Effects of Tumour Oxygenation on ^{13}C Pyruvate Metabolism

Steven Reynolds[1], Samira Kazan[2], Joanne Bluff[2], Emily Wholey[2], Martyn Paley[1], and Gillian Tozer[2]
[1]*Academic Unit of Radiology, University of Sheffield, Sheffield, South Yorkshire, United Kingdom,* [2]*Tumour microcirculation group, University of Sheffield, United Kingdom*

Introduction

Vascular targeting of tumours represents a proven complementary approach to conventional cancer therapy[1,2]. Vascular targeting drugs, for example combretastatins, cause the rapid and selective shutdown of blood flow in solid tumours. This results in extensive oxygen and nutrient deprivation, leading to tumour cell death: thus monitoring oxygenation levels is vital in helping understand this process. Pyruvate plays a key role in several metabolic pathways, and cellular oxygenation influences the relative flux of pyruvate between the citric acid cycle and lactate production. The influence of tumour oxygenation on pyruvate metabolism was investigated by determining the conversion rate, k_{pl}, of pyruvate to lactate, following administration of hyperpolarized $^{13}C_1$-pyruvic acid (PA).

Method

BD1X rats, with subcutaneously transplanted P22 sarcoma, were anaesthetised and femoral vein and artery cannulations performed for drug administration/blood pressure monitoring. The oxygenation state of the rat was changed via inspired gases through either a tracheotomy tube or nose cone. Systemic oxygen tension, pO_2, was manipulated by supplying either normal air or hypoxia (10% O_2, 4% CO_2, balance N_2). The tumour's oxygenation state was concurrently monitored during MR experiments using invasive OxyLite™ fluorescent probes. The systemic oxygenation state of the rat was determined by blood gas analysis. 5ml/kg of hyperpolarised PA was administered over 13s using an automated injection system[3]. The ^{13}C metabolite signals were localised in the tumour using a 20mm $^{13}C/^{1}H$ surface coil positioned over the tumour and 8mm thick coronal slice selection. ^{13}C spectroscopic data was acquired using a Gaussian pulse (20deg flip angle, TR=1s) in a Bruker 7T MRI system. ^{13}C peak integral versus time responses curves for pyruvate and lactate were fitted to a one-way exchange model and k_{pl} values extracted.

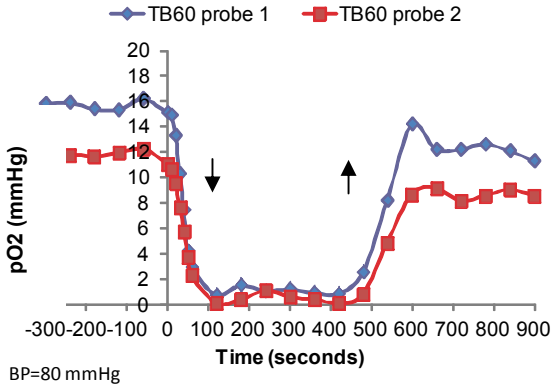

Figure 1: Tumour pO2 measured by two implanted OxyLite™ probes during a hypoxic challenge (t=0), ↓PA injection, ↑normal air.

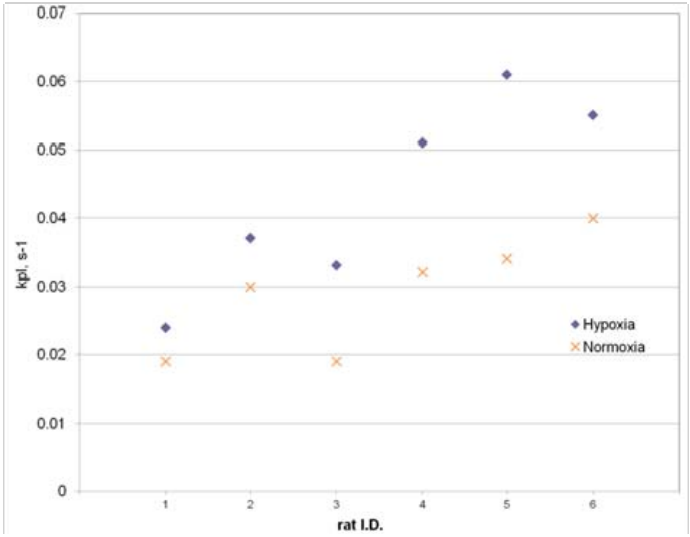

Figure 2: Fitted k_{pl} values for pyruvate to lactate flux for a normoxic and hypoxic rat.

Results

Figure 1 shows a representative trace recorded by two implanted OxyLite™ probes during a hypoxic challenge. It can be seen that hypoxia induced a rapid decrease, ~93%, in the local pO_2 environment, typically stabilising after 2 minutes. Terminating the gas challenge caused a return to near previous pO_2 levels. Hypoxia was also confirmed by blood gas analysis; pO_2 was 84.4+/-1.03 mmHg and 50.8+/-3.44 mmHg under normoxia (n=5) and hypoxia (n=4) respectively. Figure 2 shows the fitted values for pyruvate to lactate conversion, k_{pl}. The date for n=6 showed that rate of conversion of pyruvate to lactate, k_{pl}, increased from 0.029+/-0.003 s^{-1} under normoxia to 0.044+/-0.006 s^{-1} for hypoxic conditions. A paired student T-test showed that there was a statistically significant difference in k_{pl} for normoxia and hypoxia, $P<0.05$, $P=0.03$, suggesting utility of this technique for monitoring acute changes in tumour oxygenation with treatment. Further studies are in progress to assess the biochemical mechanisms behind this response.

References

1. Tozer GM, Kanthou C, Baguley BC. Nat Rev Cancer, 2005, 5, 423-35.
2. Fukumura D, Jain RK.. Microvasc. Res., 2007, 74, 72-84.
3. Reynolds S, Kazan S, Williams L, Kennerley, A, Berwick J, Tozer G, Paley M, ISMRM 2011