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Gastroschisis of fetuses induced by exposure of rats to acetylsalicylic acid

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Background: Gastroschisis is a congenital malformation characterized by the extrusion of the fetal bowel during intrauterine life, secondary to a defect in anterior abdominal wall. *Objective:* To establish an experimental model of gastroschisis in fetuses of rats exposed to acetylsalicylic acid (ASA), during pregnancy. *Methods:* Wistar rats were treated with an oral single ASA dose of 50, 500, 750 or 1000 mg/kg of maternal body weight on 6th, 9th or 12th days of gestation; with distilled water (group sham) and no treated (group control). It was evaluated the number of live, dead and reabsorbed fetuses, the weight and length of the fetuses and identified individuals with external malformations. *Results:* At dose of 500 mg was observed incidence of 18.3% of gastroschisis while at 1000 mg dose this value was 31.6%, demonstrating that increasing the dose causes an increase in the teratogenic potential of ASA. The dose of 50 mg, which reproduces the pharmacological effect in humans, was related to the occurrence of omphalocele in 7 fetuses. The 750 mg group had more fetuses reabsorbed; all groups with ASA had more omphalocele than sham and control groups. Only the group of 1000 mg on the 12th day of pregnancy had polydactyly; groups with 500 and 1000 mg had more gastroschisis. *Conclusions:* There was a predominance of abnormalities in the wall defect (gastroschisis and omphalocele) and present at all doses of ASA administered. The higher doses than the physiological dose showed other malformations described in a few previous studies, as polydactyly.

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Acetylation and neural tube defects

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Neural tube defects (NTDs) are the second commonest group of birth defects in humans. Included among the NTDs are spina bifida and exencephaly. Different lines of evidence suggest a likely role for protein acetylation status in the aetiology of NTDs. First, valproic acid (VPA), a well-known teratogen that induces NTDs in both humans and animal models, is capable of disrupting the acetylation equilibrium in target embryonic tissues. Second, genetic mutations in mice that result in altered acetylation activity also cause NTDs. HAT (histone acetyltransferase) enzymes act primarily on histones, but can also acetylate a number of other proteins, including p53. Embryos homozygous for a point mutation in the catalytic domain of the HAT enzyme Gcn5 show severe NTDs, while mice null for Cited2, which binds to the HAT p300/CBP, develop anencephaly. These results indicate a requirement for regulation of acetyltransferase activity in order for the neural tube to close successfully. In the present study, we evaluated acetylation status of proteins during neural tube closure, with a specific focus on alteration of p53 acetylation as a potential mechanism underlying development of NTDs. We show a dynamic pattern of overall protein acetylation in neurulation-stage embryos, and detect differentially acetylated proteins in Cited2 mutant embryos compared to wild-type. We also identify an increased level of acetylated-p53 in Cited2 null embryos. Our preliminary findings suggest that inducing p53 degradation rescues exencephaly in Cited2 null embryos. Acetylation status of p53 may be a key factor determining risk of defective neural tube closure in mammals.

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