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The importance of cerebrospinal fluid in cerebral cortical development

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Abstract

In this review the role of cerebrospinal fluid (CSF) in mammalian cerebral cortex development has been highlighted. Many studies have focused on the potential role of the CSF in the developmental process. In particular, the cerebral cortex develops from the germinal epithelium adjacent to the CSF. CSF contains proteins, growth factors and other neurotrophic factors which are important for neural cell survival and proliferation. The concentration of protein present in CSF during development is much higher than in adult. Draining CSF from the ventricles of the brain during development increases the number of neural cell deaths and decreases neural cell proliferation and thus thinning of the cerebral cortex. It has been shown that infusion of anti-nerve growth factor antibody into the CSF leads to decreased cell production in the cerebral cortical germinal epithelium. It has also been shown that CSF nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) concentration change during chick embryonic development. Recent evidence shows that CSF regulates relevant aspects of neuroepithelial behavior such as proliferation, survival and migration by means of growth factors, cytokines and morphogenes. According to the data presented here, it is concluded that CSF may be regarded as an important environmental influence in cerebral cortical development.

Keywords: Cerebrospinal fluid; development; cerebral cortex

1. Introduction

In addition to the body's blood and lymphatic systems, a third circulatory system exists in the central nervous system (CNS). In humans, the total cranial volume of cerebrospinal fluid (CSF) is about 140 ml with some 115 ml located in the subarachnoid space. An additional 75 ml surrounds the spinal cord. The major site of CSF production is the choroid plexuses, a vascular expansion located within the lateral, third and fourth ventricles, having a rich capillary network underlying the epithelial sheet. Blood vessels of the brain may produce 10% of total CSF [1].

CSF circulates in a regular manner that enables it to carry chemical information in a predictable way and crossing all areas of the germinal activity before following over the surface of the brain to be absorbed at the superior sagittal sinus. CSF is thought to act as a shock absorber, cooling system, and a waste disposal pathway. Recent evidence suggest other, perhaps more important roles in maintaining the physiological homeostasis of the brain environment and as a signaling pathway [1]. It seems likely that the CSF is a vital signaling system involved in the development of the cerebral cortex and probably also the rest of CNS [2]. CSF contains growth factors and other neurotrophic factors that are important in the normal development of the cerebral cortex [3]. It also contains small molecules, salts, peptides, proteins and enzymes that play critical roles in many physiological processes. Changes (concentration, modifications of proteins and peptides) in CSF compositions accurately reflect pathological processes in the CNS, and it offers a unique window to study CNS disorders [4, 5]. In recent years, several research findings have generated sufficient evidence to support the hypothesis that the CSF is directly involved in early brain development [6]. In this article, the potential role of CSF on cerebral cortical development will be addressed.

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1.1. Mammalian cerebral cortex development

The cerebral cortex develops from two lateral telencephalic vesicles by successive growth, cell proliferation and migration from the germinal epithelium. In an early stage of development, the pallium of the telencephalic vesicles consists of undifferentiated germinal cells (also referred as the neuroepithelium). Neuroepithelial cells originally

produce pluripotent progenitors generating neuronal and glial progenitors, which give rise to the cells of cerebral cortex [7]. An important issue in neural stem cell studies is the investigation of the signals and mechanisms that regulate neural stem or progenitor cell proliferation [8, 9]. Once a postmitotic neuron is generated, it must migrate away from the germinal epithelium towards their proper position within the developing cortical plate, which gives rise to the six-layered mammalian cerebral cortex [10].

The mammalian cerebral cortex is organized in six layers. They each contain neurons with distinctive shapes and connections. All of these neurons have their origin in the ventricular proliferative zone lining the inside of the neural tube, and migrate outward to their final positions along radial glial cells [11]. Neurons born at early stages of cortical development migrate to layers closest to their site of birth, whereas those born later end up further away, in more superficial layers. Thus, there is an inside-out sequence of neuronal differentiation in the neural tube, which gives rise to the cerebral cortex and other layered brain structures [12].

1.2. Molecular aspects of neurogenesis

A number of molecules have been implicated in the directed migration of CNS neurons. Astrotactin, neurogulins (secreted growth factors), reelin, heparin sulphate and Disabled-1 are the most important factors in the migration of neurons [13].

