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Cerebrospinal Fluid

Functions, Composition and Disorders

Vendelin Slavik
Tereza Dolezal
Editors

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NEUROSCIENCE RESEARCH PROGRESS

CEREBROSPINAL FLUID

FUNCTIONS, COMPOSITION AND DISORDERS

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VENDELIN SLAVIK
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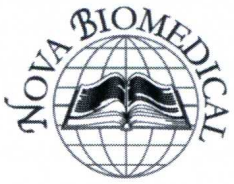

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has become an important tool in the diagnosis of neurological disorders. In small animals, CSF is usually collected from the lateral ventricle or cisterna magna. Due to the increase in using small animal models in neurodegenerative diseases, measuring biological markers in the CSF of these animals has also become essential. Moreover, the development of more sensitive detection techniques also makes the measurement of these biomarkers feasible in CSF from small animals. Finally, CSF biomarkers reflecting pathology of neurodegenerative diseases are reviewed. These markers play a role in the initial diagnosis, monitoring of disease progression as well as treatment responses.

Chapter II - Subarachnoid hemorrhage (SAH) is a special form of hemorrhagic stroke, which is followed in about 30% of the cases by severe complications, mainly symptomatic vasospasm. The patients show a rapid neurological deterioration, poor clinical outcome, and high mortality. One of the main problems is that it is yet not possible to clearly identify individuals at risk for vasospasm. In this chapter, the author describes the use of a microdialysis system for sampling an ultrafiltrate of cerebrospinal fluid (CSF), subsequently followed by proteomic analysis to identify and quantify proteins with concentration changes between patients developing vasospasm, and these who are not affected. The chapter summarizes the current technological status of cerebral microdialysis as monitoring tool in neurotraumatology and stroke, and not only for sampling microdialysate, but also as a tool to deliver substances into the brain with a therapeutic claim. Moreover, the chapter introduces advances in proteomics with regard to technological updates in two-dimensional gel electrophoresis, high-pressure liquid chromatography, and mass spectrometry. In the last part of the chapter, clinical aspects of the combination of cerebral microdialysis and proteomics are discussed, including ethics, feasibility, time-course, and therapeutic options. In conclusion, proteomics of cerebral microdialysate may be a useful tool diagnosis, disease monitoring, and therapeutic intervention of neurological patients.

Chapter III - Several neurological diseases are associated with the axonal abnormalities. Various structures of neuronal cytoskeleton can be released into the extracellular fluid and leak into cerebrospinal fluid (CSF) as a consequence of disturbed axonal integrity. Their examination in CSF may provide valuable information about the extent of axonal loss, prognosis or therapy strategy. Many studies have described the changes of CSF levels of neuronal cytoskeleton components in certain neurological disorders.

Moreover, the released neurocytoskeletal constituents may act as antigens and induce an immune response. The presence and significance of CSF anti-neurocytoskeletal autoantibodies have been also studied.

In the authors' review the authors concentrate to the selected components of neuronal cytoskeleton and antibodies against them in the cerebrospinal fluid. The authors discuss their benefits to the estimation of the extent of axonal degeneration and loss in selected neurological diseases such as multiple sclerosis, Alzheimer disease and others.

Chapter IV - The Central Nervous System (CNS), made up of the encephalon and the spinal cord, is protected from without by the dural, arachnoid and pial membranes.

The cerebrospinal fluid (CSF) is mainly produced in the choroid plexi of the lateral cerebral ventricles (I and II), and III and IV ventricles (70%) and the remaining 30% is produced from the cerebral capillaries.

The CSF produced in the lateral ventricles passes through Monro's foramen to the III ventricle and from there through Silvio's aqueduct to the IV ventricle, circulating from here through the Luschka and Magendie foramina to the spinal cisterns and subarachnoid space and through the obex to the medullary ependyma conduct. The CSF bathes the brain and the spinal cord, protecting its structures and later it is reabsorbed unidirectionally to the venous sinuses through Pachioni's arachnoid bodies in the duramater of the superior sagital sinus.

In normal conditions, the total volume of CSF produced in the adult ranges from 600 to 700 mL/day. Taking into account that, in humans, the total volume of CSF contained in the subarachnoid spaces and ventricles is approximately 40 to 60 mL in the newborn and between 110 and 170 mL in the adult, of which 25 mL are found in the ventricles, this means that the CSF is renewed several times a day at the rate of 0.45 mL/minute.

