The Role of the Brain Extracellular Matrix in Synaptic Plasticity After Brain Injuries (Review)

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The brain extracellular matrix is secreted by neurons and glial cells and represents a molecular net comprised of polysaccharides and proteins, fulfilling the space between cells in the tissue. A complex structure and ubiquitous localization of extracellular matrix underlie its involvement in numerous important brain functions, such as diffusion regulation, molecular cell-to-cell interactions, synaptic plasticity and learning. Additionally, the brain extracellular matrix participates in regeneration of neuronal connections after brain and spinal cord injuries. The ability to regenerate connections attenuates by the fast proliferation of the brain extracellular matrix, when its degradation leads to regeneration improvement. Therefore, the brain extracellular matrix represents an important direction of clinical research and possible target for therapeutic interventions. Here we not only describe the structure of the brain extracellular matrix and its sites of localization in the brain, but also make an overview of the influence of the brain extracellular matrix in synaptic plasticity, learning and memory. This review describes the role of the brain extracellular matrix for connection recovery after brain and spinal cord injuries. Here, we highlight the positive ability of enzymatic removal of extracellular matrix component — chondroitin sulphate proteoglycans by chondroitinase ABC to promote restoration of neuronal connections. In conclusion, we discuss possible side effects of treatments requiring the enzymatic removal of chondroitin sulphate proteoglycans on synaptic plasticity and speculate about future development of the field of the brain extracellular matrix research.

Key words: brain extracellular matrix; synaptic plasticity; brain injuries; spinal cord injuries; chondroitin sulphate proteoglycans; chondroitinase ABC.

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Роль внеклеточного матрикса в синаптической пластичности при мозговых повреждениях

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Внеклеточный матрикс мозга синтезируется нейронами и глиальными клетками и представляет собой молекулярную сеть, состоящую из полисахаридов и белков, которая заполняет пространство между клетками. Быстрое развитие внеклеточного матрикса в местах повреждений приводит к снижению регенеративной способности, в то время как разрушение внеклеточного матрикса — к ее увеличению. Изучение внеклеточного матрикса мозга, который может представлять собой потенциальную мишень для терапевтических воздействий, — важное направление современных исследований в области физиологии и медицины. В обзоре подробно рассмотрена структура внеклеточного матрикса мозга и его локализация в мозге, а также влияние матрикса на синаптическую передачу, обучение и память. Показана роль внеклеточного матрикса в восстановлении нейрональных связей после повреждений мозга, описано положительное воздействие на него фермента, разрушающего хондроитиназу ABC (хондроитин сульфат протеогликаны матрикса). Рассмотрены возможные влияния побочных эффектов разрушения хондроитин сульфат протеогликанов, используемых для восстановления нейрональных связей, на синаптическую передачу и память. Обозначены перспективы исследования роли внеклеточного матрикса мозга в норме и при патологии для дальнейшего развития науки.

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Ключевые слова: внеклеточный матрикс мозга; синаптическая пластичность; травмы мозга; спинномозговая травма; хондроитин сульфат протеогликаны; хондроитиназа ABC.

