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Mini Review

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Emerging Role of the Cerebrospinal Fluid – Neuronal Interface in Neuropathology

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ABSTRACT

The choroid plexus and cerebrospinal fluid have recently begun to emerge as essential regulators of neural function. Factors produced by the choroid plexus are released into the ventricular environment and thus provide a rich source of extracellular signaling molecules throughout the central nervous system. Identified factors in the cerebrospinal fluid include growth factors, hormones, proteins, peptides, lipids, glucose, microRNAs (miRNAs), messenger RNA (mRNA), and enzymes. In addition to mediating neural function, these factors have the potential to serve as biomarkers of disease states. In this review, we highlight recent advances demonstrating the importance of extracellular signaling mechanisms in mediating neural function and provide recent evidence for their role in neuropathology.

KEYWORDS: Choroid plexus; Cerebrospinal fluid; Microvesicles; Extracellular communication; Neuropathology.

ABBREVIATIONS: CSF: Cerebrospinal fluid; siRNA: short-interfering RNA; mRNA: messenger RNA; miRNAs: microRNAs; MVEs: Multivesicle endosomes; IGF2: Insulin-like growth factor 2; FGF2: Fibroblast growth factor 2; FXTAS: Fragile X-associated tremor/ataxia syndrome; AIDS: Acquired Immune Deficiency Syndrome.

INTRODUCTION

Historically, the function of the Cerebrospinal fluid (CSF) was considered to be limited to maintenance of extracellular ion concentrations and to serve as a protective 'cushion' during cranial impact. However, recent advances have revealed that the CSF provides a rich source of signaling molecules, including growth factors, hormones, proteins, peptides, lipids, glucose, microRNAs, mRNA, and enzymes.[1-5] Indeed, primary CSF removed from the brain is sufficient to maintain cortical explants and cells in culture without the presence of other factors,[6] clearly demonstrating the extent of micronutrient and growth factor enrichment in this fluid. Several initial studies of CSF function had suggested that signaling factors present in the CSF mediate satiety, circadian rhythms, and locomotor behavior.[7,8] In these early studies, reinstatement of feeding behaviour was induced by infusing CSF collected from fasted sheep into the ventricles of satiated sheep,[9] and similarly, CSF collected from sleep-deprived goats increased the duration of sleep and decreased locomotor activity when infused into the ventricles of rats.[7] These findings indicated that substances present in the CSF can exert a significant influence on motivated behaviors. More recently, Pedrazzoli and colleagues established that the peptide orexin (a.k.a., hypocretin) is increased in the CSF during sleep deprivation.[10] In addition to regulating arousal and wakefulness, orexin has been implicated in drug reinforcement, obesity and neurodegenerative diseases, such as Parkinson and Alzheimer's diseases.[11-15] As such altered expression of orexin in the CSF under these physiological conditions could be a mediating factor for the sleep-related effects in the earlier study[7] and may also have additional multifaceted effects on physiological function.

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CHOROID PLEXUS AND CEREBROSPINAL FLUID (CSF)

In vivo, production of CSF occurs at several choroid plexus sites, including the lateral, third and fourth ventricles, thus creating an independent circulatory system for the brain.[3] At each of these sites, the choroid plexus appears to differ in some respects in structure, function, and factors produced/released into the ventricles.[16] The epithelial cells that comprise the choroid plexus contain extensive basolateral infoldings and microvilli, providing an extensive surface area for transport into the ventricular fluid. These cuboidal epithelial cells exhibit a polarized shape, with differential function ascribed to the apical and basolateral membranes.[17] The apical membrane interfaces with the capillaries of the brain and mainly functions to uptake nutrients from the blood, whereas the basolateral membrane provides a removal mechanism for toxins and excess substances from the CSF, in addition to releasing factors into ventricular circulation.[17] As such, dysfunction in the transport mechanism of the choroid plexus could potentially alter CSF compositions and compromise brain health.

