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P-108 - BACE2 DEFICIENCY RESULTS IN INCREASED BODY WEIGHT GAIN IN MICE FED HIGH-FAT DIET

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Resumen

Introduction: Bace2 (β-site APP-cleaving enzyme 2) is a transmembrane protease involved, among others, in the control of glucose metabolism. Bace2 is primarily expressed in pancreatic islets, unlike its close homologue Bace1 that is more expressed in the brain. Bace2-knockout mice (Bace2-KO) presented higher beta-cell mass and proliferation and improved glucose homeostasis. Several studies reported that Bace1-knockout mice are protected against high-fat (HF) diet-induced glucose intolerance and obesity. However, the involvement of Bace2 in metabolic disturbances, such as insulin resistance and obesity, has not been yet explored.

Objectives: To investigate the role of Bace2 under a metabolic challenge caused by diet-induced obesity in mice.

Material and methods: Bace2-KO mice and their respective controls (WT) were used to analyze the phenotype after 16 weeks of chow diet or high-fat (HF) diet feeding. Glucose and insulin tolerance tests (GTT and ITT, respectively) and indirect calorimetry were performed to evaluate metabolic phenotype. Plasma insulin and leptin levels were analyzed by ELISA. mRNA expression of relevant genes from hypothalamus was determined by quantitative PCR.

Results: Individualized and grouped Bace2-KO mice fed HF diet showed 70% increase in body weight gain ($p < 0.05$), with respect to their WT counterparts. The energy expenditure and respiratory exchange ratio studies showed no differences within genotypes in the same diet. Related to food intake, the Bace2-KO fed HF diet presented a higher food intake than the WT. Also, presented a lack of response to a fasting-induced refeeding, which correlates with a lower expression of orexigenic neuropeptides. Moreover, the level of the plasma adipose-derived hormone leptin was increased in the Bace2-KO. Under HF diet, both Bace2-KO and WT animals showed glucose intolerance and decreased insulin sensitivity compared to chow diet groups. These parameters did not differ between genotypes within the same diet. However, fasting plasma insulin level in HF diet groups was higher in Bace2-KO mice compared with WT mice. Interestingly, all the groups maintained the same insulin response to glucose challenge.

Conclusions: These results indicated that the inhibition of Bace2 induces obesity, hyperphagia, hyperinsulinemia and hyperleptinemia in a HF diet. Thus, targeting Bace2 may induce metabolic side effects that should be considered in the clinical use of Bace inhibitors.