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CEREBROSPINAL FLUID REVIEW: CONSIDERATIONS FOR IMMUNOREGULATORY ROLE AND CURRENT TRENDS

M.A. Kriventsov

State Institution "Crimea State Medical University named after S.I. Geogrievsky", Human anatomy department (head — prof. Pikalyuk V.S.). 95006 Ukrain, Simferopol, Lenin Boulevard, 5/7. E-mail: maksimkgmu@gmail.com

ОГЛЯД ЦЕРЕБРОСПІНАЛЬНОЇ РІДИНИ: ОБГОВОРЕННЯ ІМУНОРЕГУЛЯТОРНОЇ РОЛІ ТА СУЧАСНІ ТЕНДЕНЦІЇ

М.А. Крівенцов

РЕЗЮМЕ

В даній оглядовій статті представлені деякі аспекти анатомії і фізіології спинномозкової рідини, пов'язані з її регулюючою роллю в організмі з врахуванням останніх наукових досліджень. У статті викладені основні дані про продукцію, циркуляцію і абсорбцію спинномозкової рідини (СМР), питання її физико-хімічного складу, значення гематоенцефаліческих бар'єрів, а також фізіологічній ролі ліквору в ембріогенезі і у дорослих людей. Грунтуючись на цих даних, особлива увага приділяється концепції відхилення імунної відповіді, пов'язаної з мозком. Нарешті, зроблена спроба надати обгрунтування експериментального використання ксеногенної СМР. Даний огляд не претендує на повноту аналізу літературних даних. Навпаки, мета даної статті полягає в акцентуванні уваги на питаннях фізіологічної ролі СМР і сучасних тенденціях і найближчих перспектив наукових досліджень в цій області.

ОБЗОР ЦЕРЕБРОСПИНАЛЬНОЙ ЖИДКОСТИ: ОБСУЖДЕНИЕ ИММУНОРЕГУЛЯТОРНОЙ РОЛИ И СОВРЕМЕННЫЕ ТЕНДЕНЦИИ

М.А. Кивенцов

РЕЗЮМЕ

В данной обзорной статье представлены некоторые аспекты анатомии и физиологии спинномозговой жидкости, связанные с ее регулирующей ролью в организме с учетом последних научных исследований. В статье изложены основные данные о продукции, циркуляции и абсорбции спинномозговой жидкости (СМЖ), вопросы ее физико-химического состава, значения гематоэнцефалических барьеров, а также физиологической роли ликвора в эмбриогенезе и у взрослых людей. Основываясь на этих данных, особое внимание уделяется концепции отклонения иммунного ответа, связанного с мозгом. Наконец, предпринята попытка предоставить обоснование экспериментального использования ксеногенной СМЖ. Данный обзор не претендует на полноту анализа литературных данных. Напротив, цель данной статьи состоит в акцентировании внимания на вопросах физиологической роли СМЖ и современных тенденциях и ближайших перспектив научных исследований в этой области.

Key words: cerebrospinal fluid, anatomy, physiology, immune system.

Cerebrospinal fluid (CSF) is a clear, colorless, bodily fluid that occupies the subarachnoid space and the ventricular system around and inside the brain and spinal cord. From historical view, the presence of fluid in the brain was known to ancient physicians. Hippocrates (460–375 BC), when describing congenital hydrocephalus, commented on "water" surrounding the brain [1]. Galen (130–200), the premier anatomist prior to Vesalius (1514–1564), referred to "excremental liquid" in the ventricles of the brain from where it is purged into the nose [2]. Starting from "scientific" discovery of the CSF by Emanuel Swedenborg (1688–1772) [3] and Albrecht von Haller (1708–1777) [4], all the directions of the CSF scientific research can be commonly classified into: issues of production, circulation and absorption of the cerebrospinal fluid; issues of normal and pathological physical and chemical composition of the cerebrospinal fluid; issues related to the regulation and permeability of the blood-brain barriers, which affect the cellularity and chemical composition of the CSF; issues of the physiological roles of the CSF during embryogenesis and in adults; aspects related to immunology of the CSF and concept of the brain-associated acquired immune deviation (BRAID); studies on the activities of the xenogenous CSF on the various tissues and organs, demonstrating range of the application points.

1. Production, circulation and absorption of the CSF. Although the classical notions of production, circulation and outflow of the cerebrospinal fluid lies in fact that the CSF is formed by choroid plexus, circulates through the inner and outer spaces of the CNS and outflows into the venous system, recent studies with the advent of new methods bring important information concerning the anatomical issues.

