ABSTRACT

CELLULAR AND BIOCHEMICAL MECHANISMS OF DIABETIC EMBRYOPATHY

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Neural tube defects are among the most common major malformations associated with diabetic pregnancies. Using in vitro and in vivo model systems, we and others elsewhere have induced malformations in diabetic offspring similar to those seen in humans. In addition, these anomalies are inducible in a dose-related fashion. In order to determine the cellular basis for neural tube defects, we used the rat embryo culture to study the organogenesis period of development. With excess d-glucose added to the serum medium in increasing concentrations, neural tube anomalies were induced for study. Light and electron microscopic examination of control 12-day-old embryos grown 48 hours in culture, revealed blast like cells with few organelles or cellular processes. Twelve-day-old embryos cultured in excess d-glucose had advanced cellular maturation with differentiation, including the presence of free polysomes and copious cell processes, regardless of whether they had an open neural tube or not. Cytoarchitectural changes such as decreased numbers of mitotic figures in the ependymal layer of the embryonic neuroepithelium and decreased daughter cells in the mantle layer, were focally distributed throughout the neural epithelium but with predominance at the site of failed closure. In vivo studies in non-diabetic rats failed to demonstrate neural processes in 12 or 14 day old embryos. In addition, the extra-embryonic membranes (yolk sac) of affected embryos demonstrated, in contrast to normal controls, marked depletion of metabolic organelles; significant functional impairment in endocytosis, and thus an overall state of yolk sac failure. Therefore, these cellular aberrations observed in the excess d-glucose treated conceptuses (embryos and yolk sacs) are characteristic of a premature maturational change. Since these cellular changes are present in excess d-glucose-exposed embryos with or without failure of neural tube closure, these maturational and cytoarchitectural changes are considered important contributors to the cellular basis of neural tube defects.

Hyperglycemia and other aberrant metabolic fuels have been shown to be teratogenic to embryos exposed during organogenesis. Conversely, the avoidance of hyperglycemia, and thus the achievement of euglycemia resulting from periconceptional glycemic control, is associated with a reduced malformation rate. The biochemical basis of embryopathy is demonstrated by

aberrant metabolic fuels inducing a membrane lipid deficiency state and excess cellular free oxygen radicals. These deficient lipids include arachidonic acid and myoinositol. Experimental replacement of some of these substrates in vitro as well as in vivo, using dietary supplementation of arachidonic acid or myo-inositol, or oral feeding of antioxidants, reduced the occurrence of diabetes-related malformations in the rat model. These and other data have led us to hypothesize that aberrant metabolic fuels are teratogenic, causing injury to the membrane of cells and cell organelles with depletion of membrane lipid components. This injury results in free influx of glucose in cells and cell organelles, which following oxidation, results in excess free oxygen radicals. This overwhelms the capacity of the scavenging enzyme system, and thus produces tissue injury and organ maldevelopment. The replacement substrates serve as rescue agents to restore membrane integrity and prostanoid balance, and permits nutrient transfer across cell membranes at the normal rate and according to the usual substance-specific transfer mechanisms.

Our on-going work advances basic knowledge in the biology of diabetic embryopathy and provides a basis for subsequent clinical trials into the prevention of these anomalies.