Amino acid transport - Translating basic discovery into improving health

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Amino acid homeostasis is mediated by the combination of amino acid absorption in the intestine, metabolism and protein turnover in all tissues and renal elimination. In 2004 the major intestinal and renal transporter for neutral amino acids (SLC6A19) was identified using linkage data from the rare human Hartnup disorder. Hartnup disorder is largely benign, but is easily detectable by the spill over of large amounts of neutral amino acids into the urine. Type 2 diabetes arises from insulin resistance of peripheral tissues followed by dysfunction of β-cells in the pancreas due to metabolic stress. While both disorders appear unrelated, elevated levels of neutral amino acids are a strong predictor of future type 2 diabetes and reduction of plasma neutral amino acid levels may be able to delay the onset of type 2 diabetes or even prevent it. Mice lacking SLC6A19 can serve as a model to study the consequences of selective depletion of neutral amino acids. Reduced uptake of neutral amino acids in the intestine and loss of neutral amino acids in the urine causes an overload of amino acids in the lumen of the intestine and reduced systemic amino acid availability. This generates two opposing signals to the body, first a signal of nutrient abundance from the intestine and second a signal of amino acid depletion from the liver. As a result, higher levels of glucagon-like peptide 1 (GLP-1) are produced by the intestine after a meal, while the liver releases the starvation hormone fibroblast growth factor 21 (FGF21). The combination of these hormones generates a metabolic phenotype that is characterised by efficient removal of glucose, particularly by the heart, reduced adipose tissue mass, browning of subcutaneous white adipose tissue, enhanced production of ketone bodies and reduced hepatic glucose output.

In conclusion, reduced neutral amino acid availability improves glycaemic control. The epithelial neutral amino acid transporter B0AT1 could be a suitable target to treat type 2 diabetes.