1.1. Production of the CSF Several CNS regions form CSF or a CSF-like fluid. Although choroid plexus (CP) tissues generate about two thirds of the total production, extrachoroidal sources make up the balance [5, 6]. The compositions of plasma and CSF are very similar, with the only major difference being protein, which has a greatly reduced concentration in the CSF. The CSF is not, however, an ultrafiltrate of the plasma

but is actively secreted by the choroid plexuses [7]. This was clearly demonstrated in experiments showing that the concentrations of some ions in the CSF are very carefully regulated, and more importantly are independent of variations in the plasma concentrations of these ions, e.g. K+ [8, 9], HCO3– [10] and Ca2+ [11]. The composition of an ultrafiltrate could not be regulated in this manner. CSF generation is a cardinal feature of brain fluid homeostasis [12]. To finely control the CSF formation rate is a challenge in treating diseases related to brain fluid disorders. Historically, emphasis has been placed on discovering new agents to relieve elevated CSF pressure, i.e., intracranial pressure (ICP), in pediatric hydrocephalus patients. Projections point to the additional compelling need for increasing CSF turnover rate in geriatric patients, since many are taking diuretics and digitalis preparations that reduce CSF formation. This implicates a wider spectrum of CSF pharmacology, including studying of the transcription factors [13, 14, 15], ion transporters [16, 17], enzymes that modulate transport [18, 19, 20, 21, 22], aquaporins or water channels [23, 24, 25, 26], and receptors for neuropeptides [27, 28, 29].

1.2. Circulation of the CSF. Choroidally secreted CSF flows down the neuraxis to the 4-th ventricle and then out through hind brain foramina into the cisterna magna and the subarachnoid space in basal regions. In addition to this classically described pathway, new evidence indicates that ventricular CSF also flows by another route to the basal and midbrain cisterns, i.e., into subarachnoid extensions [30] of the velum interpositum (from dorsal 3-rd ventricle) and superior medullary velum (rostral 4-th ventricle). One of the issues requiring attention is the close bilateral relationship between cerebrospinal fluid and interstitial fluid of the brain [31]. Parenchymal interstitial fluid is actively secreted by the capillary endothelial cells. Interstitial fluid moves from its formation at the capillary-glial complex through the perivascular and subependymal regions into the ventricular system and subarachnoid space, where it mixes with the CSF [32].

1.3. Absorption (outflow) of the CSF. The classical textbook theory assumes that the projections of the arachnoid membrane into the cranial venous sinuses represent the primary sites for CSF clearance and when absorption through these sites is blocked, this leads to disorders of the CSF system. However, this view is increasingly being contested [33–38]. The most important lymphatic CSF absorption pathway is no doubt the olfactory route leading to cervical lymphatic vessels but there are other nerves that may conduct CSF extracranially. Even though the bulk of evidence favors the olfactory nerves as facilitating CSF-lymph connections, tracers injected into the CSF system appear to exit the cranium along almost all of the cranial nerves including the trigeminal, acoustic [39], hypoglossal and vagus nerves [40]. These data are not only crucial in the pathogenesis of hydrocephalus, the approaches to its correction and the possibility of endonasal administration of drugs [41], but also of interest from the standpoint of understanding the functional relationship of the humoral environment of the central nervous system and immune system in terms of the immune function regulation.

Thus, despite the comprehensive study of the anatomical, physiological, biochemical, and molecular mechanisms of the outflow of cerebrospinal fluid, the issue of the role and functional changes of components of the CSF on the "periphery" remains unexplored.

2. Physical and chemical composition of the CSF. Historically, CSF compositional analyses have been used widely to monitor distortions in brain metabolism, evaluate disruptions of barrier transport and permeability functions, obtain pharmacokinetic parameters for drugs targeting the brain parenchyma, and identify biomarkers for aiding the diagnosis and prognosis of CNS diseases [12]. Generally, studies of the physical parameters and chemical composition of the CSF, including a number of biologically active substances, which penetrate and / or secreted into the cerebrospinal fluid by the endocrine glands, located at the peripheral of periventricular areas, suggest about direct relationship of the structural and functional state of the CNS and cerebrospinal fluid. Biochemical analysis of the CSF has immense potential for diagnostics and prognostics [42]. In disease states the CSF composition is transformed by invading immune cells, plasma cytokines and pathogens, as well as by modified active secretions from CP.