Although the composition of the CSF is similar to that of a plasma ultrafiltrate, there are differences which indicate that the CSF formed is produced by facilitated diffusion and active transport as well as by a mechanism of filtration or passive diffusion.

CSF secretion is directly proportional to the transport of Na which depends on the dependent Na/K-ATP-ase pump, there also being other pumps which exchange Cl^- for HCO_3^-, and Na^+ for H^+.

With respect to plasma, CSF contains higher concentrations of Na^+, Cl^-, Mg^{++}, and lower concentrations of K^+, Ca^{++}, glucose, albumin and globulins.

The concentration of solutes of CSF vary according to the puncture site of the sample, indicating that its composition depends on the metabolism of the

conjoining structures it bathes, hence the importance of the puncture site. Water passes from the stroma to the CSF following the concentration gradient produced by the ATP-ase dependent "ionic pumps" and carrier proteins. The water and other cellular metabolites proceeding from neurones and glial cells enters the extracellular liquid and from here joins the CSF.

The differences observed in the permeability and diffusion rate through structural and functional interphases, which establish dynamic control over the transfer of chemical substances with respect to the intracellular, intercellular and CSF compartments of the CNS, are explained by the so-called encephalic barriers: blood-encephalon barrier, blood-CSF barrier and encephalon-CSF barrier.

The CSF maintains a suitable chemical environment for neurotransmission and eliminates metabolic products and substances which are harmful for the CNS.

Chapter V - Stochastic differential equations in which the drift is a quadratic function of the state variable and the infinitesimal standard deviation is proportional to the state variable are pervasive in electrical engineering, signal processing, the neurosciences, and the management sciences. Within this class, the homogeneous case in which the drift term contains no constant parameter is well-understood but the inhomogeneous case remains less researched. The basic issues of existence, positivity and explosion of solutions for the inhomogeneous case are addressed in this paper. It is shown that these results help settle an ambiguous issue arising in a fundamental neuroscience model and are of potential value in a class of signal processing models arising in electrical engineering.

Chapter VI - Alzheimer's disease (AD), Lewy-body disease (LBD) and Frontotemporal Dementia (FTD) are the major causes of memory impairment and dementia. As new therapeutic agents are under testing for the different diseases, there is an ultimate need for an early differential diagnosis. Biomarkers can serve as early diagnostic indicators or as markers of preclinical pathological changes. Therefore, diagnostic markers in the cerebrospinal fluid (CSF) have become a rapidly growing research field, since CSF is in direct contact with the central nervous system (CNS) and is supposed to reflect the brain environment.

So far, three CSF biomarkers, the 42 amino acid form of β-amyloid (Aβ), total tau and phosphotau, have been validated in a number of studies. These CSF markers have high sensitivity to differentiate early and incipient AD from normal aging, depression, alcohol dementia and Parkinson's disease, but lower specificity against other dementias, such as FTD and LBD.

This chapter reviews CSF biomarkers for AD, with emphasis on their role in the clinical diagnosis.

Chapter VII - The barrier between blood and CSF contributes to homeostasis of the CNS and protects it from potentially harmful substances present in the blood. Lipoproteins present in the CSF are clearly distinct from their plasma counterparts. Human CSF lipoproteins contain mainly Apo AI and Apo E, the former deriving mostly from plasma after crossing the blood–cerebrospinal fluid barrier, the latter being also produced by CNS. Apo AI and E containing lipoproteins in the brain are key players in transport and delivery of lipids, cholesterol homeostasis, and are also involved in CNS remodeling mechanisms. On the other hand, the isoform apo E4 represents the most important genetic risk factor for sporadic and familial late-onset Alzheimer's disease and is involved in brain injury and neurodegenerative diseases.

Apo B containing lipoproteins are not produced by CNS and the characterization of normal human CSF lipoproteins did not allowed the isolation of low density lipoproteins. Lipoprotein(a) is a low density lipoprotein-like particle with the unique protein apo(a), which is characterized by a dimensional polymorphism. Lipoprotein(a) is a well known risk factor for athero-thrombosis. The pathological role of Lipoprotein(a) is strictly associated with its plasma concentrations and the size of apo(a) isoforms, with inverse relation. The pathophysiology of Lipoprotein(a) in cardio and cerebrovascular system is widely studied. Recently, the authors demonstrated that, in neuroinflammatory and neurodegenerative disorders, Lipoprotein(a) can cross a dysfunctional blood-CSF barrier and be found in the CSF.

