Metabonomics as an indicative tool to understand metabolic disruption linked to diet, diseases & drugs

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① Introduction

The **Zucker Diabetic Fatty** (ZDF) rat is a robust animal model that mimics closely human obesity and type II diabetes. The PK/PD properties and the **safety profile** of drugs can be deeply affected by such chronic diseases. For example, Sibutramine, an anorectic substance, went successfully through all the filters of drug development before its launching and no adverse effects were predicted by conventional preclinical tests which usually include healthy animals. However it was removed from the market after presenting cardiotoxic effects in patients at high cardiovascular disease (CVD) risk like obese and diabetic patients. Metabonomics is **an indicative tool** to detect metabolic disruption linked to **diseases** like obesity, diabetes and also to **drug induced adverse-effects.** The combination of both ZDF rat model and **metabonomics** could improve the selection of candidate molecules.

② Goals

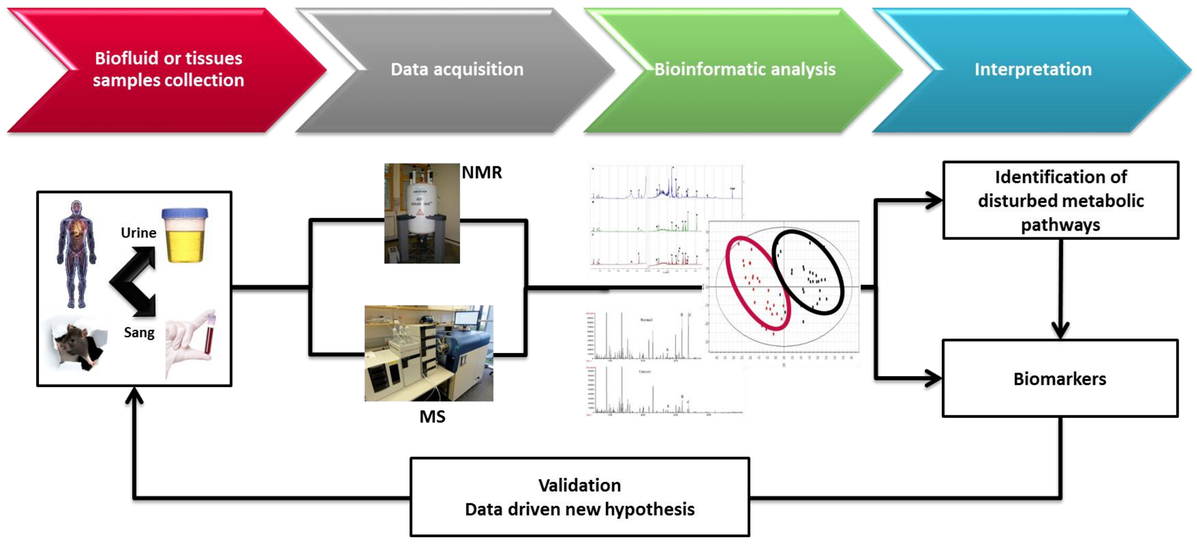
1. **Evaluate the potential of animal model of chronic diseases to better transpose from preclinical to human**
2. **Demonstrate the interest of predictive tools (i.e. metabonomics) to more rapidly evaluate drug safety**

③ Material and method

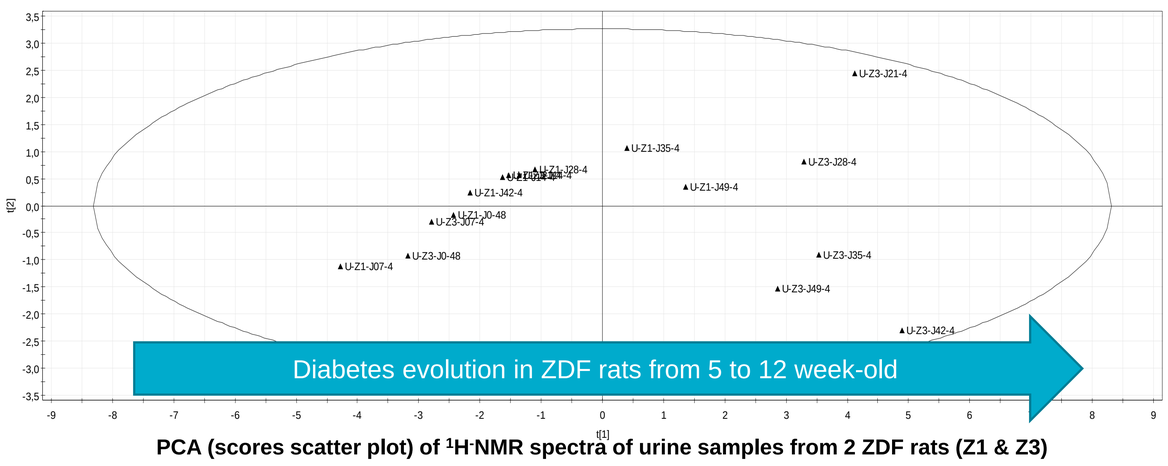
Once a day
Per os
(60 days)

