

CSF Protein Contents and Their Roles in Brain Development

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Abstract: In early stages of development, the laminated structure of cerebral cortex is organized by proliferative, morphogenetic, and migratory processes. In these stages, cells within the ependymal lining of neural tube are thought to secrete embryonic cerebrospinal fluid (eCSF). As the neural tube closes, the choroid plexuses (CPs) secrete proteins such as growth factors, cytokines and morphogens into the eCSF. The apical neuroepithelium is bathed with this fluid which plays regulatory roles in cortical cell proliferation, differentiation, and maintenance. Because of the eCSF protein contents and their impacts on neurogenesis, we focused on the effect of eCSF growth factors and their changes during brain development. Bibliographic databases including PubMed, Scopus and Google Scholar were searched between years 1990 to 2013 for the keywords "Cerebrospinal fluid" and "Neurogenesis". In the first step, 200 articles were found, after elimination of duplicates or irrelevant papers 49 papers were selected and reviewed.

Keywords: Cerebrospinal fluid; Cytokine; Neurogenesis; Choroid plexus; Cell differentiation

1. Context

The central nervous system (CNS) develops from the neural tube, a hollow structure filled with embryonic cerebrospinal fluid (eCSF) and surrounded by neuroepithelial cells. Several evidence suggest that the eCSF contains diffusible 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), and hepatocyte growth factor (HGF), regulating the survival, proliferation, and differentiation of the neuroepithelium [1]. CSF is a vital signaling system involved in the development of the cerebral cortex and probably also the rest of CNS [2]. In this review, the authors will discuss the role of the eCSF in the development of the brain and analyze its functional importance in adult and fetal brain.

2. Evidence Acquisition

Bibliographic databases including PubMed, Scopus and Google Scholar were searched between years 1990 to 2013 for the keywords "cerebrospinal fluid" and "neurogenesis". In the first step, 200 articles were found, after elimination of duplicates or irrelevant papers 49 papers were selected and reviewed.

3. Results

3.1. The Formation of Choroid Plexus (Cps)

The formation of the CPs takes place early during em-

bryogenesis. The CP differentiates from the ependymal cells lining the ventricular walls and, in fact, is frequently considered to be a specialized cuboidal epithelium of ependymal lineage [3, 4]. The CP are branched and highly vascularized structures consisting of numerous villi which project into the ventricles (the lateral, the third and the fourth) of the brain [5]. The CP develops sequentially in each ventricle in the brain such that the hindbrain/fourth ventricle CP develops first (mouse E11-12) and is quickly followed by the lateral ventricle CPs (E11-12); the mesencephalic/ third ventricle CP is the last to develop, by E14.5 [3, 6].

3.2. CSF Formation

The endothelium of the CPs capillaries is fenestrated, and the first stage in CSF formation is the passage of a plasma ultrafiltrate through the endothelium, which is facilitated by hydrostatic pressure. During the second stage of CSF formation, the ultrafiltrate passes through the choroidal epithelium at the surface of the CPs, and then into the ventricle. The passage through the choroidal epithelium is an active metabolic process which transforms the ultrafiltrate into secretion (CSF). Fluid secretion in epithelia has been found to be dependent on the unidirectional transport of ions, which creates an osmotic gradient inducing the movement of water. Osmotic gradient across the CP is strictly regulated by the transport of Na^+ , Cl^- , and HCO_3^- ions [5]. Among the numerous proteins involved in choroidal CSF production, it is known that Na^+ - K^+ ATPase, car-

bonic anhydrase II (CA II), AQP1, and solute carrier family 4, sodium bicarbonate transporter, member 10 (SLC4A10) are major contributors to CSF secretion [7].

3.3. CSF Functions

The CSF has a number of important functions. It is a physiological medium for the brain and provides mechanical support for the brain in the way that the brain floats in the CSF, reducing its effective weight. The CSF appears to serve the brain as a major biological river, transporting humoral messages from one region to another and providing a “sink” serving as an important route for the removal of a variety of waste products produced by cellular metabolism [5]. In addition to maintaining optimal hydrostatic pressure, circulating CSF exerts “nourishing” effects on the developing brain by supplying critical growth factors and other biologically active substances [3]. eCSF is capable of regulating particular aspects of neuroepithelial behavior having trophic influence on neural progenitor cell (NPC) promoting neurogenesis, cell survival and increasing their mitotic activity and replication [8]. Quantitative measurements showed that the thicknesses of the germinal epithelium and cerebral cortex in CSF drained embryos were less than those in the control group at the same age [9].

