Hepatic gene expression suggests glucose dysregulation following prenatal dioxin exposure in rats

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Whilst a positive association between exposure to environmental dioxins during adulthood and the subsequent development of diabetes has been reported, little is known about the consequences of prenatal exposure in relation to type 2 diabetes. *In utero* exposure of the foetus to excess glucocorticoid hormones has been shown to "program" hyperglycaemia in adult rodents and non-human primates. We hypothesised that prenatal exposure to dioxins through maternal diet increases risk of developing diabetes in adulthood. Pregnant female CRL:WI(Han) rats were fed 0, 2.4, 8 & 46 ng/kg/d TCCD (2,3,7,8-tetrachlorodibenzo-p-dioxin) throughout gestation. At 10 weeks of age, groups (n=8) of male offspring from treated dams were killed. Hepatic gene expression was quantified by real time RT-PCR for several metabolic markers: glucocorticoid receptors (GR), 11 β-hydroxysteroid dehydrogenase type 1 (11 β- HSD1, that reactivates inert 11 dehydo- metabolites of glucocorticoids), 5 α- and 5 β- reductases (that inactivate glucocorticoids), and the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK). Maternal TCCD treatment (46 ng/kg/d) increased hepatic GR expression (1.05±0.12 to 2.04±0.30, $P<0.05$) and decreased 5 β- reductase (1.08±0.12 to 0.67±0.09, $P<0.01$) in offspring; 11 β- HSD1 was not affected. This would be expected to increase glucocorticoid activity in F1 offspring. Indeed, liver ($P<0.05$) and body weight ($P<0.01$) were reduced with TCCD in keeping with known catabolic effects of glucocorticoids in adult rodents. However, PEPCK mRNA was decreased two-fold by the highest TCCD dose (1.17±0.30 to 0.43±0.04, $P<0.05$). PEPCK is a pivotal enzyme in the control of carbohydrate metabolism and is regulated in opposite ways by glucocorticoids and insulin: glucocorticoids promote gluconeogenesis in part by increased PEPCK expression whereas insulin has the opposite effect.

Taken together, the present results indicate that TCCD programmes gene changes consistent with increased glucocorticoid activity but that the expected metabolic outcome is opposed by unknown counter-regulatory systems. The nature and regulation of these competing endocrine process merits further investigation as they may contribute to the development of metabolic diseases affecting insulin resistance and blood pressure control.

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