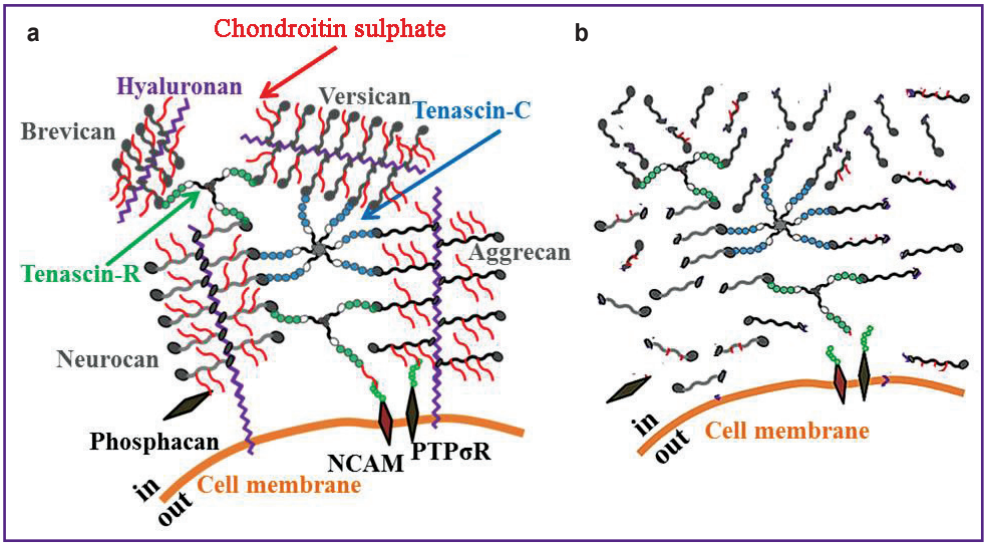
Introduction. The brain extracellular matrix (ECM) was identified in 1897–1898 by Santiago Ramón y Cajal and Camillo Golgi, but technical limitations just recently allowed to study its molecular structure. ECM represents a molecular net that surrounds brain cells and might occupy up to 20% of the brain volume [1]. ECM molecules are produced by the Golgi apparatus in neurons and glial cells [1–4]. ECM molecules play an important role during the development and in the adult brain in normal and pathological conditions, including regeneration processes [4–8]. Presently, multiple interactions between ECM molecules and a number of receptors on the cell surface, including those which are linked to cytoskeleton and tyrosine kinase were identified [9, 10]. These interactions underlay such important ECM functions as involvement in proliferation, migration, morphological and biochemical differentiation, synaptogenesis and synaptic activity [6, 7, 11]. ECM molecules interact with ion channels and receptors to neuromodulators, that allows ECM regulate synaptic transmission [12]. However, the mechanisms of this regulation are not yet well understood. Also ECM molecules participate in structural rearrangements, that take place during synaptic plasticity in the adult brain due to matrix metalloproteinases (MMP) activity [9, 13–16], and during regeneration of processes [4, 17, 18]. The expression of ECM components, however, inhibit the functional recovery after spinal cord injury [5, 19–21]. The remodeling of ECM had been demonstrated to take place after brain traumas and in the development of neurodegenerative disorders and in epilepsy. Transgenic animals lacking or having a deficient ECM structure tend to develop an epileptiform activity and characteristic changes of Mossy fibers and granule cells functioning [2, 22, 23], and astrogliosis [2, 24–26]. Additionally, ECM molecular net mechanically restricts diffusion of molecules in the extracellular space [27, 28], diffusion of ions and lateral diffusion of receptors in the cell membrane [29, 30]. The coefficient of Ca^{2+} diffusion increases after ECM removal, since it is a divalent cation and negative charges of ECM molecules electrostatically trap Ca^{2+} and reduce its mobility [31, 32]. However, it remains not well studied how ECM molecules are involved in electrodiffusion in the extracellular space though electrical interactions which can play an important role in the local electrodynamic of small cell structures like axons, spines and astrocytic processes [33, 34]. The ability of ECM molecules for hydration and trapping ions allows them mechanically protect brain cells [35]. All these properties of ECM might play a number of important functions for the nervous system and therefore, ECM might be involved in many physiological and pathophysiological conditions [5, 7, 10, 36].

ECM components and their interaction. Depending on the localization in the brain, ECM can be classified in the following categories: 1) basal membrane matrix, located between endothelial (vascular smooth muscle cells) and the parenchymal cells in the CNS (neurons and glia), composed of collagen, laminin-entactin complex, fibronectin, dystroglycan and perlikan; 2) perineuronal nets, represented by dense, well-structured nets surrounding neurons and proximal dendrites, which includes: proteoglycans, tenascin-R proteins and link proteins; 3) interstitial matrix, localized between parenchymal cells of the central nervous system, which is composed of proteoglycans, hyaluronic acid, tenascin-R, link proteins and a small amount of fibronectin and laminin [5, 37–39].

