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METABOLIC AND MOLECULAR TRAJECTORIES REVEAL THE LOSS OF METABOLIC FLEXIBILITY IN THE EARLY PROCESSES OF FRUCTOSE-INDUCED INSULIN RESISTANCE

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Insulin resistance (IR) is one of the main components of metabolic syndrome. However, the early phases of its development such as the first metabolic alterations preceding its installation remain unclear. In order to analyse the early processes over time from the gene to the metabolite levels, we have pair-fed two groups of rats with either a control (65% starch) or a high-fructose (65% fructose) diets for 45 days. The final phenotype of the fructose-fed group consisted in fasting hyperglycaemia, hyperinsulinemia, and IR at the muscle level. Several major changes were also noticed over time before the IR installation: at the molecular level, the liver expression profile (90 genes related to lipid and glucose metabolism and insulin signalling) was strongly modified at D5. This drift was quickly compensated and the differences were no longer visible between D12 and D30. Nevertheless, this phenotypic flexibility was limited over time, and after 45 days of fructose feeding, the observed profile was identical as at D5, suggesting a final drift of the molecular phenotype probably linked to IR installation. This hypothesis was further supported by the metabolic trajectory observed in urine metabolomics analysis of the fructose-fed rats, which was completely different from that of the control group. This trajectory, together with the identified metabolites between D30 and D45 (when the IR was installed) allowed us to better characterize the metabolic flexibility of the fructose-fed rats. Finally, at the metabolic level, the fructose-fed phenotype was characterized by a rapid (D5) increase in the lipogenic and gluconeogenic potentials (enzyme activities and gene expression). All together, the events preceding the fructose-induced IR were characterized by an early (D5) shift of the metabolic phenotype (at the molecular and metabolite levels) mainly reflected in a highly-induced hepatic lipogenesis. While the global phenotype partially recovered the initial profile in the middle of the trial (D12-30, concomitantly with hyperglycaemia), a final shift was observed at D45 when IR was fully installed. This final phenotype was characterized (despite fasting hyperinsulinemia) by uncontrolled beta-oxidation and gluconeogenesis and impaired insulin signalling.