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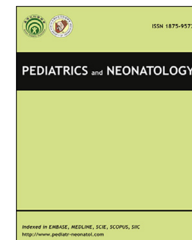

ORIGINAL ARTICLE

Prenatal Dexamethasone Exposure Programs the Development of the Pancreas and the Secretion of Insulin in Rats

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Key Words
diabetes mellitus;
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programming

Background: There is increasing epidemiological evidence indicating that many chronic diseases originate during early life, even before birth, through what are termed fetal programming effects. Prenatal glucocorticoid is frequently used clinically to accelerate the maturation of the lung, but its long-term effects remain unclear.
Methods: We gave pregnant Sprague–Dawley rats either intraperitoneal dexamethasone (0.1 mg/kg body weight) or vehicle at Gestational Days 14–20 and assessed the effects to pancreas at Postnatal Days 7 and 120.
Results: We found fewer pancreatic β cell fractions (0.31 ± 0.05 % vs. 0.49 ± 0.05 %, $p = 0.013$) and tissues (0.0017 ± 0.0002 % vs. 0.0025 ± 0.0002 %, $p = 0.042$) and decreased secretion of insulin in response to a glucose challenge at Postnatal Day 105 (1.00 ± 0.19 ng/mL vs. 1.57 ± 0.17 ng/mL at the 15-minute time-point, $p = 0.046$) in rats treated prenatally with dexamethasone. At Postnatal Day 7 in rats treated prenatally with dexamethasone, the expression of pancreatic duodenal homeobox gene-1 and V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A was lower than that in the rats in the Vehicle group (0.22 ± 0.07 vs. 1.00 ± 0.41 fold, $p = 0.01$, 0.20 ± 0.12 vs. 1.00 ± 0.35 fold, $p = 0.01$) while the histone deacetylases activity (54.2 ± 3.7 ng/h/mL vs. 37.6 ± 3.5 ng/h/mL, $p = 0.012$) and 8-hydroxy-2-deoxyguanosine staining (1.34 ± 0.01 vs. 1.00 ± 0.02 fold, $p < 0.01$) were higher.

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Conclusion: Prenatal dexamethasone exposure affects early postnatal gene expression related to pancreas development and may exert an effect on β-cell development at 120 postnatal days.
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1. Introduction

Diabetes mellitus is the most common endocrine disorder. It currently affects over 170 million people and will potentially affect over 365 million in 2030.[1] This will be accompanied by a steep rise in the complications of the disease, including ischemic heart disease, stroke, neuropathy, retinopathy, and nephropathy.[1] Type 2 diabetes is caused by a combination of genetic and environmental factors that result in decreased insulin function at its sites of action and a reduced ability of pancreatic β cells to elevate insulin secretion in response to increased blood glucose levels.[2]

There is increasing epidemiological evidence indicating that some chronic diseases originate early in life, even before birth, through what are called *programming* effects.[3] Barker[4] and Hales and Barker[5] found that low birth weight was associated with metabolic disorders later in life, including insulin resistance and glucose intolerance.

Glucocorticoids are frequently used clinically in prenatal therapy to accelerate the maturation of the lungs; however, there is debate on long-term effects into adulthood.[6] Dalziel et al[7] showed that prenatal exposure to betamethasone might result in insulin resistance in offspring at age 30 years. The underlying pathophysiological mechanisms of these effects are largely unclear.

Maternal administration of dexamethasone to sheep generated offspring that had increased reactive oxygen species production in the coronary circulation.[8] Verhaeghe et al[9] found that antenatal glucocorticoid elicited a rapid suppression of the glutathione peroxidase-3 antioxidant defense system in the umbilical vein. This may contribute to longer-lasting lipid oxidative damage.

Pancreatic and duodenal homeobox factor-1 (*PDX-1*), also known as insulin promoter factor 1, is a transcription factor that is critical for β cell function and development.[10] V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (*Maf-a*) is also a β cell-specific transcription factor that functions as a potent activator of insulin gene transcription.[11] Neuronal differentiation 1 (*Neuro d1*) and paired box gene 6 (*PAX-6*) are two critical regulators of pancreatic β cell development.[12,13]

In this study, we investigated whether rats treated prenatally with dexamethasone had deficits in pancreatic development or in glycemic homeostasis. In addition, we examined whether the expression of *PDX-1* and related genes changed in the pancreas of rats treated prenatally with dexamethasone and whether epigenetic effects played a role. We also examined oxidative stress in the programming of the pancreas of prenatal dexamethasone-treated rats.

2. Material and methods

2.1. Animals

Experiments were performed under the Guidelines for Animal Experiments of Chang Gung Memorial Hospital and Chang Gung University. Sprague–Dawley (SD) rats were housed in the animal care facility in Chang Gung Memorial Hospital in a 12-hour light/dark cycle with lights on at 7AM. SD female rats were allowed to mate with male rats for 24 hours. One day later, female rats were separated from the male rats and housed individually in a standard home cage. After confirmation of pregnancy on the 14th day after mating, pregnant females were randomly divided into prenatal steroid exposure and sham control groups.

2.2. Prenatal steroid exposure

Pregnant SD rats in the prenatal steroid exposure group were given intraperitoneal (IP) dexamethasone (0.1 mg/kg/d) at Gestational Days (GD) 14–20. The vehicle control group received normal saline IP at GD 14–20. The day of birth was designated Postnatal Day 0 (PD 0). Pups were weaned at PD 21 and had access to standard chow and water *ad libitum*. Only the male offspring were used for this study. The acute effects of prenatal programming were assessed at PD 7 while long-term programming effects were assessed at PD 120. Four groups of rats were used as follows, with eight per group: (1) Vehicle PD 7 group were rats sacrificed at PD 7 from mothers given normal saline at GD 14–20; (2) DEX PD 7 group consisted of rats sacrificed at PD 7 from mothers given dexamethasone at GD 14–20; (3) Vehicle PD 120 group consisted of rats sacrificed at PD 120 from mothers given normal saline at GD 14–20; and (4) DEX PD 120 group consisted of rats sacrificed at PD 120 from mothers given dexamethasone at GD 14–20.

2.3. IP glucose tolerance test and insulin tolerance test measurements

IP glucose tolerance test (IPGTT) was conducted with the Vehicle PD 120 and DEX PD 120 groups. After an 8-hour fast at PD 105, blood was collected at five time points from the left or right lateral tail vein: prior to injection and at 15 minutes, 30 minutes, 60 minutes, and 120 minutes after IP injection of glucose (2 g/kg body weight). Plasma glucose levels were measured at all time-points by the enzymatic (hexokinase) method using a glucose assay kit (Optium Xceed Diabetes Glucometer, Abbott Laboratories, Abbott Park, IL, USA) immediately. The serum was collected and

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