This chapter focuses on the physiological presence of the lipoproteins in CNS, on the pathological aspects deriving from their isoforms, and in particular on the anomalous presence in CSF of Lipoprotein(a).

CONTENTS

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Chapter I

CEREBROSPINAL FLUID: PHYSIOLOGY, BIOMARKER AND METHODOLOGY

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ABSTRACT

Cerebrospinal fluid (CSF) is in direct contact with interstitial fluid in the central nervous system (CNS), and biological changes in the CNS can be reflected in the CSF. Therefore, the collection of CSF has become a vital part of diagnosing different CNS diseases. In the present chapter, we will review CSF formation, describe CSF collection and discuss biological markers. Initially, two existing theories regarding the formation of CSF are reviewed. The classic theory hypothesizes that CSF is secreted mainly from choroid plexuses located in brain ventricles, circulates to the cisternae and subarachnoid space, and returns to the venous system through absorption by arachnoid villi. Recent data also support another theory that CSF is a net consequence of filtration and reabsorption of fluid volume through the capillary walls by osmotic and

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hydrostatic forces. There is a constant exchange in fluids and substances between the CSF system and surrounding tissues, which achieves homeostasis in physiologic states. Subsequently, methods for collecting CSF in human and small animals are reviewed. In human, lumbar puncture is one of the most common and effective ways to collect CSF, and has become an important tool in the diagnosis of neurological disorders. In small animals, CSF is usually collected from the lateral ventricle or cisterna magna. Due to the increase in using small animal models in neurodegenerative diseases, measuring biological markers in the CSF of these animals has also become essential. Moreover, the development of more sensitive detection techniques also makes the measurement of these biomarkers feasible in CSF from small animals. Finally, CSF biomarkers reflecting pathology of neurodegenerative diseases are reviewed. These markers play a role in the initial diagnosis, monitoring of disease progression as well as treatment responses.

Keywords: biomarkers, cerebrospinal fluid, CSF collection, neurodegenerative diseases

Cerebrospinal fluid (CSF) is a clear colorless fluid and the major part of the extracellular fluid (ECF) of the central nervous system (CNS). The CSF fills the brain ventricles and central spinal canal and forms a thin layer around the brain and spinal cord in the subarachnoid space and cisterns. Due to its proximity to the CNS parenchyma, the CSF is an optimal fluid for measurements of brain metabolism in health and disease states. The fluid is accessible for sampling by lumbar puncture in patients and has a long track record for the measurement of biomarkers.

I. CSF Functions

The CSF has a number of important functions (Ramson, 2009). It is a physiological medium for the CNS and provides mechanical support for the CNS in the way that the CNS floats in the CSF, reducing its effective weight. In the air the brain weighs 1500 grams and its weight in the CSF is less than 50 grams. This buoyancy is a consequence of the difference in the specific gravities of brain tissue (1.040) and CSF (1.007) (Ramson 2009). CSF also acts as a drainage pathway for the products of metabolism and synaptic activity. These products are removed via perivascular space. These products can also be diffused from the interstitial fluid (ISF) into the CSF through the

pia and ependymal layer, and subsequently removed through the arachnoidal villi. The brain lacks a lymphatic system and, thus, the perivascular space and CSF essentially serve as a modified transport avenue to the lymphatic system for the brain (Segal, 1993; Terlizzi and Platt, 2006). The CSF is an important route by which some nutrients reach the CNS (Segal, 2001). CSF acts as a channel of communication within the CNS, by carring hormones and transmitters between different areas of the brain. For example, hormone releasing factors formed in the hypothalamus are discharged into the CSF of the third ventricle and carried in the CSF to their effective sites in the median eminence (Terlizzi and Platt, 2006).

Table 1. The composition of the CSF and plasma[a]

	plasma	CSF	$R_{CSF/plasma}$
Na^+ (mM)	150	147	0.98
K^+ (mM)	4.7	2.9	0.62
Mg^{2+} (mM)	0.6	1.1	1.8
Ca^{2+} (mM)	1.3	1.1	0.85
Cl^- (mM)	99	113	1.14
HCO_3^- (mM)	24	22	0.92
amino acids (mM)	2.6	0.7	0.27
protein (g/dL)	7	0.03	0.004
osmolality (mOsM)	290	290	1
pH	7.4	7.31	
glucose (mM)	6.3	4.2	0.67

[a] Values are for human, Ransom 2009; Segal, 2001; Davson et al.; Glucose value is from dog, Brown et. 2004. $R_{CSF/plasma:}$ concentration in CSF/concentration in plasma.

