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50 Years Ago in *The Journal of Pediatrics*

Tolubtamide-Mediated Dysregulation of Apoptosis

Schiff D, Aranda JV, Stern L. Neonatal thrombocytopenia and congenital malformations associated with administration of tolbutamide to the mother. J Pediatr 1970;77:457-58.

A male infant born after 37 weeks gestation to a 28-year-old woman with a history of diabetes for 3 years before delivery treated with tolbutamide during pregnancy was described by Schiff et al. The infant had dysmorphic features, including large ears, a right preauricular skin tag, and an accessory right thumb. The infant also had thrombocytopenia, with a platelet count of 25 000/mm^3, a hemoglobin of 13.3 g, and a reticulocyte count of 13.6%. The tolbutamide level was 7.2 mg/dL in the infant and 2.7 mg/dL in the mother. The pattern of anomalies was thought to be more consistent with fetal tolbutamide exposure as opposed to diabetic embryopathy.

The mechanism through which tolbutamide exerts its teratogenicity is not fully understood. Tolbutamide enables insulin release through closure of ATP-regulated K^+ (K_{ATP}) channels, followed by opening of voltage-dependent Ca^{2+} channels located on the β-cell surface. This prevents K^+ efflux, resulting in depolarization of cell membranes and release of insulin from storage granules. One hypothesis for tolbutamide's teratogenicity is through its effect on (K_{ATP}) channels.

Tolbutamide exposure with concentrations comparable with those in human serum in cultured rat embryos resulted in decreases of growth and developmental measures at 100 and 1000 μg/mL. There were no observed changes in embryonic growth and development at 10 μg/mL. During programmed cell death (apoptosis), Ca^{2+}- and Mg^{2+}-activated endonucleases create double-strand breaks between linker regions of nucleosome, resulting in multiples of approximately 180 bp DNA fragments. There is also experimental evidence that tolbutamide exposure to developing rat embryos increases apoptosis-mediated markers, including annexin V binding and DNA fragmentation, in a dose-dependent fashion.[1] Although apoptosis is a necessary mechanism for normal embryologic development, based on this experimental evidence, it is hypothesized that tolbutamide-mediated teratogenesis occurs through dysregulated apoptosis.

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