Long-term consequences of neonatal glucocorticoid treatment

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Summary

Glucocorticoids (GCs) are widely used to prevent chronic lung disease in immature newborns. However, despite the evident short-term benefits, major concern has emerged about potential long-term negative effects including cardiac hypertrophy, alteration of social behavior and immune reactivity. In this thesis, I have investigated several long-term effects of early dexamethasone (DEX) treatment in rats. Male rat pups received DEX during the first 3 days after birth in dosages comparable to those used in human neonates and long-term consequences were assessed.

Growth retardation is one of the common negative effects induced by GC that has been observed in previous animal and human studies. Data described in **chapter 2 and 3** confirm that neonatal DEX treatment in the model used resulted in persistent growth retardation.

Work described in **chapter 2** addressed the short-term effects of DEX administration on energy metabolism in suckling rats. DEX induced lower plasma insulin levels, hyperglycaemia, hyperketonemia and dyslipidemia at 2 days. At the same time, DEX treatment significantly increased expression of gluconeogenic and fatty acid oxidation genes in the liver and expression of genes involved fatty acid utilization in the heart. At 7 days, DEX-treated rats showed insulin resistance with hyperlipidemia, cardiac hypertrophy, while hepatic and cardiac gene expression patterns were largely normalized. Hyperlipidemia and a significantly increased hepatic triglyceride content in DEX-treated rats were prominent at 14 days without large differences in hepatic and cardiac gene expression patterns. Thus, neonatal DEX administration transiently affects cardiac and hepatic gene expression patterns in suckling rats associated with sustained effects on plasma lipid concentrations.

In **chapter 3,** studies on the long-term effect of DEX on survival and kidney function are described. It is shown for the first time that neonatal DEX administration leads to end-stage kidney disease and reduced life span in rats. In a time-course study, it was found that neonatal DEX administration inhibits renal inflammatory response during the treatment, however, following the cessation of treatment, a rebound inflammatory response occurs that may trigger a persistent pro-fibrotic process that eventually results in progressive renal deterioration later in life. Hypertension is one of the common long-term of effects of maternal GC overexposure. In **chapter 3**, it is demonstrated for the first time that neonatal DEX administration results in increased blood pressure in adult rats. The mechanism underlying this effect is still unknown: the defective renal function might play a role herein.

The liver is the largest organ in the body and performs a variety of complicated functions. Data reviewed in **chapter 4** indicate that, GC overexposure at early lifetime may

predispose to liver dysfunction later in life, e.g., a persistently increased hepatic glucose production and increased hepatic lipid content, contributing to insulin resistance and type 2 diabetes. Hepatic synthetic function of detoxification reaction can also be affected by early exposure to GC. Persistently altered hepatic gene expression, e.g., of GR, HNF4α and 11β HSD1, induced by GC might be involved in these processes.

Bile acid metabolism is one of the most important functions of liver. However, data concerning long-term effect of early life GC overexposure on bile acid metabolism is extremely limited. Thus, in **chapter 5**, it is shown that the ontogenetic expression pattern of some of the hepatic genes involved in bile acid metabolism was influenced by neonatal GC treatment in rats, resulting in an altered expression ratio of hepatic key enzymes involved in bile acid synthesis at young adult age (8 wks of age). However, no differences in bile acid synthesis rate, fractional turnover rate or pool size of cholic acid were detected between DEX-treated and control rats at 8 wks of age, indicating that altered gene expression did not translate into quantitative change in bile acid kinetics.

This thesis work addressed several aspects of short- or long-term consequences induced by neonatal DEX administration in rats. Although it is obviously not correct to directly extrapolate the outcome of these animal studies to the human situation, data support the notion that prescription of postnatal steroids in human neonates should be carefully considered. Follow-up studies on humans that have received GC treatment at neonatal age are warranted.