II. CSF Composition

The compositions of CSF are considerably different from that of plasma (Table 1), especially in that protein is greatly reduced in the CSF. Thus, CSF is not simply a filtrate of the plasma but is a product of plasma filtration and membrane secretion. CSF, in general, is clear, colorless, nearly acellular, and has a low protein concentration. Various ions, enzymes, and other bioactive substances are also found in normal CSF. In healthy humans and animals, the

CSF composition is maintained relatively constant by various membrane interfaces.

Erythrocytes and nucleated cells: CSF normally does not contain erythrocytes (Bailey and Higgins, 1985) and the normal range for total nuclear cell count is up to 5 per mm^3 in adults and 20 per mm^3 normally in newborns (Seehusen et al., 2003).

Protein concentration: Albumin is the main protein in CSF (50–70%), and normally γ-globulin levels are very low (5–12%). When the blood brain barrier (BBB) is damaged, protein leaks into the CSF. Albumin enters the CSF in the greatest quantities because the concentration of these proteins is the highest in blood (Di Terlizzi and Platt, 2006).

Glucose in the CSF is derived essentially from the plasma and carried into the brain by facilitated transport or diffusion. Only a limited amount of glucose enters the brain by diffusion (Fishman, 1992). When the concentration of glucose in the blood is low, more glucose is transported across the capillaries by the carrier mechanism. However, high concentrations of glucose saturate the carrier molecules. Therefore, the concentration of CSF glucose depends on the blood glucose concentration, the rate of glucose transport into the CSF, and the metabolic rate of the CNS. The normal CSF glucose concentration is about 60–80% of the blood glucose concentration, reflecting in part the high metabolic rate of the CNS.

Sodium is the most abundant ion in the CSF, and is important in signal transport and osmoregulation. Sodium concentrations in CSF and plasma are closely related. Some studies reported that acetazolamide, an inhibitor of carbonic anhydrase, slows the entrance of sodium into the CSF, and vasopressin enhances the movement of sodium from blood to the CSF. The electrical charge across a membrane is determined by the distribution of charged ions including Na^+ on either side of the membrane. In epithelial cells, the electrical charge is regulated mainly by the Na^+/K^+-ATPase pump (Oppelt et al., 1964; Ransom, 2009; Speake et al., 2001).

Potassium concentration is critical for neuronal function and the release of neurotransmitters (Bradbury and Davson, 1965; Pollay et al., 1985; Rosenberg, 1990). Potassium ionic concentration is lower in CSF than in plasma and is maintained within a very narrow margin. Changes in plasma potassium concentration have little effect on the CSF potassium levels. Even with very high plasma potassium concentrations, the CSF potassium concentration remains within a normal range, because its transport into the CSF is limited. Choroid plexus epithelium has a lower permeability to potassium than to sodium, and the reverse is true at the capillary level. When

potassium levels are increased in the CSF, sodium is exchanged with potassium by an active transport mechanism.

Calcium in the CSF is normally lower than in plasma. Calcium is secreted from the choroid plexus and the amount that enters from blood into the CSF is independent of the concentration of calcium in the plasma. The low CSF concentration of calcium is maintained by transport mechanisms between blood and CSF. Both cerebrovascular endothelium and the choroid plexus participate in this active process (Wood, 1983). Acute and chronic changes in plasma calcium concentration have little effect on CSF calcium levels (Murphy et al., 1986).

Magnesium and chloride are higher in CSF than in plasma, and both ions are known to play important roles in neuronal conduction. The movement of these ions between the blood and CSF does not occur exclusively by passive transport (Wood, 1983). Some studies have reported that the intravenous administration of acetazolamide in cats causes a proportional reduction in the rate of CSF formation as well as the entry of chloride into the CSF. This finding indicates that the movement of chloride ions from blood to CSF is closely linked to CSF production (Di Terlizzi and Platt, 2006).

