Modelling the muscle metabolic response in anabolic and catabolic states using arterio-venous blood metabolomics profiles

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The *in vivo* and kinetic investigation of tissue metabolism remains currently challenging, due essentially to ethical and technical issues preventing from obtaining repeated tissue biopsies on the same individual. In this study, we propose to combine plasma metabolomics measurements with metabolic-network based modelling, to investigate the muscle metabolism in anabolic and catabolic situations.
Our underlying hypothesis is that the metabolite composition of the blood inflowing and outflowing the muscle reflects its metabolic function, with consumed (respectively released) metabolites being in higher (respectively lower) concentration in arterial inflow than venous outflow.
We therefore performed a global metabolomic profiling of plasma from incoming and outgoing muscle vessels, in hindlimb multicatheterized minipigs, using liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS). Thanks to this multi-catheterized experimental setting, blood sampling was performed in conscious animals at the fasting state and at different times during the postprandial period, in a normal vs. catabolic situation (induced by a glucocorticoid treatment).
Arterio-venous metabolic profiles obtained from plasma samples were translated into utilization and release fluxes, which we then integrated into a genome-scale metabolic network to simulate fluxes through intra-muscle metabolic reactions. The calculated metabolite ratios between arterial and venous blood allowed us to identify significantly released and consumed metabolites, which mainly belonged to amino acid and TCA cycle pathways. We used these experimental data to set constraints on exchange reactions of the metabolic network, enforcing uptake and release of the corresponding metabolites. We then applied *in silico* flux balance analysis methods to predict associated changes in intramuscular metabolic fluxes.
This allowed us to predict and explore the metabolic switch in the muscle from a catabolic (fasting) to an anabolic (postprandial) state, and to investigate how these changes were modulated in a pharmacologically induced catabolic situation, commonly observed in some pathophysiological states such as insulin-resistance, obesity, or ageing.