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CSF circulation and cerebral cortex development

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Over the past decade, studies of a number of CSF conditions, in particular the H-Tx rat and curly tail mouse, have demonstrated a critical role for CSF in the development of the cerebral cortex and, more specifically, in the developmental defect associated with fetal-onset hydrocephalus and neural tube defects. This paper is an attempt to present a CSF hypothesis for CNS and brain development.

CNS development proceeds around a fluid-filled neural tube. The source of fluid within the developing central nervous system changes from an active blood-CSF barrier in the mesencephalon transporting specific proteins and water into the growing fluid cavity and maintaining the osmotic potential of the fluid [1-3], to a high volume fluid and protein secreting choroid plexus [4]. The fluid volume output changes coincident with a change in fluid pathway from simply filling a sealed tube to bulk flow, reaching a production of 0.3 ml/min in adult brain, forcing fluid though the ventricles and out into and around the subarachnoid space [5]. Moreover the composition changes driving and supporting development of the brain stem and spinal cord and, later, through CSF output, the cerebral cortex [6]. Evidence from *in vitro* experiments demonstrates that CSF is sufficient to support the viability, proliferation and differentiation of neural stem/progenitor in age dependent manner [7]. Evidence from the curly tail mouse as well as from brain slice experiments demonstrate that CSF passage through the subarachnoid space is required for correct migration and lamination of the cortex with neurons generated in the ventricular zone. Evidence from the hydrocephalic H-Tx rat shows that CSF composition alone can arrest development through a blockade of cell division. This blockade involves abnormal folate handling and has recently been shown to be amenable to treatment through maternal folate supplementation, but not folic acid [8].

Further understanding of the role of CSF in CNS and brain development will help expose many of the missing elements in our understanding of how the CNS develops and how this can go wrong. The future may thus provide treatments to prevent and/or treat conditions of poor development.

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