

Abstract

THESIS: Dilantin Affects the Rate of DNA Synthesis via Cyclin A and Decreased Concentrations of DNA Polymerase δ in Preimplantation Mouse Embryos.

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Dilantin (DPH) is one of the most popular anticonvulsant drugs prescribed to women with epilepsy. DPH causes fetal hydantoin syndrome (FHS) characterized by mental retardation and growth abnormalities such as digit hypoplasia. DPH slows cell division in preimplantation mouse embryos, extends S phase in the second cell cycle, and deregulates cyclin A in G1, S, and G2 in the first, second and third cell cycles compared to NaOH controls. To determine if DPH is altering rates of DNA synthesis in preimplantation mouse embryos, this study examined the activity of DNA polymerase during replication in S phase of the second cell cycle in DPH treated mouse embryos compared to NaOH treated vehicle controls. DNA synthesis was measured by following incorporation of the thymidine analog, EdU, into DNA over time, which was detected using a fluorescent Alexa Fluor 488 azide stain. The results showed a 31% decline in rate of DNA synthesis in DPH treated embryos compared to controls over a 40 minute reaction period. The initial 0-5 min reaction time had an 84.5% decline in the rate of

synthesis in DPH treated embryos. These results support the hypothesis that when DPH alters the expression of cyclin A in the second cell cycle then DNA replication activity decreases. This reduction may lead to the abnormal growth patterns attributed to DPH in children with FHS.