It had been previously demonstrated that perineuronal nets and interstitial matrix carrying out an important role in synaptic plasticity [5]. The main component of these types of ECM are proteoglycans, composed of a core protein with chains of the glycosaminoglycans. These chains are represented by highly negatively charged disaccharides polymers which can be sulphated in several positions (2, 4 and 6) of carbon atoms. Depending on the type of the main disaccharide in glycosaminoglycan chains, proteoglycans are divided into several subtypes [35, 40, 41].

If the main component is the chondroitin, the complex will be called after it — chondroitin sulphate proteoglycans (CSPGs) (See Figure (a)) and similarly with dermatan — dermatan sulphate proteoglycans, heparan — heparan sulphate proteoglycans and keratan — keratan sulphate proteoglycans [5, 42]. Heparan itself composed of N-acetylglucosamine and uronic acid (D-glucuronic or L-iduronic), chondroitin and dermatan sulphates consist of N-acetylglucosamine and D-glucuronic acid, while keratan consists of N-acetylglucosamine and galactose. Glycosaminoglycan chains covalently bound to the core protein via xylose, forming a bond with serine residues in proteins and repeating disaccharide [35, 40].

There are three main families of core proteins: lecticans (aggrecan, brevican, neurocan and versican), phosphacan, neuro-glial antigen 2 (NG2) [11, 36, 43, 44]. Lecticans have tree domain structure and their the N-terminal connected to hyaluronic acid via linking proteins (protein BRAL1 or HALPN2), and the C-terminal is linked to matrix proteins, such as tenascin-R or receptors on the cell surface. Lecticans vary in molecular weight (from 95 to 400 kDa) and in the number of related glycosaminoglycan chains (from 1 to 100), any further sulphitation enhances the complexity of their structure [11, 45]. NG2 represented only in oligodendrocyte progenitor cells. CSPGs bind also to the receptor systems, including receptor of tyrosine phosphatase σ (PTPσR) [41], an antigen-associated phosphatase in leukocytes [46], epidermal growth factor (EGF) [16], NgR1 and NgR3 receptors CD44 (cluster of differentiation 44, which acts as a receptor of hyaluronic



Structure of extracellular matrix (ECM): (a) scheme of ECM structure; (b) scheme of ECM structure after the removal of chondroitin sulphate proteoglycans by chondroitinase ABC

acid), and Nogo, which are involved in the signaling pathway activating Rho and ROCK kinase. Furthermore, it had been shown that CSPGs accumulate in the Ranvier nodes of myelinated axons, which adjusts the ionic conductivity of the fibre by creating an ion barrier [47]. Also glycosaminoglycan chains can bind to neural cell adhesion molecules (NCAM) and polysialic acid through a fibroblast growth factor (FGF) on presynaptic terminal, increasing ECM accumulation and its signaling in presynapse [3].

Core proteins are capable of forming nets together with glycoproteins, such as tenascin-R, C, and reelin. Tenascin-R is a member of the family of tenascins, that specifically expressed in the brain and having a molecular weight of 160 or 180 kDa. Usually 10–20% of its weight represented by sulphated oligosaccharides chains, attached to O- or N-positions, occurring due to post-translational modifications of proteins. Tenascin-R has several domains which bind to different ligands. Fibronectin-similar domains 1–2 and 6–8 are connected to the voltage-dependent Na^+ channels, domains 3–5 connected with lecticans and 2–5 domains to neurofascin. Chondroitin sulphate chains binds to fibronectin and tenascin-C and EGF-like domain with phosphacans (soluble form PTPσR) [48, 49]. The structure of tenascin-C is similar, but it has a higher molecular weight (6 subunits with 180–250 kDa) due to a few additional fibronectin-like domains. Its expression increases in cancerogenesis [50].