The process of neurogenesis may be mediated by several different signaling molecules, which include brain derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and platelet derived growth factor (PDGF). BDNF is a member of the neurotrophin family, which includes nerve growth factor (NGF) and neurotrophins. BDNF enhances the differentiation of neural stem cell neuronal progeny and promotes the generation of neurons *in vitro* [14]. All-*trans* retinoic acid and fibroblast growth factor-2 (FGF-2) promote neurogenesis in the developing brain [15]. Leukemia inhibitory factor (LIF) and ciliary neurotrophic factor (CNTF) promote the differentiation of neuroglia progenitors derived from cortical neural stem cells [16]. It has been demonstrated that FGF signaling participate in telencephalon patterning and neurogenesis (the process of generating neurons from neuroepithelial stem and progenitor cells [17, 18]. This neuroepithelial wall also encloses a large cavity containing the embryonic cerebrospinal fluid. The brain ventricular system is a series of connected cavities that are filled with CSF and surrounded by neuroepithelium. The ventricles and the CSF they contain, together with the neuroepithelium and associated secretary structures, form the brain ventricular system. Abnormalities in brain ventricle structure and CSF regulation are associated with several common birth defects and often have severe consequences for brain function. These defects show the importance of the tubular nervous system, and most appear to relate to an absence of CSF, CSF of incorrect composition and too much CSF. These abnormalities include hydrocephalus and cranial neural tube closure defects. Hydrocephalus may result from an imbalance between CSF production and absorption and/or abnormal brain development leading to blockages of narrow canals that connect the ventricles, especially the aqueduct of Sylvious.

1.3. Origin and biochemistry of CSF

Human CSF is a clear and colorless fluid. In the adult, low concentrations of proteins are found in CSF. Detectable levels of protein in CSF can indicate infection, inflammation, damage, or other pathology in the CNS. In the developing brain, CSF contains large amounts of protein. CSF in chick embryo is as high as 30-fold richer in protein compared to adult CSF [19]. Total protein decreases as development proceeds, decreasing at a rapid rate after birth [6]. The protein composition of the embryonic chick CSF was analyzed. 21 different protein fractions were identified showing a stable ontogenic pattern during embryonic and fetal development and most of these proteins were also present in the embryonic serum [20]. The source of this protein material appears the same as the fluid itself, namely the choroids plexuses with additional material thought to be derived from the brain parenchyma, specifically the interstitial fluid and major components, in particular, large glycoproteins appearing in the fourth ventricle derived from subcommissural organ (SCO) or other circumventricular organs [4, 21-23]. SCO, an ependymal derived gland in the roof of the third ventricle, synthesizes and secretes glycoproteins to the CSF via the apical surface [24].

It was shown that the proteins identified in embryonic and fetal CSF are also present in plasma [20]. These findings indicate that CSF proteins may have their origin in serum, and it has been suggested that cellular transport mechanisms from the plasma occur; that might be species specific via the endoplasmic reticulum of particular sub-populations of endothelial cells in the choroids plexuses [25]. It was shown that the protein fractions detected in the CSF at early stages of development, when the choroids plexus is still immature, are also present in the embryonic serum of the same phase. This suggests the existence of specific transport mechanisms in the neuroepithelial

cells which form the wall of the brain. It may be possible that certain CSF proteins originate in neuroepithelial cells themselves [20].

1.4. Possible role of CSF in brain development

The high concentration of proteins in the embryonic and fetal CSF compared to that of adult CSF, suggests that the protein found in this fluid might be involved in brain development [20]. One of the functions attributed to embryonic and fetal CSF proteins is that of generating osmotic pressure inside the embryonic brain cavity, necessary for the expansion of the cerebral primordium [19]. It was shown that the origin of this pressure lies in CSF osmotically active molecules such as proteoglycans, capable of retaining water in a cavity and thereby generating a passive pressure [26]. Thus, the high concentration of CSF proteins in early developmental phases might play an important role in regulating osmolarity of the embryonic CSF [27]. It has been shown that proteoglycans in the embryonic CSF (eCSF), secreted by the neuroepithelium, also regulate fluid movement into, and the size of, the brain ventricles [26]. Moreover, CSF has an important role in proliferation, differentiation and behavior of embryonic neuroepithelial cells [19]. Albumin has been regarded as a possible transporter of functionally important molecules such as ions, hormones, and even growth factors, and it is capable of triggering the mitosis of cultured astrocytes [27]. Likewise, transferrin has been reported to be essential for normal brain development and both proteins are present in CSF during development [28].

