HYPERTHERMIA-INDUCED NEURAL TUBE DEFECTS: THE PROTECTIVE EFFECT OF FOLIC ACID

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Maternal hyperthermia accounts for approximately 10% of all Neural Tube Defects (NTD's) and may be induced through febrile illnesses, spas and saunas, exertion in a hot or humid environment, as well as through a variety of pharmacological agents. NTD's arise when the neural tube fails to close and may result in a variety of disorders such as spina bifida and anencephaly. The neural tube is susceptible to teratogenic insult during the third and fourth weeks of gestation (postfertalisation), prior to the time when most women know they are pregnant. Administration of folic acid, a B-vitamin, can prevent up to 70% of all cases of NTD's. In this study whole embryo culture techniques are utilised to assess the potential protective effect of folic acid in hyperthermia-induced NTD's. Pregnant mice were killed on embryonic day 9 (E9) (plug day = E1) by cervical dislocation and embryos between 5 and 6 somites were pre-incubated with and without folic acid (0.1mL, 2.9 x 10^{-5}M) in a 38°C dry-air incubator for 30min. Embryos were then exposed to a teratogenic hyperthermic episode (42°C) in a shaking water bath for 25min before being returned to a 38°C dry-air incubator for the completion of a 24h culture period. 5 somite embryos incubated without folic acid were the most susceptible to a hyperthermic episode of this dose, displaying generalised developmental retardation, while 6 somite embryos appeared morphologically normal. Interestingly, 5 to 6 somite embryos displayed highly localised developmental malformations confined to the craniofacial region while the remainder of the embryo remained unaffected. The highly localised malformation seen in these embryos suggest a susceptibility of neural crest cells, which migrate to form most of the craniofacial region. Addition of folic acid improved overall embryo size and improved morphogenesis in all embryos. Folic acid appears to have global protective effects in the presence of a teratogenic hyperthermic episode and these effects may extend to offer protection against exposure to other teratogens. Considering the susceptible period for a NTD is before neural tube closure in the fourth week of pregnancy it is important that folic acid is administered pre-conceptually.

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