III. CSF Production and Absorption

III.1. Classic Theory

III.1.A. CSF Production

CSF formed within the lateral ventricles drains into the centrally situated third ventricle through the two foramina of Monro (Figure 1). The CSF then passes down the narrow aqueduct of Sylvius into the fourth ventricle. It then exits the ventricular system via the foramen of Magendie and paired lateral foramina of Luschka into cisterna magna and subarachnoid space. A small quantity of CSF also passes down the spinal canal. CSF returns to the dural venous system via the arachnoid villi in the superior sagittal sinus.

It is generally agreed that the majority of CSF is produced by the choroid plexus in the brain ventricles. The choroid plexus is a branched and highly vascularized structure consisting of numerous villi which project into the ventricles (lateral, third and fourth) of the brain. Each villus is composed of a single layer of epithelial cells overlying a core of connective tissue and blood capillaries. The choroid epithelial cells are cuboidal and have an apical border with microvilli and cilia that project into the CSF in the ventricles (Figure 2).

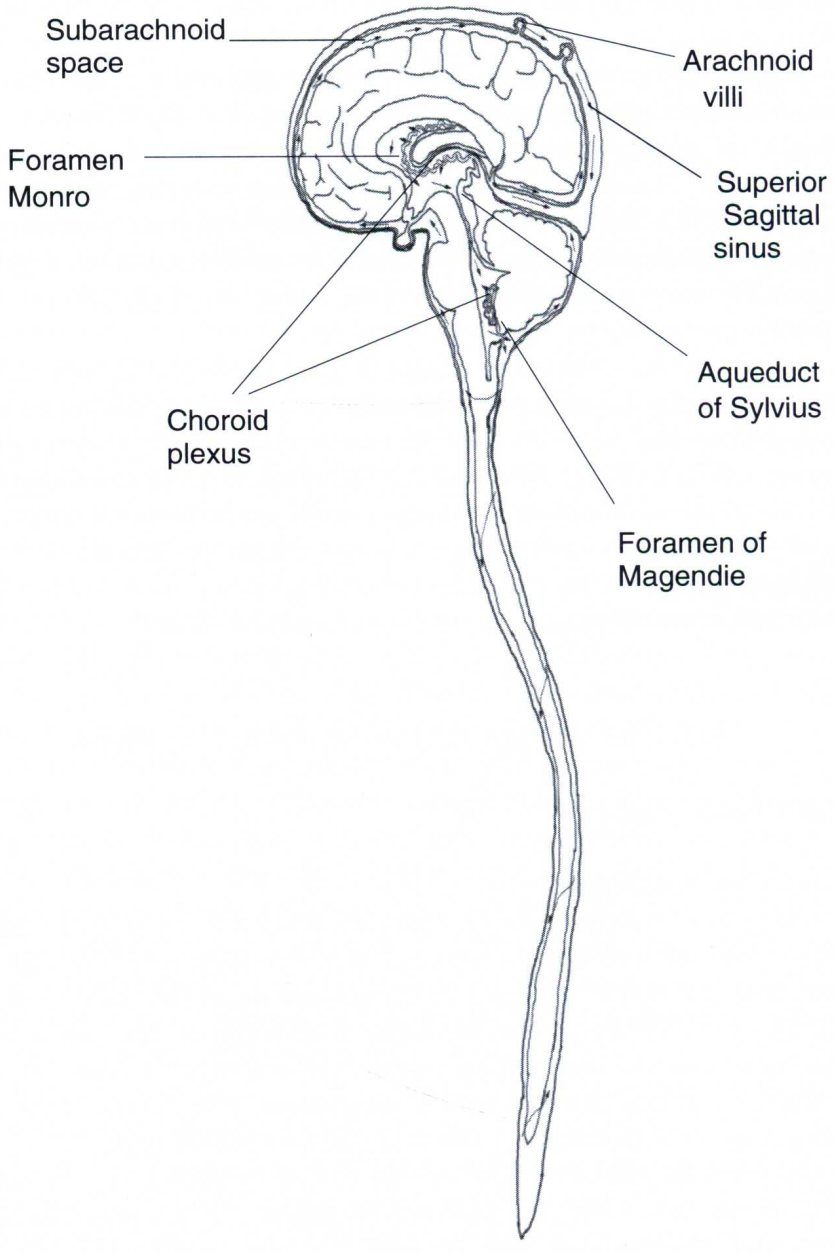

Figure 1A. Circulation of CSF.