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## Lack of formation of Reissner fiber leads to hydrocephalus

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### Background

The subcommissural organ (SCO) differentiates early in ontogeny and remains fully active during the entire life span. It secretes glycoproteins into the cerebrospinal fluid (CSF) flowing through the Sylvius aqueduct (SA); these proteins either assemble to form Reissner fiber (RF), or remain soluble in the CSF and circulate throughout the CSF compartments. Overholser *et al.* (1954) have demonstrated that offspring littered by rats maintained on a diet deficient in folic acid and/or Vitamin B12 lack a SCO and develop hydrocephalus. This led them to propose that a dysfunction of the SCO during development leads to stenosis of the SA and hydrocephalus. We have investigated several animal models in which the SCO would play a role in the pathogenesis of hydrocephalus. We have now performed a comparative analysis of the changes occurring in the SCO-RF complex of these animal models, with the aim to find a landmark common to all hydrocephalic animals that might help to unfold the mechanism of SCO-dependant hydrocephalus.

### Materials and methods

A comparative study of the SCO-RF complex and SA of five animal models characterized by a dysfunction of the SCO and development of hydrocephalus was carried out. Conventional light and electron microscopy and immunocytochemistry were applied.

### Results

Model 1. Immunological blockage of RF formation by maternal transfer of antibodies against RF-glycoproteins: undamaged and secretory active SCO, missing RF, stenosed SA and moderate hydrocephalus. Model 2. *hyh* mice with a point mutation of  $\alpha$ SNAP gene: undamaged and secretory active SCO, missing RF, obliterated SA and severe hydrocephalus. Model 3. HTx rat: subcommissural portion (two distal thirds) of SCO missing, supracommissural portion (rostral third) of SCO secretory active, RF absent, obliterated SA and severe hydrocephalus. Model 4. Transgenic mice deficient in transcription factor RFX4- $\nu$ 3: subcommissural portion of SCO missing, supracommissural portion of SCO secretory active, RF absent, patent SA and moderate to severe hydrocephalus. Model 5. *fyn* knockout mice: subcommissural portion of SCO missing, supracommissural portion of SCO secretory active, RF absent, SA with an abnormal shape and severe hydrocephalus.

### Conclusion

1. The SCO is formed by two zones: the subcommissural and the supracommissural portions. 2. Differentiation of both zones would be controlled by different genes. 3. The subcommissural portion of the SCO is essential for RF formation. Mutant and transgenic animals lacking this portion, although still have a secretory active

flow of CSF throughout SA. 6. Absence of RF could cause SA obliteration or a turbulent CSF flow through SA what, in turn, would lead to hydrocephalus. Supported by Fondecyt 1030265 (Chile), the Intramural Program of the NIH, NIEHS (USA), and MEXT (Japan).

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