‘cafeteria’ diet in rats



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Rising rates of disordered eating behaviours in Australia (e.g., bingeing and excessive restriction of intake) suggest that repeated ‘cycling’ between healthy and unhealthy eating is increasingly common. The effects of such cycling on obesity and cognitive outcomes are unknown. Here we used rats to assess the effects of cycling between chow and a cafeteria (CAF) diet rich in saturated fat and refined carbohydrates on the development of obesity and spatial