THE ONTOGENY OF THE ENDOCRINE PANCREAS IN THE PRETERM BABOON MODEL

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Background: Transient neonatal hyperglycemia is reported in 80% of extremely premature infants and is associated with increased morbidity and mortality. The pathogenesis is largely unknown. The objective of this study was to examine islet cell formation in the endocrine pancreas across varying gestational ages.

Hypothesis: We hypothesized that the beta cell mass and percentage of endocrine cell differentiation is decreased in preterm baboons.

Methods: Fetal baboons were delivered via c-section (4 each) at 125 days (d) gestational age (GA), 140d GA, or near term at 175d GA. Four animals were delivered vaginally at term (185d GA). 3 animals were delivered via c-section at 125d GA and survived for 14d. Banked samples from 73 non-diabetic adult baboons were studied for comparison. Pancreatic tissue was obtained, stained for immunohistochemistry, and analyzed via the Computer Assisted Stereology Toolbox (CAST) 2.0 system. ANOVA was utilized to assess significance.

Results: Overall, the fetal endocrine pancreas (indicated by synaptophysin staining) comprised a larger percentage of the total pancreas when compared to adults (61% vs. 2%), with no differences seen across fetal gestational ages or 125d GA 14d survivors. A large portion of the fetal endocrine pancreas remained undifferentiated (46% at 125d GA, 44% at 140d GA, 46% at 175d GA, and 56% at term). By contrast, the endocrine pancreases from 125d GA 14d survivors and adults were mostly differentiated (91% & 85%, respectively). The fetal beta cell mass at birth (14.9%), although similar across GA, was lower than that seen in 125d GA 14d survivors (28.8%) and adults (60%, p<0.05). The fetal alpha cell mass at birth, regardless of GA, is lower than that seen in 125d GA 14d survivors and adults. The delta cell mass was higher among all fetal animals (including 125d GA 14d survivors) when compared to adults, but statistical significance was only found in in 140d GA and 125d GA + 14d animals. In addition, the proportional ratios of beta, alpha, and delta cell masses were similar within each GA (NS).

Conclusions: 1) The fetal endocrine pancreas at birth occupies a large portion of the total pancreas but remains largely undifferentiated. 2) The fetal beta cell mass at birth is significantly lower when compared to adults regardless of gestational age. 3) No prevalence of a single cell type was found in the fetal gestational ages studied. 4) Significant increases in endocrine cell differentiation are seen in extremely premature infants who survive for 14 days. 5) These findings suggest that the fetal endocrine pancreas is not fully developed at birth, even by late gestation. 6) Baboons are a novel and clinically relevant model for the study of neonatal hyperglycemia.