1: Teratology. 1994 Jun;49(6):497-517. Links

Methanol-induced neural tube defects in mice: pathogenesis during neurulation.

Bolon B, **Welsch F**, **Morgan KT**.

Department of Experimental Pathology and Toxicology, Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina 27709.

A spectrum of cephalic neural tube defects was observed in near-term (gestation day [GD] 17) mouse fetuses following maternal inhalation of methanol at a high concentration (15,000 ppm) for 6 hr/day during neurulation (GD 7-9). Dysraphism, chiefly exencephaly, occurred in 15% of fetuses, usually in association with reduction or absence of multiple bones in the craniofacial skeleton and ocular anomalies (prematurely open eyelids, cataracts, retinal folds). Measurements of cerebrocortical width in grossly normal, methanol-exposed fetuses revealed significant semiquantitative differences in the thicknesses of the frontal cortex and its constituent layers (neuroepithelium, intermediate cortex/subventricular plate, and cortical layer 1) as well as apparent increases in subventricular plate cellularity relative to controls. Subsequently, the early morphogenesis of these neural changes was investigated in neurulating mouse embryos to define tissue-specific patterns of methanol-induced damage that lead to cephalic axial dysraphism. Following daily 6-hr maternal inhalations of 15,000 ppm methanol during GD 7-8, the cephalic neural fold margins were swollen, blunted, and poorly elevated on GD 8.5 and 9 relative to controls. Histopathology of exposed GD 8.5 embryos revealed microcephaly in association with reductions in the cell density and mitotic index of at least 47% in the cranial mesoderm. The mitotic index in the embryonic neuroepithelium was also reduced by 55%, and groups of neural crest cells were displaced to the neural folds dorsal to the foregut (relative to the more ventral location in the facial regions of control embryos). When examined on GD 9.5 and 10.5, maternal methanol exposure (15,000 ppm for 6 hr/day) during GD 7-9 resulted in stunting, delayed rotation, and microcephaly in over 90% of the affected embryos. Persistent patency of the anterior neuropore and prosencephalic hypoplasia were seen in > 40% and up to 90% of embryos, respectively. Shallow optic vesicles, stunted branchial arches, scoliosis, and hydropericardium were also observed. Many 10.5-day-old embryos were edematous. Occult dysraphism, recognized grossly by abnormally narrow cephalic conformation and histopathologically by the absence of mesoderm in the mesencephalon, was present in at least 21% of methanol-exposed embryos on GD 9.5 and 10.5. Nile blue vital dye staining of methanol-exposed embryos revealed no difference in dye accumulation between control and treated embryos on GD 8.5, 9.0, or 9.5. There were no apparent dysmorphogenic effects in control embryos at any stage of development.(ABSTRACT TRUNCATED AT 400 WORDS)

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