ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

# Extracellular matrix in the central nervous system

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**Abstract**

Central nervous system controls all the processes of the body through carefully honed neural network. This continuous activity is carried out with the help of neurons, glial cells and extracellular matrix. This review presents the main components of the extracellular matrix and characteristics of their participation in normal and pathological processes occurring in the central nervous system, as well as perineuronal networks that represent a unique variety of extracellular matrix surrounding neuronal cell bodies, their axons, dendrites, and glial cells. As a rule, perineuronal networks are localized around soma and dendrites and delimit synapses on neuronal surfaces. We have identified the prevailing mechanisms of interaction of brain cells with extracellular matrix, which provide modulation of neuronal plasticity and are crucial for the development and functioning of the central nervous system.

**Keywords:** extracellular matrix, neurons, glia, astrocytes, proteoglycans, lamins, tenascins, reelin.

## INTRODUCTION

Central nervous system (CNS) controls all the processes of the body through a carefully honed neural network. This continuous activity cannot be carried out on its own. It has been proved that glial cells [1], as well as the extracellular matrix, which is a three-dimensional structure on the similarity of the network that surrounds cells, help neurons in their control activity [1]. Thus, properties of the glia are determined by the particularities of this or that tissue. Moreover, in the CNS, the extracellular matrix can perform several functions:

1. It it a biological scaffold supporting CNS structure;
2. It controls the diffusion and availability of various molecules necessary for biochemical signaling and communication;
3. It monitors biochemical properties of the central nervous system [2].

At the same time, the ability of tissues to regenerate is associated with the extracellular matrix, since various violations in mechanical transduction or abnormalities in the extracellular matrix result in a loss of tissue and cell capacity for regeneration. Corresponding immune and toxic responses to infectious agents are also determined by the correct ratio of components of the extracellular matrix [3].

In CNS the components of extracellular matrix are synthesized and secreted by both neurons and glial cells, while qualitative and quantitative composition of the extracellular matrix depends on the stages of brain development, and, accordingly, on the processes of neuro- and gliogenesis. The latter in turn also depend on the extracellular matrix composition. Moreover, composition of the extracellular matrix influences the processes of synaptogenesis and functioning of synapses, on the basis of which the concept of a four-quadrant synapse was proposed. It is the extracellular matrix that plays one of the leading roles in the functioning of synapse [4]. It is able to develop with the formation of specific perineuronal networks. Thus, extracellular matrix acts as a kind of mediator between neurons and astrocytes, due to which it can modulate working of receptors, ion channels, and transmit diffuse molecular signals by using the products of proteolytic cleavage of molecules released by neurons and astrocytes.

In this review, we will present the main components of the extracellular matrix and their participation in normal and pathological processes occurring in the central nervous system, as well as perineuronal networks, which represent a unique type of extracellular matrix.

**Main components of the extracellular matrix**

Extracellular matrix of the brain is a scaffold that fills the intercellular space of the central nervous system. At the same time in the adult brain the volume of the extracellular matrix reaches 20% [5].

Main components of the neuronal extracellular matrix are chondroitin sulfate proteoglycans of the lectin family and heparan sulfate proteoglycans, as well as tenascins, laminins and thrombospondins belonging to the class of glycoproteins [6]. Together, these substances can form macromolecules, which were called “matrisome” in papers of Naba and Hynes et al. [7, 8]. Also it has been found that core of the matrisome is encoded by about 300 genes, the products of which are expressed by different types of brain cells (Table 1). In this case, components of matrisome structure the extracellular space and serve as scaffolds when different molecular ligands are bound to the cell membranes.

Extracellular matrix has the ability to organize the environment in such a way that it can mediate a wide range of intracellular interactions in the central nervous system

**Table 1 - Origin of extracellular matrix components [6]**

| Name of extracellular matrix component | Neurons | Astrocytes | Oligodendrocytes | NG2 glia |
|---|---|---|---|---|
| Hyaluronic acid | ++ | ++ | - | - |
| Aggrecan | ++ | - | - | - |
| Brevikan | + | +++ | - | - |
| Neurocan | +++ | - | - | - |
| Phosphocan | ++ | ++ | ++ | ++ |
| Versican | - | - | +++ | ++ |
| Tenascin-R | ++ | - | ++ | ++ |
| Tenascin-C | + | +++ | - | - |

Note: “+++” - high expression at the level of protein and/or mRNA; “++” - dependence of expression on physiological conditions; “+” - low or temporary expression in specific type of cells; “-” absence of expression in this type of cells.

