

WP3: Effect on metabolic fluxes of food products varying in protein, sugar and lipid contents

Background: Human physiology needs to be well adapted to cope with major discontinuities in both the supply of and demand for energy. This adaptability requires a clear capacity to switch between utilization of carbohydrates and lipid derivatives, including ketone bodies, as fuel substrates [19]. This capacity has been termed 'metabolic flexibility' [20], and growing evidence has demonstrated 'metabolic inflexibility' as a key dysfunction in pre-diabetic (metabolic syndrome) and diabetic disease states. In obese and diabetic individuals this inflexibility leads to impaired sensitivity to insulin in skeletal, muscle and liver, conceivably because of defective transport of substrates into the cell and abnormal intracellular metabolism. These steps are important sites for regulation, but despite decades of intense research into these regulating mechanisms, it remains uncertain which specific regulatory steps are defective and thus receptive for targeted treatment.

Objectives: →To use DNP to demonstrate the metabolic inflexibility in diabetic or obese persons to switch (metabolic flexibility) between utilization of carbohydrates and lipid derivatives, including ketone bodies as fuel substrates; →To use DNP in studies of preventive interventions like exercise, high glucose diet, high fat diet or anti-inflammatory treatment affecting the dys-metabolic state of obese subjects, with or without diabetes or metabolic syndrome; →To use DNP to document the influence of diets varying in type and content of digestible and non-digestible carbohydrates in liver and muscle metabolism in miniature pigs; →To obtain DNP spectroscopic mapping of the downstream metabolic products, [1-13C]lactate, [1-13C]alanine and [1-13C]bicarbonate in the diabetic kidney.

Method: Bio-probes for DNP: [1-13C]pyruvate (human and animals) and [1-13C]alanine (animals only). Other [1-13C]amino acids bio-probes will be applied to quantitate transaminase activities. Use of [1-13C]alanine as bio-probe for human use can only be expected in the very late part of this WP running time.

Outcome: Liver and muscle data on possible metabolic inflexibility in obesity and diabetes and influence of dietary changes; kidney data on metabolic changes in the diabetic kidney.

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