Understanding the role of neutral amino acids in insulin resistance

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Elevated levels of neutral amino acids are an early indicator for the development of insulin resistance. It has been proposed that high levels of neutral amino acids cause insulin resistance, through activation of the mammalian target of rapamycin (mTOR) pathway. Plasma amino acids stimulate 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 mice with reduced plasma amino acid 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 in 2 months and 6 months old mice 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.

Secretion of GLP-1 and GIP after a meal is increased in $B^0AT1^{-/-}$ mice but paradoxically the insulin levels are lower in $B^0AT1^{-/-}$ mice. This indicates the presence of an unknown mechanism controlling insulin release in the pancreas of $B^0AT1^{-/-}$ mice. Analysis of blood metabolites revealed reduced serum urea and triglyceride and elevated serum ketone bodies in $B^0AT1^{-/-}$ mice.

These results support the idea that a reduction of neutral amino acids in the blood plasma can improve insulin sensitivity and could delay the onset of T2D.