3.4. CSF Circulation and Absorption

CSF passes from the lateral ventricles into the third ventricle via the foramina of Monro and then into the 4th ventricle through the aqueduct of Sylvius. During early development of the nervous system, CSF passes down the central canal of the spinal cord and there is no external component of the CSF pathway. Sometime during this period, the CSF breaks out of the ventricular system into the basal cisterns through the foramina of Lushka and Magendie in the 4th ventricle. CSF passes out of the brain from the 4th ventricle entering the cisterna magna before passing through the subarachnoid space, circulating around the brain and spinal cord until it exits into the sagittal sinus, facial lymphatics, and other unidentified sites through absorptive mechanisms including aquaporins and the Na⁺-K⁺ATPase pumps [10].

There is a belief that arachnoid villi of the dural venous sinuses are primarily responsible for the drainage of CSF from the subarachnoid space to the cranial venous blood by means of a hydrostatic gradient. Also, in spite of some other proposed places of CSF absorption, in physiological conditions the dural sinuses are still the main place of CSF absorption [5]. The fluid volume output changes coincident with a change in fluid pathway from simply filling a sealed tube to bulk flow influence development of the brain stem and spinal cord and cerebral cortex [11].

3.5. Role of CSF Hydrostatic Pressure

Several research findings have shown that the normal

growth and morphogenesis of the embryonic brain requires the pressure generated, within a closed ventricular system, via accumulation of CSF within them, and that this accumulation of CSF within the embryonic brain ventricles occurs via an osmotic gradient. Hydrostatic pressure generated by active transport of Na⁺ and transport or secretion of proteins and proteoglycans. The CSF pressure promotes the expansion of the brain creating a tension state in the neuroepithelium which stimulates cell proliferation and suggests the presence of tension receptors [12, 13] ventricular hydrostatic pressure created by eCSF accumulation inside the brain ventricles has been demonstrated to be directly responsible for brain expansion and morphogenesis in chick and rat embryos [8].

3.6. CSF Components

The complex protein composition of eCSF suggests that this trophic action of eCSF may be due to the presence of molecules with high biological activity, such as growth factors and morphogens [8]. It also has been shown that CSF plays a key role in cortical development during fetal stage. CSF contains many neurotrophic and growth factors and has been shown to be capable of supporting viability, proliferation and differentiation of primary cortical progenitor cells [14]. The CPs have an important role in the homeostasis of nutrients in the CSF since the kinetic parameters of glucose and amino acid transport across the CPs are the main reason for the low concentration of these molecules in the CSF. The CPs appear to be source of CSF-borne hormones and growth factors also synthesis of the thyroid transporting protein transthyretin and transferrin and can chelate heavy metals [15].

CSF proteins could have three different origins: 1- transport across the neuroepithelium from an outside source, most likely the serum. 2- ubiquitous synthesis and apical secretion from neuroepithelial cells. 3- synthesis and apical secretion from a specific cellular population such as in the SCO or other circum ventricular organ [10]. A majority of proteins found in the human and rat eCSF are secreted proteins which compose 27% and 33% of the total proteins found within the CSF, respectively [16]. Although it has also been demonstrated that the protein composition of embryonic CSF is more complex than that of adult CSF, our results indicate that adult CSF has the capacity to influence the behavior of adult NSCs in the adult brain, too [1, 17, 18]. The amount of protein in the CSF is low (normally < 0.5%) when compared to plasma, but the protein composition of this fluid is complex [3]. The steady state concentration of a single plasma protein in CSF depends on the absolute level of the serum concentration, the gradient and the CSF flow rate [19]. Proteins common to human and rat CSF presumably represent proteins related to fundamental CSF functions. For example, eCSF contains many transport and carrier proteins including transferrin, albumin, alpha-fetoprotein, transthyretin,

ceruloplasmin, and plasma retinol-binding protein that are all involved in either metal ion or vitamin transport through fluid or across cell membranes [16].

3.7. Epidermal Growth Factor (EGF)

EGF is a common mitogenic factor that stimulates the proliferation of different types of cells, especially fibroblasts and epithelial cells. EGF activates the EGF receptor (EGFR/ErbB), which initiates, in turn, intracellular signaling. EGFR family is expressed in neurons of cerebral cortex. EGF enhances the differentiation, maturation and survival of a variety of neurons [20, 21].

