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Evidence from Animal Studies on the Etiology of Neural Tube Defects

Animal models of neural tube defect (NTD) have been examined and manipulated to elucidate the mechanisms of abnormal neurulation and to test etiologic hypotheses suggested by human epidemiological data. Neurulation in mouse and in human embryos appears to be quite similar, at least anatomically, whereas neurulation in the chick embryo differs in several ways. Neural tube closure is a complex and incompletely understood morphogenetic process. The neural plate arises from the embryonic ectoderm, a layer of epithelium held together laterally by cell adhesion molecules and basally by a basement membrane. Neurulation results from both proliferation and change in shape of these neurectoderm cells: change in cell shape results in elevation of the neural folds and cell proliferation results in their elongation. Extracellular matrix deposition apparently maintains this change in tissue form (Copp and Bernfield, 1994).

Most studies have used the mouse because it provides the best compromise of developmental similarity and ease of genetic and environmental manipulation. However, NTD phenotypes in the mouse are varied and none resembles the human in every respect. Moreover, the mechanism of action of any suspected human NTD gene will need to be investigated in animal models, such as mouse models containing induced mutations in the corresponding mouse gene or mice of appropriate genetic background that contain a mutation in the suspect gene.

Numerous mouse genetic models now exist and include sponta-
neous mutants (at least 13 models, 3 of which have been shown to be due to a specific gene) as well as an increasing list of induced genetic mutants in which the resultant NTD phenotype was often unexpected (Copp and Bernfield, 1994). Most of the models exhibit isolated exencephaly (an anencephaly equivalent in the mouse) and some show solely posterior NTD (Copp and Bernfield, 1994), but most are associated with malformations outside the central nervous system, growth retardation, or both. One model, the curly tail mouse, shows NTD as its sole defect (Gruneberg, 1954). Curly tail mice exhibit both anterior and posterior NTDs, which can closely resemble the common forms of human NTD (Seller and Adinolfi, 1981). As in humans, there is incomplete (60 percent) penetrance, which varies with genetic background. This suggests the presence of modifier genes, one of which has been genetically mapped (Letts et al., 1995).

**NUTRITION STUDIES**

Several nutritional deprivations can produce NTDs in rodents (Hurley, 1980). For example, zinc deficiency in rats results in 47 percent of offspring with NTDs (Hurley and Shrader, 1972). Severe folate deficiency, induced by dietary depletion together with gut sterilization to reduce microbial sources of folate (Walzem et al., 1983), does not yield NTDs in mice (Heid et al., 1992). However, these studies have not been done in genetic NTD models. One mouse model shows reduced neural abnormalities with huge folic acid supplements (2.5 to 3.0 mg/kg of body weight/day) (Zhao et al., 1996). Despite many other attempts, folate supplementation has not been associated with changes in NTD incidence in rodent models, including the curly tail mouse model (Seller, 1994). Because evidence suggests a genetic basis for erythrocyte folate values in humans (Mitchell et al., 1997), significant interspecies differences are conceivable. Further study is needed to determine whether mice handle folate more efficiently than humans and whether they have a lower threshold for folate sufficiency.

Supplementation with other nutrients can reduce the incidence of NTDs in some rodent models. Methionine supplements reduce the incidence of rat embryo NTD induced by homocysteine in culture (Vanaerts et al., 1994). The axial-defects mouse mutant shows a reduction in posterior NTD penetrance after parenteral methionine in the pregnant dam at the onset of neural tube closure; however, large doses of folic acid and vitamin B_{12} were without effect (Essien, 1992). Inositol administration can reduce NTD incidence in the
curly tail mouse model (Greene and Copp, 1997). If curly tail is a suitable mouse model of human NTD, markers of inositol status should be evaluated with regard to human NTDs.

TERATOLOGY STUDIES

Many teratogens produce NTDs in rodents; exencephaly is especially common. Examples include ethanol, retinoic acid, vitamin A, and valproate (Sulik and Sadler, 1993). The NTD phenotype depends on the timing of administration. Early administration (before closure of the anterior neural tube at mouse embryonic day 9) most often results in exencephaly whereas later administration yields posterior defects. Valproate-induced NTDs are strain specific in the mouse (Finnell et al., 1988), highlighting the importance of genetic predisposition in NTD etiology. Although some studies show an alteration in folate levels (Hendel et al., 1984) and a protective effect of coadministered folic acid in valproate-induced NTD (Trotz et al., 1987), the metabolic mechanism of valproate teratogenesis is unclear (Nau, 1994).

In humans, carbamazepine is a commonly used antiepileptic drug that has been reported to cause NTDs at a higher-than-normal rate (Rosa, 1991). The absolute risk estimated from 21 cohort studies is approximately 1 percent (Rosa, 1991).

REFERENCES


