Exploring the metabolic interactions between the heart, liver and kidneys in type 2 diabetes using hyperpolarized magnetic resonance

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Background

Abnormal substrate metabolism in type 2 diabetes is well studied but frequently organs and tissues are studied in isolation and the inter-relationships between organs are ignored. For example, substrate cycles (such as the Cori and Cahill cycles) between the liver and the heart are dysregulated in type 2 diabetes and frequently altered by anti-diabetic therapies. Previous work from our laboratory has used magnetic resonance imaging (MRI) and hyperpolarized magnetic resonance spectroscopy (MRS) to provide novel insights into the mechanism of action of the anti-diabetic drug, Metformin. In this work, alterations in the cardiac and hepatic cytosolic redox potential were observed and shown to affect the cycling of lactate between the heart and liver.

Hypothesis

Hyperpolarized magnetic resonance imaging provides a novel tool to study the metabolic interactions between multiple organs, e.g. the heart, liver and kidneys, and can be used to explore the cardiac, hepatic and renal effects of anti-diabetic medications such as GLP-1 agonists and SGLT2 inhibitors.

Aims

(1) To develop appropriate metabolic probes and acquisition sequences for hyperpolarized MRS to study alterations in the metabolism of the diabetic heart, liver and kidney.

(2) To apply these developments in rodent models of type 2 diabetes and to explore the cardiac, hepatic and renal effects of GLP-1 agonists and SGLT2 inhibitors.

(3) To translate these developments into clinical tools for the study of patients with type 2 diabetes to provide novel insights into the inter-relationships between different organs in humans.

Work Description

The initial work on this project will focus on the development of new metabolic probes (e.g. [1-^{13}C]lactate, [1-^{13}C]alanine & [2-^{13}C]dihydroxyacetone for the assessment of the metabolic inter-relationships between the heart, liver and kidneys in type 2 diabetes. In addition to this, work will involve the implementation of hyperpolarized MRS acquisition sequences to enable the simultaneous acquisition of data from all three organs.

Subsequent work will involve the application of these developments in a rodent model of type 2 diabetes that combines the provision of a high-fat diet with a low-dose injection of Streptozotocin. Initially, the metabolic and functional alterations that occur with the progression of diabetes will be

assessed using hyperpolarized MRS, CINE MRI and echocardiography and subsequently, the effects of therapeutics such as the glucagon-like peptide 1 analogue, Liraglutide, and the SGLT2 inhibitor, Empagliflozin, will be explored.

These pre-clinical studies will then be followed by the clinical translation of these novel imaging techniques into diabetic patients using the clinical hyperpolarized MRS system at the John Radcliffe Hospital.

Supervisor's recent relevant publications

1. Le Page LM, Ball DR, Ball V, Dodd MS, Miller JJ, Heather LC, **Tyler DJ**. Simultaneous in vivo assessment of cardiac and hepatic metabolism in the diabetic rat using hyperpolarized MRS. *NMR Biomed* 2016;29:1759-1767. PMID: 27779334
2. Lewis AJ, Miller JJ, McCallum C, Rider OJ, Neubauer S, Heather LC, **Tyler DJ**. Assessment of Metformin Induced Changes in Cardiac and Hepatic Redox State Using Hyperpolarized[1-13C]Pyruvate. *Diabetes* 2016;65:3544-3551. PMID: 27561726
3. Le Page LM, Rider OJ, Lewis AJ, Ball V, Clarke K, Johansson E, Carr CA, Heather LC, **Tyler DJ**. Increasing Pyruvate Dehydrogenase Flux as a Treatment for Diabetic Cardiomyopathy: A Combined 13C Hyperpolarized Magnetic Resonance and Echocardiography Study. *Diabetes* 2015;64*:2735-43*. PMID: 25795215
4. Schroeder MA, Clarke K, Neubauer S, **Tyler DJ**. Hyperpolarized magnetic resonance: a novel technique for the in vivo assessment of cardiovascular disease. *Circulation* 2011;124:1580-94. PMID: 21969318
5. Schroeder MA, Cochlin LE, Heather LC, Clarke K, Radda GK, **Tyler DJ**. In vivo assessment of pyruvate dehydrogenase flux in the heart using hyperpolarized carbon-13 magnetic resonance. *Proc Natl Acad Sci U S A.* 2008;105:12051-6. PMID: 18689683