3.8. Fibroblast Growth Factors (FGFs)

Although several members of the family of FGFs are expressed in the developing brain, only FGF7 (keratinocyte growth factor) and FGF2 (basic FGF), are expressed in the embryonic CP. It is possible that CP - derived FGF2 not only affects the development of the CP, but also controls the growth of other parts of the central nervous system (CNS) [3].

3.9. FGF2

FGF2 is known to be one of the prototypic heparin binding growth factors (HBGF) and may act over longer distances. In chick embryos at early stages of CNS development, eCSF contains FGF2, that this FGF2 is involved in regulating the behavior of neuroectodermal cells, including cell proliferation and neurogenesis [8]. FGF2 also promotes NSCs proliferation at early stages of neural development and induces expansion of neurospheres [22].

3.10. Insulin like Growth Factors (IGFs)

IGF2 is highly expressed in the CP, even at early stages of mammalian development. Interestingly, in both humans and rodents, there is a biallelic expression of the IGF2 gene in the CP, whereas in many other tissues, this gene is expressed only from the paternal allele which is necessary for normal development of the CNS [3]. The CP is the most prominent source of IGF2 in CSF. IGF2 signaling likely promotes proliferation of progenitor cells during cerebral cortical development. Expression of IGF2 in rat CSF was temporally dynamic; it peaked during periods of neurogenesis and declined in adulthood [23]. IGF1, a functional component of CSF, promotes NSC proliferation and cooperates with EGF [22]. There are 2 types of insulin - like growth factor receptors (IGF1R, IGF2R). The IGF1R mediates the mitogenic and neurotrophic effects of IGFs [3].

3.11 Glial Cell derived Neurotrophic Factor (GDNF)

GDNF is a potent peptide that has been purified and cloned based on its ability to protect and rescue dopaminergic neurons *in vitro*. Since its discovery, three other members of its family, including neurturin, persephin

and artemin, have been identified. The early expression within radial glial processes, glia limiting and migrating neurons suggests a potential role in migration and final positioning of cerebral cortical neurons [24]. GDNF also is a pro-differentiation factor for neural progenitors [22].

3.12. Platelet Derived Growth Factor (PDGF)

PDGF signaling also occurs via the primary cilium and, interestingly, the PDGF signaling pathway modulates neural stem cells and affects lineage fate. For instance, *in vitro* experiments showed that PDGF increased neurosphere formation. Infusion of PDGF into the ventricle is known to bolster proliferation in the sub ventricular zone (SVZ). CP expresses several PDGFs mRNAs with particular emphasis to PDGF α [25].

3.13. Retinoic Acid (RA)

RA, an active derivative of retinol (vitamin A), is essential for normal development of the CNS [3]. When RA is taken up by the target cells, it binds to specific nuclear receptors (RAR), regulating a series of genes involved in neural differentiation and patterning of anterior-posterior and dorso-ventral axes [26]. RA is an essential factor for inducing neural stem or precursor cells that give rise to olfactory receptor neurons (ORNs) and olfactory bulb interneurons (OBINs) during embryonic development [27].

3.14. Transthyretin (TTR)

TTR, is a carrier protein for thyroxine (T4). Synthesis of TTR begins at an early stage of brain development in choroidal epithelium. Researchers demonstrated that TTR is secreted into the CSF. TTR - T4 complexes reach the brain parenchyma via the CSF pathways. TTR may have other important functions, such as the regulation of β - amyloid metabolism the CNS [3].

3.15. CP - Derived Chemorepellents

Difusible chemorepellents play a critical role in axon guidance during the development of the CNS. Studies have demonstrated that the CP has the ability to synthesize and release such chemorepellents, suggesting that this tissue can provide the guidance cues for growing axons [3].

3.16. Membranous Particles

Analyses of eCSF content have revealed a high protein concentration and the presence of membranous particles. eCSF function could be mediated not only by soluble proteins, but also by particles present in the fluid. eCSF contains two different pools of particles, (1) lipoproteins mostly involved in brain growth, but which could also promote the neuroepithelial cells differentiation and (2) membranous particles that might play a role in the modulation of signal transduction. Lipoproteins are phospholipid monolayers surrounding a core of esterified cholesterol and tri-

glyceride, scaffolded by one protein named apolipoprotein. eCSF could also contain a second pool of particles named Exosomes-like particles that present at the edge of neuroepithelial cells. Furthermore eCSF contains Tsg 101, a protein that is highly enriched in exosomes fraction [28].

