Screening of chemical compounds to identify specific inhibitors of the nutrient transporter B^0AT1, a potential drug target to treat type 2 diabetes

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Introduction: Apical **b**road-spectrum neutral (**0**) **a**mino acid **t**ransporter B^0AT1 (SLC6A19) is a Na^+-dependent neutral amino acid transporter mainly expressed in intestine and kidney. It is co-expressed with the carboxypeptidase angiotensin-converting enzyme 2 (ACE2) in the intestine or its homolog collectrin (TMEM27, transmembrane protein 27) in the kidney, which are critical for the activity of the transporter. Our lab previously reported that $B^0AT1^{-/-}$ mice had improved glycemic control, reduced body weight and insulin secretion in response to food ingestion, indicating that the depletion of the transporter led to improved insulin sensitivity and better resistance to high-fat diet induced obesity.

Methods: Chinese Hamster Ovary (CHO) cells, stably transfected with B^0AT1 and collectrin, were validated as a tool for compound screening. A fluorescent membrane potential assay and a radioactive uptake assay were optimised to observe transporter function.

Results: We have identified a number of compounds with IC50 ~40-60μM. Compound NSC63912 was identified as a non-competitive inhibitor, whereas compound NSC22789 was a competitive inhibitor. The specificity was tested by using the endogenous Na^+-independent transport activity of CHO cells and other cell lines expressing other neutral amino acid transporters.

Conclusion: The inhibition of B^0AT1 using chemical compounds could lead to new drugs to treat type 2 diabetes.