# Postprandial NMR-Based Metabolic Exchanges

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The postprandial period represents one of the most challenging phenomena in whole-body metabolism, and it can be used as a unique window to evaluate the phenotypic flexibility of an individual in response to a given meal, which can be done by measuring the resilience of the metabolome. However, this exploration of the metabolism has never been applied to the arteriovenous exploration of organs metabolism. We identified for the first time a postprandial signature associated to the insulin resistance and obesity outcomes, and we showed that the splanchnic postprandial metabolome was considerably affected by the meal and the obesity condition. Some of our results reflect a loss of flexibility in response to the high fat-high sucrose meal challenge in unsuspected metabolic pathways that must be further explored as potential new events involved in early obesity and the onset of insulin resistance.

metabolomics mini-pigs postprandial phenotypic flexibility

## 1. Introduction

The postprandial period represents one of the most challenging phenomena in whole-body metabolism, given that following meal intake, body metabolism must adapt to major changes in the blood composition of nutrients. Interestingly, this adaptation could be used as an indicator of adapted or altered response to a given nutritional challenge, which is named today as the “phenotypic flexibility”, and relates to the multiple processes in the (molecular) physiology involved in maintaining this metabolic resilience [1]. Whereas during healthy physiological conditions, this flexibility will be able to handle the energy and nutrients overload resulting from a single and acute high fat meal, the adaptive processes guaranteeing homeostasis might reach their limits if exposure to such a diet becomes chronic. It is as yet unclear at which stage during overfeeding these adaptive processes can be regarded as part of normal metabolic flexibility or whether they reflects negative side effects in the spectrum of the metabolic syndrome [2]. Thus, we have recently shown that in mini-pigs overfed with a high fat–high sucrose (HFHS) diet for two months, major modifications in the postprandial metabolism occur after only one week of feeding [3][4][5][6].

## 2. History and Development

In the last decade, metabolomics has proved to be a valuable tool for gaining better understanding of metabolic processes [7][8] and to be particularly adapted for studying the time-course adaptations of the metabolism to

obesogenic diets, as shown by us and others [3][9][10][11][12]. Beyond the fasting condition, measuring the postprandial metabolome in response to a given meal (such as an HFHS meal), is of prime importance since human beings spend most of their time in the postprandial state [13]. Interestingly, it has been shown that during the postprandial period the metabolome is highly responsive and flexible [14] and that the number of metabolites signing a particular pathophysiological condition was significantly increased with respect to the fasting condition [15].

However, so far, the majority of untargeted metabolomics studies has focused on discovering biomarkers by profiling blood or urine samples [12][16], which provides an interesting static snapshot of the whole body metabolism but offers limited mechanistic information to which tissues/organs respond differentially [17]. Only by determining the arteriovenous (AV) concentration of metabolites across a given organ is it possible to know what is up-taken or released, and then estimate the metabolic modifications of the organ explored. AV analysis of the metabolome is therefore a particularly relevant approach to better understand the metabolism of a given organ by extending the exploration to not only a few, but rather hundreds of metabolites, as demonstrated in healthy humans [17] and pigs [18]. We recently explored this concept further, by applying this strategy across the liver and the intestine of obese insulin resistant (HFHS-fed) mini-pigs [19]. However, this study was performed in the postabsorptive period (overnight fasting) only, when homeostasis had most likely returned to steady state following the last HFHS meal.

To reveal other metabolic adaptations and have a better overview of modifications occurring outside the fasting state, in the current study we extended the metabolomics AV strategy to the postprandial period, during which more sensitive changes in the metabolic resilience have been demonstrated [20]. We used the multi-catheterized mini-pig model of obesity and insulin resistance to apply a metabolomics approach (NMR-based metabolomics platform) allowing the multi-organ and high-throughput exploration of the metabolism [19].

## 3. Conclusions

Here, we showed that the unique exploration of the metabolome exchanges across the intestine and the liver allowed determining that obese mini-pigs not only adapted their splanchnic postprandial metabolism to the most abundant nutrients available, but also that hepatic metabolism was reorganized to maintain whole body glucose homeostasis and avoid the drift from insulin resistance onset into prediabetes. Thus, the splanchnic area remained flexible enough to adapt some aspects of the mainly glucose related metabolism, while other aspects (lipid handling, glycine, and creatine metabolisms) started to indicate the limit of adaptive capacities, which could eventually lead to overt prediabetes. On the other hand, metabolites related to lipid handling and energy metabolism showed a blunted postprandial response in the obese animals across organs, reflecting a loss of flexibility in response to the HFHF meal challenge in unsuspected metabolic pathways (paradoxical glycogen synthesis, formic acid use related to purine metabolism, etc.). We also showed that the proportion of the metabolome able to discriminate healthy from obese animals was greater after the meal than during the static homeostasis balance (fasting), particularly at the hepatic level. Finally, the specific postprandial changes of some of the metabolites discussed here (lactate, ethanolamine, glutamate, propionate, acetate, etc.) were particularity

well correlated with the healthy outcomes (HOMA-IR or weight gain), and could constitute a postprandial signature of insulin resistance and obesity onset.

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