3.17. Transforming Growth Factor α (TGF α)

Probable source of EGFR signaling occurs via TGF α , given its expression in the CP [29]. TGF α signaling via EGFR was also shown to influence the migratory properties of oligodendrocyte precursors derived from SVZ cells. CP is a source of TGF α /EGF for the modulation of the subventricular zone (SVZ) [25]. TGF- α as other TGF- α members (EGF, HB-EGF) also promotes NSC proliferation [21].

3.18. Pigment Epithelium Derived Factor (PEDF)

PEDF was only found in the human eCSF. This secreted serpin family member, known to be released by retinal pigment cell into the matrix, is a known neurotrophic protein involved in survival and potentially differentiation of specific neurons. It is likely that PEDF is released by the photoreceptor cells or proliferating neuronal progenitor cells into the matrix and taken up by the CSF and may act on cell types and neurons by diffusion through the CSF [14].

3.19. Hepatocyte Growth Factor (HGF)

HGF, is a growth factor which promotes the survival and migration of immature neurons. HGF is widely expressed in the developing brain. The relative CSF HGF expression increased from E12 to E18 and decreased from E19 until birth. After birth there was a rapid increase in HGF expression until day P2, and thereafter the levels decreased from day P4 to P9. Respectively, days E16 - E18 and P1 - P3 coincide with the onset of neurons and glial migration in the cerebral cortex. Since CSF is in contact with the cerebral cortical germinal epithelium, changes in the HGF expression may reflect neuroepithelial cell migration. HGF is involved in the development of cortical neurons. There are reports that HGF/c-Met signaling plays an essential role in the development and maintenance of the nervous system. HGF participates in early neural tube development and supports the survival of motoneurons. HGF and its receptor are expressed within developing cerebral cortex. It is concluded that HGF might be involved in cerebral cortical development and it is a constant component of CSF during mouse embryonic development [30].

3.20. Vascular Endothelial Growth Factor (VEGF)

The human VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). The VEGF family of receptors consists of three protein-tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3) and two non-protein kinase co-receptors (neuropilin-1 and neuropilin-2) [31]. VEGF achieves its effects by acting on the neuronal micro-

tubular content, which is involved with growth, stability and maturation. VEGF is neurotrophic and neuroprotective independent of a vascular component that play seminal pleiotropic roles in CNS development [32].

3.21. Cystatin C (Cys C)

Cys C, also known as gamma trace, belongs to the cystatin type 2 super family. It is ubiquitously expressed by all mammalian tissues and is secreted into all body fluids [33]. Cystatin C concentrations in CSF might be just such a biomarker. This low molecular weight proteinase inhibitor, present in microglia, astrocytes, the CPs, and some neurons, binds to lysosomal cysteine proteases such as cathepsins B, H, and L. Since it appears early in life, reaching adult levels by birth, it is speculated to prevent abnormal tissue destruction during remodelling of the nervous system during early development [34]. Enhanced Cys C expression occurs in specific neuronal cell populations in the brains of human patients with Alzheimer's disease [32]. Cystatin C cooperates with bFGF signaling to induce NSC proliferation [21].

3.22. Transforming Growth Factor- β (TGF- β)

The members of the superfamily of TGF- β have been recognized as important regulators of various cell functions, including proliferation, differentiation, and survival. There are 3 isoforms of TGF- β : TGF- β 1, TGF- β 2, and TGF- β 3. Only TGF- β 3 is expressed in embryonic CP. This growth factor plays a role in controlling the neuronal organization of developing CNS. TGF- β has been shown to play an important role in both the induction and survival of dopaminergic neurons in the midbrain [3]. TGF- β tends to promote NSC differentiation. TGF- β 1 induces astrocytic differentiation of radial glia [21].

3.23. Bone Morphogenetic Protein (BMP)

BMPs are pleiotropic cytokines, known to be involved in the patterning and regionalization of the nervous system. The BMPs comprising more than 20 members by now [35]. Several members of this subfamily are present in the embryonic mouse brain, with BMP4, BMP5, BMP6, and BMP7 being expressed in the CP [1, 3] BMPs, have been shown to inhibit the production of oligodendrocyte precursors [36]. BMPs mediate a diverse array of developmental processes including cellular survival, proliferation, morphogenesis, lineage commitment, differentiation and apoptosis. In addition, there is increasing evidence that BMPs might exert selective effects on the survival and phenotypic maturation of neuronal progenitor subpopulations during later developmental stages [34].