Sibutramine

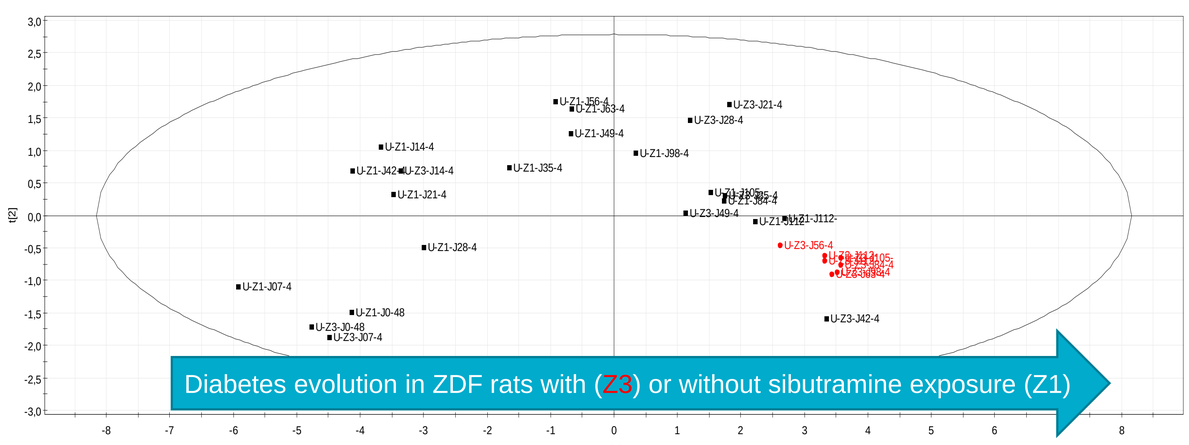
ZDF rats



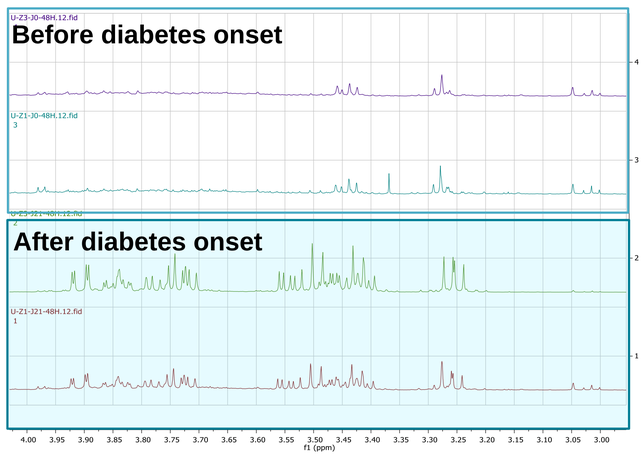
④ Results and Discussion



PCA (scores scatter plot) of ^{1}H-NMR spectra of urine samples from 2 ZDF rats (Z1 & Z3)

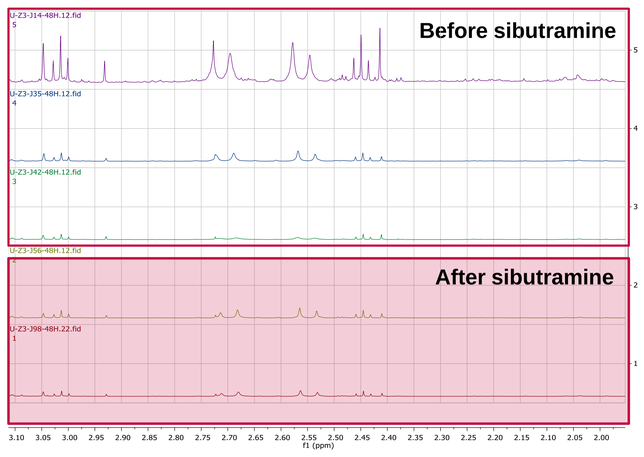


PCA (scores scatter plot) of ^{1}H-NMR spectra of urine samples from 2 ZDF rats (Z1 & Z3) before and after sibutramine (Z3)



Diabetes evolution in ZDF rats involves glycosuria development as well as decreases in creatinine and hippurate. Moreover, the diabetes evolution leads to a reduction in some TCA cycle intermediates (citrate and alpha-ketoglutarate).

^{1}H-NMR urine spectra of ZDF rats (Bruker 500MHz, NOESYpresat)
Zoom from 3,00 to 4,00 ppm



In this rat (Z3), sibutramine slows down the evolution of diabetes. The TCA cycle intermediates, which gradually decrease before sibutramine administration, partly recover under sibutramine. As for, glycosuria and creatininuria, they are less affected.

^{1}H-NMR urine spectra of ZDF rats (Bruker 500MHz, NOESYpresat)
Zoom from 2,00 to 3,10 ppm

⑤ Conclusion

Obesity and type II diabetes are systemic conditions which can lead to severe metabolic disturbances and other complications. So far, the main changes observed in ZDF rats, including the variation of glucose, creatinine and hippurate, can sign a kidney injury which is a well-known complication of diabetes also observed in humans. Some of these metabolic variations could also be due to the administration of sibutramine and its pharmacological or even toxic effects.

⑥ Perspective

Our model (ZDF + metabonomics) could also be used to assess the benefice of food diets specially developed for the management of diabetes/obesity.