The potential for CSF-derived factors to impact neural function may be further imparted when one takes into account that the total surface area at the choroid plexus-CSF interface is roughly the same as the entire blood-brain-barrier.[16] As CSF is generated, it moves transcellularly and paracellulary among the epithelial cells of the choroid plexus to be released into the ventricular space.[16] Since the amount of CSF produced allows for turnover of approximately four times per day in humans,[18] the levels of circulating factors has the potential to be continuously regulated to influence neuronal function. It has also been proposed that the apical membrane of the choroid plexus expresses receptors that function as feedback loops to mediate the further release of certain factors into the ventricles,[16] and thus the presence of growth factors, neuropeptides, proteins, cytokines and hormones may be regulated in this manner. Indeed, this feature of the choroid plexus has been experimentally exploited to alter growth factor release; genetically displaying growth factor ligands on bacteriophage coats binds the construct to receptors on the choroid plexus cell surface, thus altering further release of the growth factor into the ventricle.[19] In addition to factors produced by the epithelial cells of the choroid plexus, the presence of blood vessels in the choroidal stroma allows for the presence of the CSF-blood interface through which factors from the blood may enter the central nervous system through leaky endothelial junctions.

EXTRACELLULAR TRANSPORT IN THE CSF

It has been proposed that the transport of factors from the choroid plexus into the ventricular CSF may occur *via* three main routes: (1) transport in the CSF itself as the choroid plexus is permeable for smaller molecules, (2) membrane-bound transport mechanisms on the plasma membrane of choroidal epithelial cells, (3) release from the intracellular compartment as extracellular vesicles[20] (Figure 1). In the prior literature, these extracellular vesicles have been referred to as either exosomes or microvesicles, although this terminology inconsistently varies across fields.[21] Van der Pol and colleagues propose that the main distinction between the two types of vesicles concerns their size, with exosomes being smaller in diameter than microvesicles when examined from the same cell. However, this distinction is not clearly defined when one considers varying types of cells. For instance, exosomes have been most commonly reported to range from ~50-100 nm in diameter, and microvesicles from between ~20-1000 nm in diameter; as can be seen, these classifications provide a range of overlap.[21] Both types of extracellular vesicles can be formed by an outward blebbing of a cell's plasma mem-

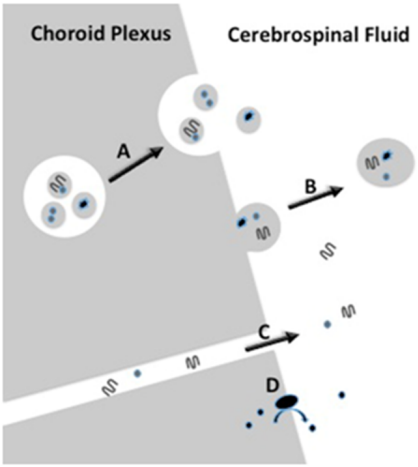

Figure 1: Mechanisms of extracellular transport from the choroid plexus into the cerebrospinal fluid. Factors derived from the choroid plexus may be released into the ventricular space: (A) as exosomes released from intracellular Multivesicle endosomes (MVEs) through exocytosis, (B) *via* blebbing of the cellular membrane as a microvesicle or exosome, (C) transcellularly and/or paracellulary with release of cerebrospinal fluid, or (D) *via* membrane-bound transport mechanisms located in the epithelial plasma membrane.

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brane, but exosomes may be additionally formed as intraluminal vesicles within multivesicle endosomes that are then released from the cell as the endosome fuses with the plasma membrane. For the purposes of this review, we will employ the general terminology of extracellular vesicles to refer to both exosomes and microvesicles, and moreover, it should also be noted that this classification is distinct from membrane particles or apoptotic vesicles.[21] Many cell types have been shown to release extracellular vesicles *via* budding of the cell membrane, including epithelial, immune, tumor and stem cells,[22,23] and the resulting vesicles differ in content and function. Whereas initial investigations assumed extracellular vesicles contained cellular debris, growing evidence has established that these compartments are enriched with a vast source of signaling molecules that have crucial roles in a number of physiological processes. Release of extracellular vesicles has been shown to occur *via* Ca2+-, protein kinase C-, or ceramide-dependent mechanisms, and after entry into the CSF, the vesicles may immediately breakdown to dump contents into the fluid or can travel to a distant site to fuse with the membrane of a target cell and transfer genomic material.[22-24] The method of vesicular packaging for extracellular communication may be preferred for mRNA and miRNAs transport, as exposure to circulating RNAses are limited and long-distance communication may be achieved *via* cell-specific targeting motifs on the vesicle surface. Importantly, several recent reports have demonstrated that mRNA from microvesicles can become integrated and translated into the proper protein within the target cell,[23,24] short-interfering RNA (siRNA) packaged into exosomes can efficiently silence gene expression,[25] and epigenetic changes can be induced in target cells *via* transfer of miRNAs.[22] In consideration of these findings, elucidation of the structure and function of these packaged compartments could hold promise as a novel avenue for therapeutic delivery of preloaded vesicles with mRNA, miRNA, siRNA or pharmacological compounds into the central nervous system.

