Metabolism disorders induced by prenatal exposure to androgens in rats: a histological and metabonomic study

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Hyperandrogenization is a major characteristic of the polycystic ovary syndrome (PCOS). The etiology of the pathology is still unclear. On the one hand, maternal environment during pregnancy (genetic factors and high level of testosterone) and, on the other hand, endocrine disruptors during fetal life and childhood can contribute to the development of the syndrome. Women have PCOS which is characterized firstly by folliculogenesis alterations and then by metabolic disorders (insulin resistance and type II diabetes). Even if this syndrome affects especially females, some spermatogenesis and metabolic abnormalities can be found in male offspring of women with PCOS. Testosterone exposure during prenatal life seems to be the most reproducible animal model for this syndrome. In the present study, pregnant rats (Sprague-Dawley) received subcutaneous injections of testosterone (1mg/kg and 3 mg/kg) between day 16 and 19 of gestation. The aim of this study is to establish if prenatal androgen exposure induce morphological and physiological alterations on endocrine part of pancreas in male offspring and the aim of the metabonomic analysis is to follow up changes in urinary metabolites from the 5 th week until the 8 th week of postnatal life. Results point to a significant decrease in alpha and beta cell populations of islet of Langerhans in males aged two months exposed in utero (Testo 3mg/kg) accompanied by an increase of glycemia. Metabonomic data point on one hand to a decrease in alphaketoglutarate, citrate and succinate suggesting a disruption in Krebs cycle and on the other hand an increase in hippurate and allantoin resulting from an oxidative stress. In conclusion, the morphological and the IPGTT results suggest Langerhans’s islets alterations were accompanied by a significant increase in glycemia in males exposed to 3 mg/kg in utero. Therefore, prenatal hyperandrogenization could be the cause of an abnormal development of the islets of Langerhans and may induce, at the adult stage, an insulin resistance which can lead to type II diabetes. The 1H NMR metabolomics approach demonstrates a disruption in Krebs cycle and metabolites of oxidative stress associated with a pre-diabetic stage in the males exposed in utero to androgens. This metabonomic fingerprint is more accentuated at the puberty stage. All of these histological, physiological and metabonomic alterations are interdependent and indicate that endocrine disruption during fetal life has important repercussions on energetic metabolism in adults.