3.24. BMP7

BMP7 is necessary for the correct regulation of cortical plate size. Bmp7 is produced in regions adjacent to the developing cortex; the hem, meninges, and choroid

plexus can be detected in the cerebrospinal fluid. Bmp7 deletion results in reduced cortical thickening, impaired neurogenesis, and loss of radial glia attachment to the meninges. Subsequent *in vitro* analyses of E14.5 cortical cells revealed that lack of Bmp7 affects neural progenitor cells, evidenced by their reduced proliferation, survival and self-renewal capacity [37].

3.25. BMP4

BMP4 levels did not increase until E16, which is late for an effect on neurogenesis or dorsal-ventral specification but appropriate for an effect on gliogenesis. Observations suggest that BMP4 directs progenitor cells *in vivo* to commit to the astrocytic rather than the oligodendroglial lineage. BMP4 may have promoted accelerated differentiation of radial glia and astrocyte [38]. BMP4 was shown to induce neuronal differentiation of NSCs [17].

3.26. Growth Differentiation Factor-5 (GDF-5)

Mature GDF-5 is a dimer protein. Expression of the dopaminergic neurotrophin GDF-5 in developing rat ventral mesencephalon was found to begin at embryonic day E12 and peak on E14, when dopaminergic neurons undergo terminal differentiation [39].

3.27. Interleukin-1 beta (IL-1 β)

Interleukin-1 beta (IL-1 β) is a member of the IL-1 family of cytokines which have potent pro-inflammatory properties. In the central nervous system (CNS) IL-1 β is primarily produced by microglia and invading monocytes/macrophages, but other types of resident cells of the nervous system, including neurons and astrocytes, are also capable of its production. IL-1 β has even been seen to display beneficial effects towards neuronal survival in the CNS. IL-1 β differentially regulates the effect of NT-3 on neuronal survival and neurite extension [40].

3.28. Interleukin 6 (IL-6)

IL-6 is a cytokine. It may act as a developmental neurotrophic factor and it has been shown to improve survival *in vitro* of several classes of neurons and promoting the growth of axons and consequently the number of synapses in a region. Furthermore, IL-6 is found to regulate survival of differentiated neurons and the development of astrocytes [41]. The cytokine IL-6 and its action mediating soluble receptors (sIL-6R and sgp130) were measured in cerebrospinal fluid [42].

3.29. Ciliary Neurotrophic Factor (CNTF)

CNTF, a member of the IL-6 family [43], promotes both survival and maturation of a variety of neuronal and glial cell populations, including oligodendrocytes [44].

3.30. SCO-Spondin

One possible candidate as eCSF morphogenetic molecules is SCO-spondin. This high molecular mass glycoprotein is secreted to the eCSF by the sub commissural organ (SCO). The SCO is one of the 1st structures to differentiate in the chick brain, expressing SCO-spondin as early as the third day of development. SCO-spondin affects the behavior of neuroepithelial cells during early brain development. SCO-spondin is crucial for CP formation and for proper brain development. SCO-spondin regulating the balance between proliferation and differentiation of the brain neuroepithelial cells [1].

3.31. Neurotrophins (NT)

Neurotrophins regulate development, maintenance, and function of vertebrate nervous systems. They also regulate cell fate decisions, axon growth, dendrite pruning, the patterning of innervation and the expression of proteins crucial for normal neuronal function, such as neurotransmitters and ion channels. These proteins also regulate many aspects of neural function. Neurotrophins activate two different classes of receptors, the Trk family of receptor tyrosine kinases and p75NTR [45]. P75NTR may also affect the survival pathways in the choroid plexus and also undergoes regulated proteolysis with metalloproteases [46]. There are four neurotrophins characterized in mammals. Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) are derived from a common ancestral gene, are similar in sequence and structure, and therefore are collectively named neurotrophins. These proteins are involved in many more aspects of neural development and function. Cell fate decisions, axon growth, dendrite pruning, synaptic function, and plasticity are all regulated by the neurotrophins [44]. NGF, NT-3, and NT-4 are potent regulators of neurogenesis that inhibit proliferation and promote differentiation of cortical progenitors [21].