Hyaluronic acid (hyaluronan) is a polymer with a high molecular weight that consists of disaccharides: N-acetylglucosamine and D-glucuronic acid, but is not sulphated. Hyaluronan binds to core proteins, and anchors in the cell membrane, forming the main carcass for ECM structure, binding through versican or specific receptor for hyaluronic acid — CD44. Glial cells are also capable of binding to hyaluronic acid via same receptor, at the same time expressing specific protein, which N-terminal is capable of binding to hyaluronic acid [51].

The complexity of the ECM structure allows multiple interactions between matrix components and various cell receptors. This makes ECM an important element of the nervous system that is capable of affecting the functioning of the nervous system via a number of divergent mechanisms.

The role of ECM in synaptic transmission. Recent studies have been demonstrated that ECM components are involved in the regulation of synaptic plasticity by several mechanisms [52]. For example, removal of the ECM by an enzyme chondroitinase ABC (See Figure (b)) changes the efficiency of synaptic transmission [53]. Transgenic mice lacking the gene responsible for the expression of certain components of the ECM also show changes in synaptic transmission; however, this effect can be reversed by ECM injection. Expression of ECM in the mature brain depends on the neuronal activity. Manipulation with the ECM leads to changes in the number of synapses, distortions of the cycle of vesicles and alterations in the number of receptors and their densities [4]. Since ECM is a multicomponent system, different elements might have different impact on synaptic transmission. For example, the removal of hyaluronic acid reduces the activity of L-type voltage-dependent calcium channels (VDCC), and therefore, a reduction of long-term potentiation (LTP) induction, that highly depends on L-type of VDCC. That effect is mediated by exogenous hyaluronic acid that selectively increases the current mediated $Ca_v1.2$ subunit [54]. The removal of hyaluronic acid causes an enhancement in lateral diffusion of membrane receptors, including AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionic) receptors, thus reduces paired depression of AMPA currents due to more rapid change receptors and their displacement [30]. Transgenic mice lacking the tenascin-C show no morphological disruptions

in the nervous system during the development, including migration, the distribution of oligodendrocytes, and myelination of processes. Despite the normal histology of hippocampus and the behaviour in the water maze, LTP significantly decreases after tetanic stimulation caused by a decrease in Ca^{2+} entry through L-type of VDCC [55]. Moreover reduction in the number of interneurons cause an enhancement of theta and gamma rhythms in CA1 region of the hippocampus [56]. Transgenic mice lacking the tenascin-R showing a reduction in GABA (gamma amino acid receptors, type A)-mediated currents, and an increased level of excitation [57]. Attenuation of tenascin-R reduces an inhibition and correlates with an increase in the threshold for LTP generation, acting on L-type of VDCC channels and phosphatases [58]. LTP is controlled via the influx of Ca^{2+} to the cell and the level of inhibition in CA1 pyramidal neurons [2]. Activation of reelin facilitates NMDA receptor phosphorylation (N-methyl-D-aspartate) by the tyrosine kinase receptor in CA1 pyramidal neurons and increases their activity. Transgenic mice overexpressing reelin show facilitated LTP *in vivo*, the larger number and size of the spines [59]. Enzymatic removal of CSPGs enhances plasticity in the visual cortex and other types of plasticity in adult animals, promotes the vision recovery in amblyopia and following the spinal cord injuries [9]. Transgenic mice lacking brevican and neurocan also show reduced LTP [60, 61]. Recent studies demonstrate that developmental increase in the ratio of 4-sulfo/6-sulfo (4S/6S) CSPGs determines the critical periods in the visual cortex development. The removal of the ECM also controls the diffusion of molecules and the size of the intercellular space [32]. That can cause significant changes in calcium signaling in neurons, and astrocytes and can seriously affect synaptic transmission. All of these changes, affecting synaptic transmission may have an impact at a higher level by changing the processes of learning and memory.