In some subpopulations of neurons, the extracellular matrix develops with the formation of specific perineuronal networks (PNS), which were first described by Kamilo Golgi as a kind of sediment around subpopulation of neurons stained with silver, and reminiscent of honeycomb structure.

These subpopulations of neurons include fast-discharging GABAergic interneurons expressing parvalbumin, and sometimes other types of neurons, for example, pyramidal neurons, which can also exhibit similar macromolecular structures [9].

In the structure of perineuronal networks, as well as in the developing CNS, the expression of some chondroitin sulfate proteoglycans, in particular aggrecan, brevikan, neurocan and versican is observed, while the expression of PNS components in different regions of the brain is heterogeneous. It is suggested that chondroitin sulfate proteoglycans are involved in many processes that ensure normal brain function, for example, in maintaining ion concentration, protection against oxidative stress and stabilization of synapses [10]. Let us now examine in detail individual components of the extracellular matrix and their functions in the central nervous system.

**Proteoglycans**

Proteoglycans are complex proteins with a high degree of glycosylation, the carbohydrate part of which consists of glycosaminoglycan chains. Proteoglycans are widely expressed in the brain and participate in its development, which is confirmed by the fact that enzymatic cleavage of chondroitin sulfate proteoglycans (on the example of cell culture) leads to disruption of the neural stem cells development. However, in case of model animals, in particular mice, no phenotypes associated with impaired functioning or lack of proteoglycans were found. It may be due either to their functional excess or to early embryonic death [11]. Perlecan is the only exception - a component of the basal plate, which plays a key role in the development of neocortex, while the removal of the basal plate has a negative effect on the cells of radial glia. Genetic ablation of perlecan leads to exencephaly, followed by the destruction of the basal plate or neuronal ectopia but with less marked defects of the basal lamina, with a possible decrease in the expression level of the components of the Sonic Hedgehog signaling pathway however [12].

Also, proteoglycans are capable of inhibiting growth of axons, which in turn affects the processes of central nervous system regeneration after various injuries. During in vitro experiments it has been found that phosphocaine and all soluble chondroitin sulfate proteoglycans (aggrecan, versican, neurocan and brevikan) inhibit axon growth, while their enzymatic cleavage inhibits an inhibitory effect, promoting axon growth and functional recovery after spinal cord injuries [13].

**Laminins**

Laminins are high molecular weight heterotrimeric proteins (1000 kDa) containing α, β and γ chains. Laminins are the main components of the basal lamina, which includes laminin 2 (α2β1γ1), laminin 8 (α4β1γ1) and laminin 10 (α5β1γ1). They were also found in the ventricular zone of the neocortex at the stage of its development [14].

During in vitro studies it has been found that laminins promote the expansion, migration and differentiation of neural stem cells. In addition, an expression of certain laminin subunits in the culture of neural stem cells is influenced by RE1 Silencing Factor (REST), which regulates neurogenesis through the repression of neurogenic genes in non-neuronal tissues [15]. Thus, Sun and colleagues in 2008 showed that embryonic cells devoid of this transcription factor have impaired cell adhesion and, accordingly, form defective neural stem cells that are not capable of neuronal differentiation. However, this phenotype can be restored by adding exogenous laminin. It was also established earlier that the absence of γ1 laminin in mice caused their death at the stage of embryogenesis, while its inactivation in a subset of cortical neurons caused defects in the organization of cortex to different layers [15].

In vivo experiments have shown that laminins control the behavior of neural stem cells by interacting with the receptors of dystroglycans and integrins, while cortical ectopia is observed in human carriers of the mutation in the sequence coding the enzyme that glycosylates

dystroglycan. In mice, the absence of dystroglycan in the central nervous system or the presence of mutations in dystroglycan glycosyltransferases causes destruction of the basal plate and disruption of migration of neuronal cells, while inactivation of β1 integrin in radial glial cells leads to defects in the organization of the cortex to different layers, as well as to the fusion of the cerebellar gyrus. Neurons of animals with integrin β1 deficiency are able to bind intact radial glial cells and migrate through them. However, this can lead to the formation of ectopia in the cortical marginal zone. A similar effect in mice causes the absence of α6 and/or α3 integrin subunits forming heterodimers with β1 subunit, thus forming receptors for laminins [16]. At the same time, other integrin subunits, including β4, β8, α3, α4 and α5, may be involved in neural stem cell development, neocortical stratification, and/or neuronal migration. Moreover, extracellular matrix molecules and integrins can perform various roles, for example, in the adult brain, β1 integrins and α2/α4 laminins are necessary for the formation of cellular chains in the rostral migration tract.