NGF is an important neurotrophic factor in cerebral cortical development by its ability to stimulate neuronal precursor cell proliferation [47]. NGF levels in the chick CSF decreased from E10 to E16. There was a rapid increase in total protein content on E17 and E18, and thereafter the levels decreased from E19 to E21. Days E17 and E18 coincide with the onset of neuron migration, proliferation and organization of the cytoarchitecture of the developing cerebral cortex [18]. BDNF is a small dimeric protein. BDNF control a variety of brain processes, including the growth, development, differentiation, and maintenance of neuronal systems, neuronal plasticity, synaptic activity and neurotransmitter mediated activities. Cortical BDNF production is required for the correct activity of the corticostriatal synapse [48]. BDNF induces premature radial glia differentiation in the developing brain and have proliferating effects on embryonic NSCs and wide role in neurogenesis [22].

3.32. Sonic Hedge Hog (*Shh*)

Recent evidence demonstrates that the hindbrain CPs secrete Shh into the CSF. CSF-Shh is a key mitogen for proliferating cerebellar granule precursors and cerebellar progenitor cell development [6].

3.33. Wnt

The role of Wnt protein derived from the CP-CSF during development has been shown. BMPs, that together with Wnt and FGF proteins, participate in cortical development [35]. The CSF contained Wnt signaling activity, based upon phosphorylation of LRP6, a Wnt co-receptor in response to CSF exposure. Frizzled receptors, which bind LRP6 to transduce Wnt signals, showed enhanced expression in ventricular progenitors [23]. Wnt may rather play a role in maintaining the SVZ stem cell pool [35, 49].

3.34. Amyloid Precursor Protein (*APP*)

One factor in the eCSF is amyloid beta A4 protein precursor (APP), which we identified in rat CSF at E12.5, E14.5, and E17.5 and human CSF at CS20. The soluble form of APP has been shown to stimulate proliferation of embryonic neural stem cells. APP may play a role during neurogenesis not only within the cell, but may be released in the extracellular space and taken up in the CSF in order to diffuse throughout the CSF and play a function at more distant sites [16].

3.35. L1-Like Protein

The neuronal cell adhesion molecule L1-like protein, also found only in the human eCSF, is known to play important roles in neurite outgrowth and neuronal survival [16].

3.36. Extracellular Matrix Factors

CSF contains multiple critical extracellular matrix factors including fibronectin, laminin, tenascin, fibulin, versican, and neurocan core protein. Since many of these factors can support or orient neuronal migration, it raises the possibility that they may also be acting in the CSF as external cues for proliferating and differentiating neuronal progenitor cells. Only in rat eCSF did we find the extracellular superoxide dismutase, a protein known to remove free radicals that can be toxic to cells [16].

3.37. Cortical Development

Many critical genes involved in development of the CNS, and of the cerebral cortex in particular, have been identified as have a large number of the molecular mechanisms involved in neurogenesis, differentiation, and migration. Briefly, the cortex is initially constructed by processes of proliferation and differentiation of neurons and glia in the germinal matrix. The neuroepithelium that forms the

neural tube contains neural stem cells that proliferate to produce daughter cells that migrate from this region to form the neurons and glia of the cortex. The cortical plate consists of layers of neurones arriving from the germinal matrix and sandwiched between the subplate neurones and another layer of neurones in the marginal zone. One of the first cells to appear is radial glia that forms connections between the ependymal surface of the neural tube and the meningeal surface of the growing cortex. Cells generated in the germinal matrix migrate along radial glial fibres, through the intermediate zone and a layer of chondroitin sulphate positive subplate neurones into the cortical plate. Neuronal cells migrate along the radial fibres through adhesive interactions and in response to reelin signaling [10, 47].

4. Conclusions

eCSF contains concentrations of neurotrophics, growth factors and cytokines such as TGF- β , NGF, BDNF, NT-3, IGF and HGF. The level of these factors has significant changes in prenatal, postnatal and adult CSF. This fluid may have important roles in brain development such as neurogenesis, proliferation and differentiation of neural progenitor cells. Based on these important components of eCSF, we conclude that CSF is vital in controlling brain development specifically when we considering its changes in details by time and by species.

Authors' Contributions

All authors had equal role in work and manuscript writing.

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