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A study of the incidence of hydrocephalus and cortical development in HTx rat fetuses treated with folate supplements

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Background

Our previous studies of early onset hydrocephalus in the HTx rat fetus have identified prenatal events in the aetiology of the condition [1]. We have demonstrated that the developing hydrocephalic cerebral cortex is subject to a CSF dependent cell cycle arrest that results in cortical impairment prior to onset of raised intracranial pressure [2]. Detailed analysis of CSF composition has led us to develop a method to prevent this condition developing in significant numbers of fetuses by folate supplementation throughout gestation.

Materials and methods

H-Tx and Sprague-Dawley (SD) rats were given a daily subcutaneous injection of folinic acid combined with tetrahydrofolate (4.5 mg/kg) from 3 days pre-conception to embryonic day (E) 20. Pregnant dams were injected with 2-bromodeoxyuridine (BrdU) at E17 and fetuses were collected at E20. Individual CSF samples were taken from the cisterna magna of unaffected H-Tx, control SD fetuses and the lateral ventricle of affected H-Tx fetuses. The fetal brains were fixed in paraformaldehyde, cryoprotected in sucrose and sectioned coronally at 25 μm. CSF samples were analysed by Western blot for levels of the folate enzyme 10-formyl tetrahydrofolate dehydrogenase (FDH). Dot blots were performed to analyse relative levels of 5-methyl-tetrahydrofolate and protein assays were run to determine total protein content of the CSF. Brain sections were immunostained with antibodies to BrdU and Nestin (a marker for neural progenitor cells). E19 SD primary cortical cells were cultured for 48 hours in the presence of 20% hydrocephalic CSF from E20 HTx fetuses to which folate metabolites were added.

Results

We found that a key enzyme in folate metabolism, FDH, is under-expressed in hydrocephalic rat fetuses. Our *in-vitro* studies have shown that the cell cycle arrest seen in the presence of hydrocephalic CSF can be circumvented by the addition of folate metabolites. *In-vivo*, we found that daily administration of the folate metabolites, tetrahydrofolate together with folinic acid (4.5 mg/kg), to the H-Tx dam before and throughout gestation decreases the incidence of hydrocephalus in the resulting litters.

Immunohistochemical analysis showed a greater density of BrdU labelled cells in the cortex of treated fetuses and an increase of Nestin-positive cells in treated affected compared to untreated affected HTx fetuses.

Conclusion

These findings demonstrate a means of reducing the incidence of hydrocephalus in susceptible cases and to improve brain development in cases where hydrocephalus persists.

References

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