The role of ECM in learning and memory. Manipulation with the ECM molecules might cause changes in synaptic transmission and lead to distortion of learning and memory processes [62] in a component-dependent manner. In behavioural experiments, an enzymatic removal of hyaluronic acid before training reduces the efficiency of learning in a fear conditioning paradigm [29]. Transgenic mice lacking the tenascin-R show an enhanced learning ability, improved working memory, increased performance in the objects recognition task, which can be associated with a reduction in GABAergic innervation in the dentate gyrus and improved signal-to-noise ratio during behavioural tasks [57]. In addition, the LTP induction phase and behavioural tests performance are accompanied by the activation of MMP-9 and 3, when the MMP inhibitors cause a reduced ability of animals for learning and habituation to new conditions. Therefore, the activation of MMP-3 and 9 is critical for memory formation at the cellular and system levels [13]. In normal conditions, the activation of MMP-9 contributes to the local ECM remodeling [15, 63] with parallel activation of cofilin in postsynaptic side by integrins, providing the possibility for spine enlargement [63–66].

Thus, ECM is essential for the normal functioning of the nervous system, maintenance of synaptic transmission and plasticity. Moreover, the ECM is also involved in pathophysiological and behavioural processes, including brain injuries.

The role of ECM in brain injuries. Brain injuries trigger specific response to it, that often is accompanied by reactive gliosis, so called glial "scar" [67–69]. Mainly, this response has the same development regardless of the source of damage, but the immune response still can vary depending on the particular type of pathology and localization [69–72]. Equivalent traumas of the brain and spinal cord trigger significantly lager leucocytes activation in the first case, causing more prominent damage compare to the second case [70, 73, 74]. After initial stage of trauma, when cell death, axon damage and demyelination are taking place, the glial scar starts developing [5, 75]. Following, the production of ECM molecules increases at the damage [76, 77]. Then activation and migration to the damage site of microglia occur, where they serve microphage function, particularly by removing disturbed myelin [78]. On the next step the density of hypertrophied astrocytes increases and their processes form a dense net [75, 79]. Glial cells dividing at the damage site due to an appearance of progenitor cells [80]. As a result, at the damage site the dense glial scar occurs, that inhibits axonal grow and myelination. Along with the loss of oligodendrocytes it prevents the reestablishment of neuronal connections [81].

It is not yet fully understood which particularly type of glial cell is playing a critical role in this process and require additional studies [81]. It had been shown that components of the glial scar might interact with ECM molecules [26] via numerous receptors [82–84], such as neurocan [85], PTPσR [86, 87], CSPGs [87–89] etc., preventing axonal regeneration [26]. Particularly, an interaction between astrocytes and CSPGs inhibits regeneration abilities [5]. Notably, the enzymatic removal of CSPGs by chondroitinase ABC at the damage site leads to significant improvements in the connections reestablishment, and more important, to functional recovery of motor functions [20, 21, 53, 90, 91]. One possible mechanism for it could be facilitation of oligodendrocytic migration, and, therefore, promoting remyelination [5, 55, 92, 93]. Moreover this positive effect of chondroitinase ABC treatment remains sufficient to promote motor recovery on day 2, 4 and 7 following injury [20]. However the recovery of fine movements is the most efficient when the enzyme is applied following the injury [53]. Chondroitinase ABC treatment also promotes the recovery in peripheral nervous system [94, 95]. Moreover, chondroitinase ABC treatment has a positive effect on chronic spinal cord injuries, which considered as the most difficult for treatments since permanent loss of neurons lead to an occurrence of cavities, preventing axonal grows [96, 97]. The combined treatment with chondroitinase

ABC, with a complex of grows factors (EGF, bFGF, PDGF-AA) and with transplantation of progenitors gives the most prominent recovery of motor functions [98]. The treatment with chondroitinase ABC and induced pluripotent stem cells also promotes axonal repairmen and recovery of motor functions [90, 99].

