Mice lacking amino acid transporter B^0AT1 (Slc6a19) have improved glycaemic control

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Elevated level of neutral amino acids is an early indicator for the development of insulin resistance. It has been proposed that high level of neutral amino acids stimulates amino acid-sensing mTOR pathway, resulting in phosphorylation of downstream proteins, such as p70S6 kinase and insulin substrate receptor-1 (IRS-1), thereby inhibiting insulin signaling and insulin-stimulated glucose transport in muscle and adipose tissue.

We hypothesized that mouse with reduced plasma amino acids level could have improved insulin sensitivity and might be less prone to develop T2D. To test this hypothesis, we have employed B^0AT1 (Slc6a19) knockout mice. B^0AT1 is the major neutral amino acid transporter in the intestine and kidney. Glucose tolerance test and insulin tolerance test were used to test insulin sensitivity in 2 months and 6 months old $B^0AT1^{-/-}$ and $B^0AT1^{+/+}$ mice. The results show that $B^0AT1^{-/-}$ mice have better insulin sensitivity than $B^0AT1^{+/+}$ mice. Western blot results also indicate reduced mTOR pathway activity in $B^0AT1^{-/-}$ mice in a variety of tissues. Furthermore, when kept on a high fat diet, $B^0AT1^{-/-}$ mice gained 30% less weight than wild type littermates after 4 months feeding period. Higher levels of “starving hormone” FGF21 and incretin GLP-1 have also been found in $B^0AT1^{-/-}$ mice, which we think the combination of these hormones generate insulin-independent phenotypes in $B^0AT1^{-/-}$ mice like reduced adipose tissue, browning of subcutaneous adipose tissue and elevated ketone bodies production. Results so far support the idea that a reduction of neutral amino acids in the blood plasma can improve insulin sensitivity and develop anti-diabetic phenotypes in mice.