45

FGF21: A crucial metabolic regulator in mouse and human. Is it coming soon to a pharmacy near you?

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46

Changing the food environment to reduce risk for obesity: What we have learned and future challenges

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47

Amino acid balance in appetite, obesity and ageing

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48

An endocrine-hepato-muscular metabolic crosstalk links sarcopenia and hyperglycaemia in obesity

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49

Disrupting amino acid homeostasis to improve metabolic diseases

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Introductory statement: Dietary protein restriction in general and restriction of specific amino acids, such as branched-chain amino acids, methionine or tryptophan has been shown to have a number of metabolic benefits in animal studies, such as improved glucose tolerance, increased use of fatty acids as energy metabolites and increased life span. The overall aim of our studies is to develop a pharmacological induced amino acid restriction phenotype. Dietary restriction of specific groups of amino acids is difficult, but absorption of methionine, branched-chain amino acids and tryptophan is mediated by a single transporter in the intestine, namely SLC6A19.

Basic methodologies: To study the metabolic phenotype of neutral amino acid restriction, a mouse model lacking SLC6A19 was employed and a variety of metabolic tests performed. Biomarkers were developed to evaluate inhibition of SLC6A19 in vivo and a variety of assays were developed for high through-put screening of chemical compound libraries to identify novel inhibitors of SLC6A19.

Major findings: In earlier studies we could demonstrate that SLC6A19 knock-out mice have improved glucose tolerance, browning of white adipose tissue, reduced activation of mTORC1 and increased production of FGF21 and GLP-1. Further characterisation of the phenotype demonstrated improved insulin sensitivity, reduced hepatic glucose output and reduced hyperglycemia after STZ-induced diabetes. GC-MS based metabolomic approaches were used to identify biomarkers of amino acid restriction in urine, faeces and serum samples. Cell lines overexpressing SLC6A19 were used to generate fluorescence-based high-throughput screening assays. These were used to identify novel compounds that inhibit SLC6A19 with high potency and specificity.

Conclusion: Pharmacological inhibition of SLC6A19 could represent a strategy to induce the metabolic phenotype of protein restriction and could be administered as an orally available drug.

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50

The effectiveness of dietary interventions for adolescents affected by overweight and obesity

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Dietary interventions for adolescents affected by overweight and obesity–the evidence from randomised controlled trials.

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