and female transcriptome. Ingenuity Pathway Analysis revealed that the most significantly altered pathway altered (Z score >2) with both sGCs is Inositol Phosphate metabolism. Cardiac hypertrophy, Tec kinase, and Th1 pathways were unique to Beta stimulation, whereas Melatonin, Neuropathic Pain and IL6 signaling pathways were specific to Dex stimulation. Both Dex and Beta significantly alter genes implicated in proliferation and differentiation as also described in other studies, therefore the biological response of NSC to sGCs stimulation was compared. Only Dex significantly decreased the rate of proliferation over a 72 hour. In-vitro differentiation studies reveal that both Dex and Beta reduced oligodendrocyte differentiation without altering neuronal differentiation when cells were exposed to sGCs as progenitors. However, when cells were exposed to sGCs during differentiation, Dex increased oligodendrocyte and neuronal maturation while Beta only increased oligodendrocyte differentiation. These results reveal gene targets, cellular pathways and processes that are differentially altered by prenatal Dex versus Beta exposure. Prenatal sGCs administration provides clear benefits for neonatal outcome, however, a detailed understanding of their targets in the brain is required to identify alternative sGCs drug regimens to reduce adverse neurological effects. Our finds may provide insights into the sex specific neurological outcomes observed in children exposed to sGCs in-utero.

Neuroendocrinology and Pituitary

ADVANCES IN NEUROENDOCRINOLOGY

Role of the Glucocorticoid Receptor Phosphorylation in Neural Development

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Synthetic glucocorticoid (sGC) administration in pregnancy has greatly reduced the risk of respiratory distress, intraventricular hemorrhage and necrotizing enterocolitis in premature infants. Significant evidence has accumulated in human and animal models that prenatal exposure to sGCs can lead to adverse side effects such as reduced birthweight, increased risk for hypertension, cardiovascular, metabolic, and neurological problems later in life. Phosphorylation of the glucocorticoid receptor (GR) has been shown to play a significant role in a cells response to sGC administration, altering target gene activation versus repression, the magnitude and duration of the response. The GR receptor is phosphorylated on three sites (S203, S211, S226) in the N-terminal. An increased in the ratio of phosphorylation on S211 to S226 is associated with enhanced transcriptional activation. Furthermore, changes in S221/S226 ratio are associated with distinct neurological disorders in humans. We have previously shown that in-utero exposure to a single dose of dexamethasone (Dex) reduces proliferation in cerebral cortical and hypothalamic neural stem cells (NSCs), alters neuronal differentiation, neuronal morphology and adult behavior. To investigate the role of receptor phosphorylation on NSCs biology and brain development, mice with a serine (S211) to alanine (S211A) knockin were generated. NSCs were isolated from the mouse E14.5 cerebral cortex and the transcriptional and biological response of cells were examined in response to sGC or vehicle stimulation. Affymetrix complete genome arrays were used to identify changes in global gene expression in response to 4 hours of 10-7 M Dex exposure. Basally, 2651 genes were >1.5 fold ($p < 0.05$) differentially regulated in S211A versus wildtype, with 929 distinct upregulated and 1722 downregulated. Sex specific differences were observed basally, with 382 upregulated and 824 down regulated in females compared to 1191 upregulated and 1353 downregulated in males. Ingenuity pathway analysis (IPA) revealed that the only significant pathways that were altered basally in S211A versus wildtype were valine and isoleucine degradation, fatty acid beta oxidation and glutathione redox reaction I, all with negative Z scores (Z scores -2.1 to -3.16, P < 1.3E-01 to 1.3E-06). In response to a 4-hour Dex stimulation, 473 and 657 genes were upregulated and 782 and 996 genes were downregulated in females versus male respectively in S211A compared to wildtype. IPA analysis revealed that only one significant pathway with a Z score >2 that was altered in S211A versus wildtype in response to dex was of activation LPS/IL1 mediated inhibition of RXR function (Z = 2.82, p <3.08E-03). Some of the most significant genes changed basally in S211A versus wildtype include genes involved in the cell cycle. To determine if these transcriptional changes led to a distinct biological response, proliferation and differentiation studies were performed. Basally, S211A cells exhibit enhanced proliferation compared to wildtype cells in vitro. These findings were validated by in-vivo findings demonstrated by increased expression of TBR2, an immediate progenitor cell marker in the cerebral cortex at E17.5. These studies identify distinct pathways and developmental neurological processes that are sensitive to phosphorylation of GR on S211 basally and in response to sGC exposure.

Diabetes Mellitus and Glucose Metabolism

METABOLIC INTERACTIONS IN DIABETES

Sequential Testing to Assess Insulin Resistance in the Course of Participation in a Diabetes Prevention Program (DPP)

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Obesity has become increasingly prevalent in the United States and diabetes prevalence has increased dramatically.