RELEVANCE TO NEUROPATHOLOGY

With the exception of hydrocephalus, the CSF has not traditionally been considered a vital regulatory mechanism of and/or implicated in human disease states. However, recent reports are beginning to redefine our understanding of choroid plexus and CSF function as they demonstrate the importance of factors derived from the CSF in maintaining physiological function (Table 1). For instance, growth factors produced by the choroid plexus, such as Insulin-like growth factor 2 (IGF2) and Fibroblast growth factor 2 (FGF2), have been shown to regulate neurogenesis throughout the lifespan.[3,6] Further, an elegant study from Sawamoto and colleagues recently demonstrated that the CSF directly interacts with cilia in the subventricular zone to mediate the migration of progenitor cells in the adult brain.[26]

Choroid plexus transport has been implicated as a contributing factor for certain neurodegenerative diseases. For instance, Fragile X-associated tremor/ataxia syndrome (FXTAS) is associated with iron dysregulation in mitochondria.[27] Interestingly, post-mortem FXTAS subjects exhibit an accumulation of iron in the stroma of the choroid plexus and decreased amounts of transferrin, ferroportin, and ceruloplasmin, all of which are essential to the transport of iron.[27] These findings suggest that abnormal transport of iron within the choroid plexus may contribute to pathophysiology exhibited by FXTAS subjects. Another disorder, cerebral folate transport deficiency, is characterized by a lack of B-vitamin within the brain. The polarized cells of the choroid plexus have been shown to translocate the folate receptor α(FRα) in a unilateral direction from the basolateral to the apical compartments, leading to exocytosis into the CSF and subsequent integration in the brain parenchyma.[28] Thus, abnormal transport of substrates involved in the production of B-vitamins may underlie the pathology found in this disorder.

To date, dysfunction of the choroid plexus has been most studied as a mediating factor of Alzheimer's disease. Post-mortem, neural pathology in the Alzheimer's brain is evidenced by a build-up of amyloid-β (Aβ) plaques and intracellular neurofibrillary degeneration of hyperphosphorylated tau (neurofibrillary tangles).[29,30] Under normal circumstances, the Aβ protein is produced by the brain and subsequently becomes cleared through enzymatic degradation, capillary reabsorption, and/or CSF transport through the choroid plexus.[29,31] In contrast, pathological accumulation of Aβ plaques and neurofibrillary tangles in the disease state leads to dysfunction of neurons and synapses throughout the brain, most notably those in brain regions involved in memory and cognitive function, such as the hippocampus and cortex.[32] As such, recent evidence suggests that the choroid plexus and CSF may play a significant role in the pathology of Alzheimer's disease.[1,31,33] Altered clearance of Aβ by the CSF with aging results in accumulation of Aβ protein, thus promoting the formation of plaques. In late onset Alzheimer's disease, structural abnormalities of the choroid plexus, which in-

Disease	Fragile X-Associated Tremor/Ataxia Syndrome	Cerebral Folate Transport Deficiency	Alzheimer's Disease	Multiple Sclerosis	AIDS
Choroid Plexus Characteristics	Iron accumulation in stroma	Failure to transport FRα along with B-vitamin	Failure to clear amyloid-β (Aβ) plaques	HLA-DR expression	Accumulation of HIV-1
CSF Characteristics	Low iron levels	Low FRα and B-vitamin levels	Accumulation of amyloid-β (Aβ) protein	Increased CD4/CD8 ratio	To be further investigated