Thus, the CSF pathway can be regarded as a one-way flowing river carrying signals. Brain development requires the simultaneous expansion of ventricles and neuroepithelium growth. The expansion of ventricles is driven by internal hydrostatic pressure generated by an osmotic mechanism. CSF positive pressure might play a role in early brain growth. Studies on chick embryos have suggested that intraluminal pressure resulting from the accumulation of eCSF is necessary for normal brain development and consistent intubation of the chick embryonic hindbrain ventricle results in a collapse of ventricle [29]. The main source of eCSF is the neuroepithelial tissue surrounding the ventricles [30]. Draining of CSF for 24 hours decreases the intra-luminal pressure. It was shown that growth was significantly decreased. Further, the disruption of the CSF circulation in the chick embryo causes a decrease in the thickness of the cerebral cortex and an increase in the number of dying cells [3], in addition to a decrease in the number of cells produced in the germinal epithelium [5], indicating that eCSF is necessary for normal neuronal development. Neuroepithelial proliferation occurs almost exclusively at the ventricular surface, and contact with eCSF and the factors it contains may be a prerequisite for production of early pluripotent neuroepithelial cells. Only a few neuronal progenitor populations undergo mitosis distal to the ventricles. Moreover, there is a striking correlation between brain ventricle size and the amount of neuronal cell proliferation within the corresponding periventricular region [31]. Consistent with these observations, drainage of eCSF leads to reduced cell proliferation and increased neural cell death in the developing chick brain [32], indicating that eCSF is necessary for normal cortical development. CSF has the potential to act as a signaling pathway for physiological control systems, as it has been demonstrated to contain molecules such as corticotrophin-releasing factor, leptin, leukoterienes, neurotransmitters and neuropeptides. Moreover, CSF contains growth factors such as transforming growth factor-β (TGF-β), nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), insulin-like growth factor (IGF) [33-35]. Recently, it was shown that CSF plays an essential, active role in distributing signals in the CNS. It contains growth factors including IGF2 that bind to the apical domain of cortical progenitor cells, stimulating their proliferation [36]. It was also suggested that IGF in the CSF may regulate postnatal neurogenesis. Given the active role of CSF in instructing neurogenesis in the developing cortex, modulation of the proteomic composition of the CSF may provide new ways to regulate the CNS in the health and disease of human beings [37]. Total protein concentration changes during embryonic development. Our studies using neutralizing antibody suggest that NGF is an important factor in cerebral cortical development, stimulating neuronal precursor proliferation [38]. Indeed, we find that CSF alone supports viability as well as proliferation of cerebral cortical cells both *in vivo* and *in vitro* [39]. In our studies of the hydrocephalic Texas (HTx) rat we have also found that CSF obstruction has a potent inhibitory effect on cell proliferation in the germinal epithelium of the cerebral cortex [40]. It has been shown that abnormal factors within CSF may be responsible for pathology in certain cases of hydrocephalus. While normal embryonic CSF (eCSF) promotes cell proliferation, eCSF obtained from the enlarged ventricles of hydrocephalic Texas rat model inhibits cell proliferation in culture. It was previously shown that cortical periventricular cells in the HTx rat brain do not divide, they proliferate normally once they are removed from the in vivo environment and cultured in vitro with normal eCSF [41]. Increased level of CSF NGF has

been seen in some neurological diseases including Alzheimer's disease [5] and hydrocephalus [42]. These results all suggest that abnormal regulation of eCSF factors may be an underlying cause of hydrocephalus. A wide range of neurodevelopmental disorders including Down's syndrome, idiopathic and syndromal mental retardation have been correlated with more subtle abnormalities in brain ventricular shape and size [43, 44].

2. Discussion

The central nervous system (CNS) of mammals originates from neuroepithelial cells located within the embryonic neural tube. Several mitogenic and trophic factors have been implicated in the processes of cortical cell proliferation and differentiation. These include fibroblast growth factor (FGF), insulin-like growth factor (IGF) and other neurotrophic factors [45, 46]. FGF promotes the proliferation of stem cells isolated from the brain and directs them toward specific fates [47].

Following neurolation, the anterior end of the neural tube undergoes a dramatic increase in size due mainly to enlargement of the brain cavity. This cavity is filled with so-called neural tube fluid (NTF), which has been shown to play a key role in brain development [48]. Later in development, the choroid plexuses produce CSF, which circulates inside the brain and in the subarachnoid space. Neuroepithelial behavior in the earliest stages of development could be influenced by the CSF regulating the survival, replication and differentiation of the cells, probably by the presence of cytokines and/or growth factors in the fluid [49].

CSF contains cytokines and growth factors, which may affect the proliferation of stem cells in the germinal epithelium and/or migration of cells generated in the germinal epithelium. It has been demonstrated that component carried in the CSF not only circulate rapidly through the CSF pathway, but also have fast access to most regions of the brain, gaining entry across the pia and ependymal layers as well as by active transport or diffusion [50]. Thus, the CSF is an important and rapid route for molecular signal transfer between different areas of the brain including molecules delivered into the CSF by the choroid plexus.