Therefore the basic CSF estimated parameters are: the nutritional and trophic status of the brain in patients with hydrocephalus or dementia [43]; the purifying capacity of central anion and peptide reabsorptive systems in aging and Alzheimer's disease [44]; the therapeutic or cytotoxic concentration of certain CSF-borne agents targeted to neurons or meninges [45]; the presence of abnormal solutes [46], or normal molecules in atypical concentrations.

There are a lot of publications devoted to determination and evaluation of various chemical (biologically active) substances at the CSF of the patients with Alzheimer's disease, ischemic and hemorrhagic stroke, hydrocephalus, and various inflammatory, autoimmune, dystrophic-degenerative diseases of the CNS. For example, the total number of publications during the search at the PubMed database with TITLE keywords "Cerebrospinal fluid AND Alzheimer's disease" is more than 450.

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. These proteins may originate from several sources: exclusively from plasma, like albumin; primarily from plasma, but are also with a significant proportion synthesized intrathecally, like soluble intercellular cell adhesion molecule 1; primarily from the choroid plexus, like transthyretin; or primarily from brain parenchyma, like Tau protein

[47]. Peptide repertoire of the CSF includes hormones of the hypothalamus, pituitary gland, pineal gland, brain-specific hormonal active substances, hormones of the peripheral endocrine glands, various growth factors. One of the most comprehensive sources of information on protein composition of CSF is the monograph ‘’The CSF proteins” [48].

In addition to the compounds of protein nature cerebrospinal fluid contains a variety of biologically active substances of non-protein nature, such as amino acids, neurotransmitters, hormonally active substances, vitamins, cytokines etc. Some of them, such as melatonin, are secreted directly into the CSF to produce higher level at the CSF compared to plasma [49].

Cellurarity of the CSF at normal and pathological states is well described at the monograph “Integrated Cytology of Cerebrospinal Fluid” [50].

3. Regulation and permeability of the blood-brain barriers. The central nervous system (CNS) is tightly sealed from the changeable milieu of blood by the blood–brain barrier (BBB) and the blood–cerebrospinal fluid (CSF) barrier (BCSFB). While the BBB is considered to be localized at the level of the endothelial cells within CNS micro vessels, the BCSFB is established by choroid plexus epithelial cells. Unlike the capillaries that form the blood-brain barrier, choroid plexus capillaries are fenestrated and have no tight junctions. The endothelium, therefore, does not form a barrier to the movement of small molecules. Instead, the blood-CSF barrier at the choroid plexus is formed by the epithelial cells and the tight junctions that link them. The study of blood-brain barrier is a separate and independent direction of the scientific research. Most of the publications in this area are devoted to study the permeability of the blood-brain barrier, and factors affecting it. However, to understand the functional role of the CSF, the permeability of the blood-brain barrier is a key factor. Moreover, recent studies have demonstrated the possibility of penetration of the cells through the intact blood-brain barrier [51], contrary to classical ideas about the impenetrability of the barrier for large molecules and cells. This fact indicates a closer relationship between the periphery and, in particular, the immune system and cerebrospinal fluid. Recent data suggest that maintenance of normal CNS function and induction of regeneration may be absolutely dependent on the initiation of specific types of immune response [52, 53, 54]. Cell-cell adhesion is critical in the migration of blood immune cells through the blood-brain barrier and is dependent upon the expression of a variety of immune regulatory factors. Adhesion molecules, selectins and chemokines are major players in this scenario [55, 56, 57, 58]. Interestingly, pro-inflammatory cytokines such as interleukin (IL) –1β, IL-6, and tumor necrosis factor (TNF) -α, which are released after a brain insult, can enhance the expression of adhesion molecules and chemokines in astrocytes, microglia, and endothelial cells in vitro, and so may contribute to the extravasation of leukocytes into the brain [59, 60, 61]. Despite considerable advances in understanding immune cell migration into the CNS, the invasion of different immune cells is only understood in part.

4. Physiological roles of the CSF during embryogenesis and in adults. Knowledge of the physiological role of cerebrospinal fluid are of great importance not only in understanding the pathological changes of the CP — CSF system, but also in the formation of theoretical concepts of the functional relationship of the nervous, endocrine and immune systems.

Based on the embryogenesis, cerebrospinal fluid is the CNS humoral environment, which is phylogenetically and ontogenetically is a link between CNS interstitial fluid, central endocrine glands and peripheral body systems, separated by the blood-brain barrier [62, 63].

In accordance with the classical concepts, CSF has several functions: physical support for the brain; protection against acute changes in arterial and venous blood pressure; waste excretion, replacing in many ways the function of lymphatics, so-called “sink” function; intracerebral transport, e.g. hypothalamic releasing factors; maintaining the homeostasis of the CNS.