Similar consequences leading to glial scar and aggregation of ECM might occur following a stroke in the brain, when on earlier stages it plays a protective function [100]. However, on later stages they prevent axonal growth and connections recovery, and as a result, losing normal function of damaged region [79, 101, 102]. The treatment with chondroitinase ABC decreases chronic effects of stroke, particularly, the aggregation of CSPGs and neurocans, and improves anatomical, histological and functional conditions of the damaged region [97, 103].

Thus, attenuation of ECM, and particularly of CSPGs, allows significant improvement of the reestablishment of neuronal connections and they functioning in the spinal cord and in the brain, that makes chondroitinase ABC an important target for therapeutic interventions.

Possible effects of the removal of CSPGs on synaptic transmission. The tight connections between different ECM components and membrane receptors and lack of knowledge about the wide range of their possible interactions leave a great chance of side effects of the treatments with chondroitinase ABC. It had been demonstrated that the treatment with chondroitinase ABC abolishes LTP in CA1 pyramidal neurons following five theta-burst stimulation of Schaffer collaterals using field recordings [104]. That can represent a consequence of the change in the excitation of inhibitory neurons [104], but it was not yet studied sufficiently. Similar observations were obtained in whole-cell patch clamp recordings in CA3-CA1 synapses, where LTP could not be triggered after the removal of CSPGs [105]. This phenomenon was not due to increased excitability of interneurons, but due to a decrease of excitability of CA1 pyramidal neurons, because of upregulation of small-conductance, calcium activated potassium channels [90]. However, it was not the only pathway that was altered by the treatment with chondroitinase ABC, in parallel the ROCK-pathway (Rho-associated kinase) were upregulated, leading to persistent potentiation of CA3-CA1 synapses [105]. CSPGs removal triggers structural plasticity via ROCK-pathway, that leads to the cytoskeleton rearrangements and can cause spines enlargements, causing LTP [105]. In hippocampal cultures enzymatic removal of hyaluronic acid leads to epileptiform activity [106, 107] and to an increase of lateral diffusion of AMPA receptors [30], that can significantly affect synaptic plasticity. However, the lateral mobility of AMPA receptors is not altered in hippocampal slices [105]. Thus, the treatment of the brain injuries with chondroitinase ABC affect basic neuronal functions, such as synaptic transmission and plasticity, which should be considered in clinical applications. Additionally, the treatment with chondroitinase ABC alters calcium signaling in astrocytes, causing an increase in the duration of astrocytic calcium events, that can significantly affect a number of biochemical cascades in astrocytes via longer presence of Ca^{2+} in cytosol [105]. Therefore, these aspects of treatments with chondroitinase ABC further investigated.

Conclusions. Thereby, ECM is involved in the brain functioning via a number of mechanisms at different levels and at different stages of the development, in physiological and pathophysiological conditions. Nevertheless, the particular mechanisms of those interactions remain understudied and require further interrogation of involved molecular cascade. Enzymatic attenuation of ECM, solely or accompanied with stem cells treatments, represents an important therapeutic strategy for recovery of neuronal connection after brain injuries. However, the possible side effects of the treatment with enzymes targeting ECM structure, such as chondroitinase ABC, appeal for an additional attention. The ability of chondroitinase ABC to affect at least two independent pathways leading to different types of plasticity and alter calcium activity in astrocytes in hippocampus *in vitro*, points out the necessity of careful consideration of the treatment in clinical practice, especially in the case of brain injuries. Therefore, ECM has a complex influence not only on neuronal functioning, but also on astrocytic functioning and its calcium activity. More detailed studies of effects of ECM and its components on synaptic transmission in different brain regions, and particularly *in vivo*, are necessary for better understanding of ECM functions in the brain. The precise mechanisms of ECM influence of astrocytic functions remain uninvestigated, despite a crucial role of astrocytic functioning in physiological and pathophysiological conditions. Therefore, understanding of the ECM role in the brain remains a priority of current studies and require thorough and detailed investigations.

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Conflicts of Interest. The authors do not have any conflicts of interest.

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