Table 1: Summary of neuropathology associated with abnormal choroid plexus and CSF.

clude cellular atrophy, calcification and fibrosis, and thickening of the basement membrane,[29] are evidenced. These abnormalities are thought to lead to altered synthesis, secretion, clearance and transport of factors between the choroid plexus, cerebrospinal fluid and blood.[29] Therefore, in patients with Alzheimer's disease, choroidal dysfunction prevents adequate clearing of Aβ from the CSF and promotes Aβ accumulation in the brain.[29,33] Another possible role for CSF in the pathogenesis of Alzheimer's disease is through transport of melatonin. The pineal gland directly secretes melatonin into the CSF of the third ventricle,[34] or, alternatively, the hormone may enter *via* leaky endothelial cells of blood vessels in the choroid plexus.[35] Interestingly, recent findings suggest that the amount of melatonin in the CSF is negatively correlated with the status of Alzheimer's disease symptoms.[36] Through its actions as an antioxidant it has been proposed that melatonin exerts neuroprotective effects by counteracting oxidative damage.[36] In the younger brain, evidence suggests that melatonin administration can result in anti-amyloid and antioxidant effects; however, administration of melatonin to the aged brain has been shown to exert a minimal effect on pre-existing amyloid deposits.[37] Thus, as a therapeutic approach, strategies to increase melatonin in the CSF may be of benefit in the early stages of Alzheimer's disease and/or as a preventative measure based on familial considerations.[38]

The choroid plexus also functions as a principal mediator of the innate immune response of the central nervous system. Peripheral immune molecules interact with receptors located on choroid plexus cells to initiate the release of proinflammatory molecules, such as interleukins, into the CSF.[16] Myeloid progenitors located in the vascularized choroid stroma have also been shown to provide a source of brain macrophages.[39,40] Moreover, inflammatory processes mediated by the choroid plexus have been speculated to contribute to the heightened immune response found in multiple sclerosis and encephalitis.[41] In addition, the choroid plexus is a main entry point for viruses to infiltrate the brain from the periphery. For instance, the presence of HIV-1 in the choroid plexus has been suggested to occur prior to the onset of Acquired Immune Deficiency Syndrome (AIDS) and immunosuppression,[42] and infected CSF or choroid plexus-derived macrophages can induce toxic effects on neurons *in vitro*.[43] HIV-1 or other viruses may also be capable of altering the expression of signaling molecules within the epithelial cells of the choroid plexus to permit enhanced entry of the virus into the CSF, a possibility which needs to be more systematically investigated in future studies.

Finally, given the close proximity of CSF to brain regions implicated in substance abuse, such as the habenula, hippocampus, and interpeduncular nucleus,[44,45] signaling molecules in the CSF could potentially regulate the neural processes underlying the addictive state. Interestingly, nicotine has been shown to mediate the function of the choroid plexus.[46,47] Transthyretin, the plasma thyroid hormone transport protein, is produced by the choroid plexus and acts to transport thyoxine across the blood-brain barrier,[48] and nicotine administration has been found to increase the synthesis and release of transthyretin into the CSF.[47] Further, prenatal exposure to nicotine has also been correlated with an increased incidence of pathological features of the fourth ventricle choroid plexus and premature death.[46] However, further investigations will be critical to ascertain whether extracellular factors from the choroid plexus/CSF are important mechanisms that mediate the development and maintenance of drug dependence. "If established, these findings have the potential to redefine our understanding of novel signaling mechanisms within the brain and in doing so, could provide a foundation for more efficacious therapeutic approaches Table 1."

CONCLUSION

Our current understanding of the function of the choroid plexus and CSF has begun to be transformed, and as such, the emerging importance of these signaling mechanisms must now be recognized as putative essential mediators of brain function. Extracellular signaling factors have been shown to integrate in and modulate function of neurons within the brain and thus, have the potential to both maintain normal homeostatic function and/or contribute to pathological disease states. Moreover, CSF-derived factors also hold the potential to serve as biomarkers of disease. As the field progresses, the vital function of factors derived from the choroid plexus will likely continue to emerge, and these advances may then provide a foundation for novel approaches to treat neuropathology in humans.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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