Immunomodulatory function of CSF recent studies consider, as a separate functional role of cerebrospinal fluid. For example, soluble factors present in the CSF can differentially influence the phenotype and functions of myeloid dendritic cells which, in turn, may affect the character of the T cell response [64]. CSF composition most probably changes with age, as does the proliferation potential of cells in the developing cerebral cortex. CSF alone supports viability as well as proliferation of cortical cells. 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 [65]. One of the most important functions of CSF is a regulatory function, providing, at least, local regulation of the CNS activities and, probably, in part, regulating activities on the peripheral systems of organism. Principally, this functional ability is supported by the wide range of the biological active substances at the CSF.

As it was mentioned previously, in addition to blood-derived proteins in the CSF (approximately 80%), the other proteins (about 20%) originate from within the CNS, from neurons, glial and leptomeningeal cells [66]. The choroid plexus itself synthesizes proteins, some of them abundantly, such as transthyretin, a carrier for thyroid hormones. Once secreted into the CSF, such proteins are thought to influence distant parts of the brain [67].The direct or indirect activation of brain areas bordering the ventricular system or subarachnoid space has been shown to result in increased levels of neuropeptides released into the CSF [68, 69, 70]. The circadian variations in CSF concentrations without concomitant changes in peripheral concentrations provide additional evidence for selective release of neuropeptides such as oxytocin into the CSF [71, 72, 73, 74].

Specific dendritic release mechanisms occur in brain areas such as the paraventricular and supraoptic hypothalamic nuclei, leading to as much as a thousand fold increase in the local extracellular cerebral fluid peptide concentrations [75]. Experiments involving ablation and transplantation of the suprachiasmatic nucleus in the golden hamster showed that the release of a diffusible signal was most likely carried by the flow of CSF [76, 77]. It has been shown that the suprachiasmatic nucleus releases at least some of its contents into the CSF in order to reach specific target areas [78]. So, active release of neuropeptides into the CSF has to be considered as a probable mechanism for message transmission via the CSF to distant brain areas.

In addition to the neuronal release from specific brain areas, the presence of wide spread supraependymal cell clusters, fibers and plexuses of neuronal and other cellular elements, including macrophages, have been described [79]. Their abundant presence near the median eminence suggests that these supraependymal elements are involved in a variety of functions [80, 81]. Among these, serotonergic fibers have been described as originating from the raphe nuclei with nerve terminals located in the CSF [82, 83]. In addition to the supraependymal elements, many fibers containing specific neuroactive substances can be observed in the subependymal layer. Many of these are of hypothalamic origin and may contain peptides like luteinising hormone releasing hormone (LHRH), CRF or adreno-corticotropic hormone (ACTH) [84, 85].

From the available data, differential distribution of the structures over specific regions of the ventricular walls strongly suggests two possibilities: local effects and/or specific effects on receptive distant target areas.

Two interesting cases of substances released into the third ventricle, going with the flow to reach their target areas, have been studied in detail so far: melatonin and the LHRH system, also known as the gonadotropin-releasing hormone (GnRH) system.

The pineal gland produces the hormone melatonin at night. The gland is located dorsal to the third ventricle and has access to the CSF via the pineal recess. In a series of experiments in sheep, it was shown that the main effects of the pineal gland occurred through release of melatonin into the dorsal tip of the third ventricle. At the exit of the pineal gland, concentrations were about 10 times higher than in the rest of the ventricular system and about 100 times higher than in peripheral blood [86, 87]. Melatonin also regulates the CSF levels of another hormone, estradiol [88], which may result in additional indirect effects. However, its main site of action to control reproduction is located in the premammillary hypothalamic nucleus, where it stimulates luteinizing hormone secretion in the ewe. Apparently, transport mechanisms from the pineal gland via the CSF to the premammillary hyp LHRH, also known as GnRH, is released in a pulsatile manner into the portal system and stimulates the gonadal hormone production of the pituitary gland [89, 90]. However, GnRH is released into the CSF as well, because the influx of peripheral GnRH across the blood-brain barrier into the CSF is so limited that it cannot explain the observed levels of CSF GnRH which are comparable to those in the portal blood stream [91]. Function of CSF GnRH expresses itself in behavioral effects, induced by volume transmission via the flow of CSF to affect distant brain areas, such as periaqueductal gray matter and hippocampal regions, which contain high densities of GnRH receptor expressing neurons [92]. The periaqueductal gray matter is strongly involved in sexual behavior [93, 94, 95, 96] which can be elicited by intraventricular but not by intravenous administration of GnRH [97].

