Identification of novel inhibitors of the amino acid transporter B^0AT1 (SLC6A19), a potential target to induce protein restriction and to treat type 2 diabetes

Q. Cheng,[1] N. Shah,[1] A. Broer,[1] S. Fairweather,[1] Y. Jiang,[1] D. Schmoll,[2] B. Corry[1] and S. Broer,[1] [1]Research School of Biology, Australian National University, Canberra, ACT 2601, Australia and [2]Sanofi-Aventis Deutschland GmbH, Industriepark Hoechst, Frankfurt am Main 65926, Germany.

Introduction: The amino acid transporter B^0AT1 (Slc6a19) has recently been identified as a possible target to treat type 2 diabetes and related disorders. B^0AT1 mediates the sodium-dependent uptake of all neutral amino acids. For surface expression and catalytical activity, B^0AT1 requires coexpression of collectrin (TMEM27). In this study we established tools to identify and evaluate novel inhibitors of B^0AT1.

Methods: A Chinese Hamster Ovary (CHO)-based cell line was generated, stably expressing collectrin and B^0AT1. Using this cell line, a high-throughput screening assay was developed, which uses a fluorescent dye to detect depolarisation of the cell membrane during amino acid uptake *via* B^0AT1. In parallel to these functional assays we ran a computational compound screen using AutoDock4 and a homology model of B^0AT1 based on the high resolution structure of the highly homologous Drosophila dopamine transporter.

Results: We characterized a series of novel inhibitors of the B^0AT1 transporter. Benztropine was identified as a competitive inhibitor of the transporter showing an IC50 of 20±7μM. The compound was selective with regard to related transporters and blocked neutral amino acid uptake in inverted sections of mouse intestine.

Conclusion: The tools established in this study can be widely used to identify new transport inhibitors. Using these tools we were able to identify compounds that can be used to study epithelial transporters or be developed further through medicinal chemistry.