Laminins as well as proteoglycans are able to influence the growth of neuronal processes. For example they promote growth of axons. In mice with laminin γ1 deficiency, abnormal myelination of axons in the corpus callosum is observed, as well as disturbance of neuronal migration. The absence of α2 laminin leads to the delay in the development of oligodendrocytes from precursor cells, which causes hypomyelination [16].

Also, laminins are able to affect peripheral nervous system through exposure to Schwann cells surrounded by a basal lamina. This effect consists of violation of the processes of myelination and proliferation of Schwann cells, which can lead to the development of diseases such as demyelinating peripheral neuropathy. At the same time, the absence of integrin β1 in Schwann cells contributes to the disruption of their migration and leads to hypomyelinization, but the cells survive and retain the ability to proliferate normally, which confirms the involvement of β1 integrin only as mediator in certain functions of laminins [16].

**Tenascins**

Tenascins are extracellular matrix glycoproteins. A total of four members are identified in the tenascin family and only two of them are expressed in the brain - tenascin-C and tenascin-R. As a rule, expression of tenascin-C is observed in regions of the brain with ongoing active neurogenesis, while expression of tenascin-R is observed in myelinating glia, interneurons and deep layers of olfactory bulbs. In the cultures of neural stem cells, tenascin-C causes a switch from the production of neuronal precursors to glial precursors, while tenascin-R inhibits the migration of neurons originating from neuronal stem cells. In vivo experiments have found that tenascin-C regulates the development of the myelinizing glia line and glomerogenesis in olfactory bulbs. In turn, tenascin-R promotes destruction of the cellular chains of neuroblasts in the rostral migratory tract, which leads to disruption of their migration within the olfactory bulb [17].

Tenascins as well as proteoglycans and laminins regulate myelinization of glial cells and functioning of axons. In olfactory bulbs, tenascin-C inhibits the growth of axons of sensory neurons until the end of glomerulogenesis. In addition, tenascins influence the processes of differentiation of oligodendrocyte precursors, in particular, the absence of tenascin-C leads to the acceleration of this process [18].

**Reelin**

Reelin is the most well-studied glycoprotein of the extracellular matrix in the central nervous system. It is secreted at the stage of brain development by Kahal-Retzius cells in the marginal areas of the cerebral cortex and hippocampus where it plays an important role in controlling the migration of neurons and the formation of cell layers during brain development. Reelin also secrets granular cells in the cerebellum and GABA-ergic interneurons of hippocampus and cortex in the adult brain. Reelin is a protein consisting of 3,461 amino acid residues forming a signal peptide, F-spondyl-like domain, eight reelin repeats (RR1-8), and positively charged sequence at C-terminus. Reelin binds to the receptors of ApoER2 and VLDLR lipoproteins, which are expressed by

migrating neurons and radial glial cells. Binding of reelin to these receptors causes phosphorylation of the adapter protein Dab1 [19].

In CNS, reelin is necessary to support the processes of synaptic plasticity, learning and memory. Mutations in reelin-signaling pathway in humans cause such diseases as lissencephaly and hypoplasia of the cerebellum, while in mice they cause defects in the functioning of the central nervous system, characterized by disruption in the organization of the layers in cerebellum, hippocampus and neocortex. Violation of the organization of layers in neocortex is caused by the fact that newly formed neurons move incorrectly relative to their predecessors, which, in turn, causes violations of cytoarchitecture, which loses layered organization pattern typical for neocortex. It is assumed that reelin controls the migration of these newly formed neurons, since it does not affect their formation. One way to control this is to influence the migration of neurons through radial glia fibers, as demonstrated by the addition of recombinant reelin to cultured brain sections of mice without reelin expression, which in turn has resulted in the restoration of neuronal migration [20].