These findings concerning the distribution and behavioral effects of melatonin and GnRH via the CSF comprise compelling evidence for CSF messages controlling aspects of behavior.

Totally, it can be concluded, that CSF integrates a multiplicity of functions for the CNS. From fetal life through adulthood, and extending into terminal stages, CP-CSF actively engages in building, maintaining and repairing the brain. Efficient CSF homeostatic mechanisms are vital to neuronal networks [12, 98]. Borison et al, (1980) states, that "the simple concept that the subarachnoid space constitutes a catch basin for interstitial fluid is no longer tenable. Rather, the CSF of that space must be considered as being in dynamic chemical communication with all parts of the central nervous system" [99].

5. Concept of the brain-associated acquired immune deviation (BRAID). Due to the immunological aspects of the cerebrospinal fluid, it must be emphasized that the central nervous system is an immunologically privileged area, in addition to such areas as the anterior chamber of the eye, testis, and uterus during the pregnancy. Central nervous system immune privilege is an experimentally defined phenomenon. Tissues that are rapidly rejected by the immune system when grafted in sites, such as the skin, show prolonged survival when grafted into the CNS. Initially, CNS immune privilege was construed as CNS isolation from the immune system by the blood–brain barrier (BBB), the lack of draining lymphatics, and the apparent immunoincompetence of microglia, the resident CNS macrophage. CNS autoimmunity and neurodegeneration were presumed automatic consequences of immune cell encounter with CNS antigens.

Recent data have dramatically altered this viewpoint by revealing that the CNS is neither isolated nor passive in its interactions with the immune system. Peripheral immune cells can cross the intact BBB, CNS neurons and glia actively regulate macrophage and lymphocyte responses, and microglia are immunocompetent but differ from other macrophage/dendritic cells in their ability to direct neuroprotective lymphocyte responses [100].

Thus, the mechanism of immunological tolerance to the antigens of cerebral origin can be represented as follows: soluble antigen of the cerebral interstitial fluid

passes through the high-permeability CSF-brain barrier, where it binds with the circulating, antigen-presenting, dendritic cells. Through the flow of the CSF by the lymphatic drainage way these cells carry the antigens of the cerebral origin to the immune cells of the cervical lymph nodes. This leads to the differentiation of special pool of regulatory T cell suppressor, inhibiting the development of immunopathological reactions to this antigen.

6. Xenogenous CSF. First of all, it should be noted, that issues related to the experimental using of the xenogeneic CSF are not well highlighted in the English-language literature and has been for a long time a priority of scientific research at the Soviet Union (since the 50-s of last century) [101, 102, 103].

Nevertheless, there are present several theoretical background factors for xenogenic CSF using: unique opportunity to get reactions to the parenteral administration of CSF due to the presence of high concentrations of biologically active substances, in particular those formed at the periventricular sites; possibility to obtaining the expected reactions depending on the functional state of the donor's CNS, because of the close functional relationship of CSF and functional neuroendocrine activity; possibility to obtain complex effects, in contrast to the use of the individual hormonally active substances or "artificial" CSF; low antigenic exposure and, consequently, the possibility to use the xenogeneic (cross-species) CSF without risk of the hypersensitive reactions development, which is based on the low protein concentration in the CSF; wide "raw-material" base for the native CSF obtaining; scientists of the Crimean State Medical University developed in vivo method of obtaining the bovine cerebrospinal fluid. P.W. Ramwell (1964) showed the response of the isolated frog muscles on the administration of the xenogenic CSF [104]. Another study demonstrated the ability of the xenogeneic cerebrospinal fluid (goat) to influence on the processes of sleep and wakefulness in rats [105].

In experimental work carried out at the Crimean State Medical University, was studied the morphological changes of the cardiovascular system, some organs of the endocrine, immune and reproductive systems of rats, exposed to the xenogeneic cerebrospinal fluid [106, 107, 108]. Revealed changes suggest a significant biological activity of the CSF, which requires further study, using modern techniques.

CONCLUSION

Thus, the review of the literature suggests considerable scientific interest in the issues devoted to the study of cerebrospinal fluid. Unfortunately, to date, cerebrospinal fluid is one of the less studied humoral environments of the organism, which is especially important for theoretical, basic information of its functional role in the implementation of the physiological activity of the central nervous system and body as a whole.

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