

Poster

Possible preventive effect of inositol in folate-resistant spina bifida occulta mouse model



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ABSTRACT

Motivation: Neural tube is the embryonic structure that develops into the brain and spinal cord. Failure in the process of neural tube closure during embryonic development results in severe birth defects called neural tube defects (NTDs), including anencephaly and spina bifida. Susceptibility to NTDs is influenced by genetic and environmental factors including maternal nutrition. Clinical trials demonstrate that up to 70% of NTDs can be prevented by folic acid supplementation in early pregnancy whereas the remaining NTDs are resistant to folate. Spina bifida occulta (SBO) is included in these folic acid non-responsive NTDs. Previous studies demonstrate that inositol, a water-soluble vitamin, prevents NTDs in genetic mice models of folate-resistant NTDs, such as curly tail mutants mice. Moreover, D-chiro-inositol isomer is more effective than myo-inositol reducing the frequency of spina bifida in curly tail mice. Loop-tail mutants mice are also resistant to supplementation with folic acid. These Loop-tail (Lp) mice are mutants for Vangl2 gene implicated in the non-canonical Wnt signalling pathway (Wnt-PCP), which have a crucial role in the beginning of the closure of the neural tube. At embryonic day 11.5 (E11.5) is evident the failure of dorsal fusion of neural folds in Lp^{+/-} embryos and a cellular aggregate appears covering this defect. This aggregate resembles the lipoma characteristic of lipomyelomeningocele, the most common form of SBO. In this project, we are going to study the possible effect of D-chiro-inositol maternal supplementation to reduce the incidence of dorsal fusion failure and the formation of the cellular aggregate in Lp^{+/-} embryos and in Lp^{+/-}: Daam1^{+/-} double mutant embryos (both genes are members of the Wnt-PCP pathway), in which the cellular aggregate also develops.

Methods: Oral administration of D-chiro-inositol to pregnant mice was performed twice daily intervals from E8.5 to E10.5. These females were paired either with Lp^{+/-} or with Lp^{+/-}: Daam1^{+/-} double mutants male mice and they were sacrificed at E12.5. Embryos were genotyped and the results were compared to the macroscopic phenotype that was previously registered. Histological studies allowed us to verify the existence of the cellular aggregate in Lp^{+/-} and Lp^{+/-}: Daam1^{+/-} embryos. In addition, hybridization in situ and immunohistochemistry were carried out to analyze the expression of certain genes to characterize the cellular aggregate.

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