In addition, disturbances in proteolysis of reelin lead to the development of cognitive dysfunctions and neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia. Also, by using model animals with epilepsy, it was found that changes in the processing of reelin can affect the control of seizures [21].

Thus, the participation of reelin in learning and memory processes is confirmed, which determines the significance of this signaling pathway and the need to influence it in the treatment of neurodegenerative and neuropsychiatric diseases.

**Thrombospondins**

Thrombospondins (TSPs) are a family of calcium-binding glycoproteins that undergo transient or longer-term interactions with other extracellular matrix components and with an array of membrane receptors and cytokines. This family have five members (TSPs 1 – 5). The TSPs have the domain structure, which includes the invariant C-terminal regions comprise a series of EGF-like domains, thirteen calcium-binding type 3 repeats, and a C-terminal domain structurally homologous to the L-type lectin domain. In contrast, the N-terminal regions of TSPs are much more varied in domain composition, with the laminin-G like N-terminal domain being the most widely conserved domain [22].

In mammalian cells, the TSPs participate in cell attachment, proliferation, and differentiation, as well as in apoptosis and in inhibition of angiogenesis, and synaptogenesis. In brain, the TSPs are secreted by astrocytes and TSPs can regulate synaptogenesis through the receptor α2δ-1 and neuroligin 1. There are evidences that TSP1 and TSP2 are critical for the support of astrocyte-induced synaptogenesis because astrocytes from TSP1/2$^{-/-}$ mice cannot support synaptogenesis in retinal ganglion cells in vitro [23]. Removing astrocytes from the retinal ganglion cell culture lead to significantly reducing of synapse number. At the same time, TSPs do not influence on expression and degradation of pre- and postsynaptic proteins (synaptotagmin, PSD95) that indicate on participation of TSPs in regulating their transport or cellular localization [24].

Furthermore TSPs are highly expressed during development, but down regulated after maturation, which confirm that TSP1 and TSP2 regulate synaptogenesis only at development stage, and that they are not essential for maintaining synapses in the mature organism. At the same time, TSPs expressions increase in response to purine signals and mechanical irritation. For instance, TSP1 and TSP2 levels are elevated after stroke, but decreasing expression of TSP1 are associated with neuropathological condition in Down's syndrome patients [24].

Thus, TSPs play a critical role in synaptogenesis and maintains synapse stability.

**Perineuronal networks**

PNS is a unique specialized form of the extracellular matrix surrounding the bodies of neuronal cells, their axons, dendrites, glial cells. As a rule, PNS are localized around soma and dendrites and demarcate synapses on neuronal surfaces. This fact allows us to suggest their

involvement in neuronal plasticity regulation, and in the maturation and maintenance of the functioning of neural networks. The formation of PNS is initiated by the production of hyaluronan by hyaluronan synthetase on the inner surface of the plasma membrane. Linear unsulfated chains of hyaluronic acid located on the cell surface bind to extracellular chondroitin sulfate proteoglycans; these interactions are enhanced by links to additional proteins and tenascin-R. In addition, N-terminus of chondroitin sulfate of proteoglycan binds to hyaluronic acid and C-terminus to tenascin-R, resulting in the formation of three-dimensional cross-links that establish stoichiometric relationships, which in turn determine the organization of PNS, which can control the behavior of these cells by binding superficial chondroitin sulfate proteoglycans [25].

PNS as well as other extracellular matrices provide structural support to cells and participate in the functioning of organs, while any changes in the composition or organization of the extracellular matrix affect the functional state of the particular organ. For example, enzymatic cleavage of PNS leads to elongation of the period of plasticity, which is especially important in case of CNS regeneration in lesions [6]. Moreover, an increased density of the extracellular matrix around the neurons can inhibit their growth at the end of the developmental stage. Moreover, an increased secretion of chondroitin sulfate proteoglycans inhibits regeneration and recovery of nervous tissue after trauma, which only aggravates an initial damage [25].