CSF contains growth factors or other signaling molecules that are required for the normal activity of the stem or progenitor cells in the germinal epithelium. CSF may also be an important signaling pathway linking the germinal epithelium with the dorsal surface of the cerebral cortex, which is involved in coordinating the activity of the germinal epithelium and the migration of cells into the cortex. CSF composition changes with age, as does the proliferation potential of cells in the developing cerebral cortex. We have previously shown that CSF alone supports viability as well as proliferation of cortical cells *in vitro*. The CSF was able to maintain viability of the cortical epithelial cells and stimulate their proliferation. In fact, given that at the early stages of development the cortical epithelium contains only germinal matrix stem cells, it is highly likely that the CSF can maintain the viability and induce proliferation of these brain stem cells in *in vitro* cultures [39]. CSF must therefore be regarded as an important environmental influence in brain development and can be used *in vitro* to maintain both the viability of cortical progenitor cells and their age-related proliferative potential.

Morphological and electron microscopic studies have shown that some of the cells underlying the ependyma (presumably neurons or glia) have processes passing between the ependymal cells that are in contact with the CSF [40]. Together, the results of these studies indicate that CSF is an important and rapid route for molecular signal transfer between different areas of the brain, including molecules delivered into the CSF by the choroid plexus and the subcommisural organ.

It was shown that these molecules in the CSF can enter the brain tissues [1]. The cells forming the CSF–brain interface are linked by gap junctions. Upon secretion into the ventricles peptides, growth factors and other macromolecules are conveyed by CSF bulk flow to various regions of the brain and spinal cord. This convective distribution of peptide signal and trophic factors places many neurons in contact with the products and secretions of the choroid epithelial cells [51]. Many of these peptides, e.g. hepatocyte growth factor (HGF), IGF-II and FGF-2 are secreted by the fetal choroid plexuses to provide trophic support for the developing brain [6]. There are high concentrations of proteins in fetal CSF, which are not due to immaturity of the blood–brain barrier but a result of the specialized transcellular mechanisms that specifically transfer some proteins across the choroid plexus epithelial cells in the immature brain [19].

In previous studies on a rat model of hydrocephalus, the hydrocephalic Texas (H-Tx) rat, we showed that CSF has a potential role in the development of the cerebral cortex [52, 53, 40, 2, 41]. More recently we have shown that disruption of the CSF flow in the chick embryo causes defective cortical development [5].

Increase in the number of dying cells in the CSF-drained embryos observed in our experiments may be due to a decrease in the amount of trophic factors that are necessary for neural cell survival. Increase in the number of dying cells in the cerebral

cortex from CSF-drained chick embryos shows that normal CSF circulation inside and around the brain is important in neural cell survival. In the CSF-drained embryos, CSF does not reach all the areas of brain tissue normally accessed.

Draining of CSF may decrease the amount of trophic factors that are necessary for stem and progenitor cell proliferation. As CSF contains growth factors, which are important for neural cell survival, its draining may lead to a critical decrease in the level of the factors and other neuropeptides available and this could result in increased neural cell death. This may explain why the cortical mantle of fetuses with spina bifida is thin. The CSF in these fetuses escapes out of the ventricular system down the open central canal in the spinal cord and leaks into the amniotic fluid. In the fetuses with spina bifida, CSF does not reach all the areas of brain tissue normally accessed.

The data from our study show that disruption of the CSF circulation in the chick embryo causes a decrease in the thickness of the cerebral cortex and an increase in the number of cells dying when compared with the control group. These data indicate that normal CSF circulation is important for the survival and proliferation of cells in the developing cerebral cortex. Future work will investigate the factors in the CSF controlling the activity of the cells in the germinal epithelium during cortical development.

3. Conclusion

The body of evidence presented here suggests that there is an important role for CSF flow in the development of the cerebral cortex, and that CSF controls the multipotential progenitor/stem cell behavior in the germinal epithelium and that disruption of this flow alone is sufficient to cause the observed cortical deficiencies. Our studies on the H-Tx rat have also identified a critical role for CSF in cortical development. This fluid is far from being just a buffer for the brain. It is capable of influencing germinal epithelium cell functionality and disruption of its normal flow pathways leads to abnormal fetal cortical development. Moreover, a greater understanding of the role of CSF in development, particularly neurogenesis, migration and lamination of neurons in the developing cortex could influence the management of other developmental defects of the brain as well as the therapeutic use of neuronal stem cells and/or pharmacological agents. It is also concluded that CSF is vital in controlling development of the nervous system along the whole length of the neural tube and that the externalization of CSF during development is essential for the formation of the layers of neurons in the cerebral cortex.

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