In addition, PNS can modulate various types of neuronal plasticity, including effects on neural network remodeling and synaptic plasticity. It has been established in vivo that the expression of the molecules forming the PNS coincides with the completion of the critical period during the development of the brain, which leads to the conclusion that PNS undergoes remodeling in correlation with brain activity. It is proved that PNS limits the growth of neural processes and the development of synapses at the structural level [21]. At the level of synapses PNS compartmentalizes the neuronal surface and limits mobility of glutamate receptors, thus ensuring synaptic plasticity and stabilization of synapses [8]. In addition, PNS can limit the mobility of AMPA receptors, leading to reduction in short-time plasticity in primary neurons in rats, thus indicating the involvement of PNS in memory formation. Moreover, individual components of PNS can also have an effect of synaptic plasticity. For example, neurocan deficiency decreases the stability of the late phase of long-term potentiation of synaptic transmission, ablation of brevikan - to disruption of long-term potency [26].

In transgenic mice of the Alzheimer's disease model, an increase in the amount of amyloid-β is accompanied by an increase in concentration of some components of the extracellular matrix. Besides changes in extracellular matrix begin to appear even before the formation of amyloid plaques and are accompanied by a decrease in long-term potentiation in CA1 of the hippocampal region associated with cognitive functions including those with memory impairments. Confirmation of the involvement of extracellular matrix in the development of this pathophysiological state was achieved by administration of chondroitinase ABC, which resulted in the restoration of long-term potentiation and memory [26].

Synaptogenesis of PNS is controlled by a signal pathway involving integrin, since astrocytes can contact the neurons through the integrin receptors. In this case, activation of integrin leads to global activation of protein kinase C, resulting in stimulation of synaptogenesis [9]. In addition to the integrin signaling pathway, PNS can mediate the transfer of molecular signals between neurons and astrocytes through a large number of regulatory molecules captured by them, including semaphorins, among which semaphorin 3A is the most interesting. It is synthesized in both astrocytes and neurons, and it affects the growth of axons, their regeneration, establishment of neuronal polarity, and the development of dendritic spines. Manifesting synergistic effects together with chondroitin sulfate proteoglycans, semaphorin 3A can regulate the migration of neurons [27].

PNS is polyanion in its composition, which acts as the most important element of the

system of regulation of neuronal excitability. PNS can buffer cations near the neuronal membrane, providing fast adhesions. Moreover, some hydrated components of PNS are necessary to maintain intercellular space in the brain. So, for example, knockout of hyaluronic acid synthase leads to a reduction in the intercellular space in the brain, diffuse insufficiency and epileptiform activity [27].

## DISCUSSION

Central nervous system controls all the processes of the body through carefully honed neural network. This continuous activity is carried out with the help of neurons, glial cells and extracellular matrix. This review presents the main components of the extracellular matrix and their participation in normal and pathological processes of the nervous system, as well as perineuronal networks, which are unique type of extracellular matrix, surrounding neuronal cell bodies, their axons, dendrites, glial cells. As a rule, PNS are localized around soma and dendrites and delimit synapses on neuronal surfaces. Based on the foregoing, it can be concluded that extracellular matrix takes an active part in functioning of neurons. It is possible to single out the prevailing mechanisms of interaction of brain cells with extracellular matrix, which provide modulation of neuronal plasticity that is crucial for the development and functioning of central nervous system:

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1. Maintenance of the ionic gradient and extracellular space by the penetration and diffusion of various molecules into extracellular space, including the release or removal of chemokines and growth factors, is necessary for the development and inhibition of neurons at certain stages of brain development
2. Compartmentalization of the neuronal surface in order to block and stabilize the formation of synapses;
3. Blocking synaptogenesis by suppressing the signal pathway with participation of integrin;
4. Indirect transmission of molecular signals for synaptogenesis and synaptic plasticity.

In addition, forming the PNS, an extracellular matrix can be involved in the development of some neurodegenerative diseases, for example, epilepsy, schizophrenia and Alzheimer's disease, in which change in the expression of some of PNS components is observed [28].

## CONCLUSION

Thus, a detailed study of the extracellular matrix in order to improve the understanding of the spatial and temporal expression of its components, their interactions and degradation suggests an effective possibility of using separate components of the extracellular matrix to stimulate the restoration of the functional state of the nervous system under various pathophysiological mechanisms and pathologies. The review of morphofunctional analysis of the extracellular matrix has made it possible to single out the prevailing mechanisms of interaction of brain cells with extracellular matrix, which provide modulation of neuronal plasticity that is crucial for the development and functioning of the central nervous system.

## ACKNOWLEDGEMENT

This work was supported by the grant from Federal Target Program No. 14.575.21.0036 (unique identifier - RFMEFI57514X0036).

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