Functional and developmental properties of the extracellular matrix of the central nervous system of the rat and the chicken

PhD thesis

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INTRODUCTION

The central nervous system of vertebrates is not solely composed of cells. A substantial part of its volume is extracellular space, which is filled by the meshwork of the extracellular matrix. This matrix is composed of a variety of proteins and polysaccarides, which are secreted locally by neurons and glial cells.

These molecules are mainly the members of the proteolgycan and glycoprotein families. Proteoglycans are proteins that are heavily glycosylated. The basic proteoglycan unit consists of a "core protein" with covalently attached glycosaminoglycan (GAG) chains. Glycosaminoglycans are long unbranched polysaccharides consisting of a repeating disaccharide unit. The main component of perineuronal nets, proteoglycans, can be categorised according to the nature of their glycosaminoglycan (GAG) chains attached to the core protein. According to the combination of these sugars, the GAG chains are subclassified into heparin/heparan-, keratan-, dermatan- or chondroitinsulfates. Hyaluronan is an anionic, nonsulfated and core protein-free glycosaminoglycan. The most prominent binding partners of hyaluronan in the nervous system are the extracellular matrix proteoglycans of the lectican family. As a main matrix component, we labelled the aggrecan molecule of the lectican family which is produced by neurons. Aggrecan is a high molecular weight proteoglycan. It exhibits a bottlebrush structure, in which chondroitin sulfate and keratan sulfate chains are attached to an extended protein core. The interaction between hyaluronan and lecticans is reinforced by small link proteins.

The extracellular matrix of the central nervous system of animals including human is rich in hyaluronan, chondroitin sulfate proteoglycans (aggrecan, versican, neurocan, brevican, phosphacan), link proteins and tenascins (Tn-R, Tn-C). Extracellular matrix molecules can regulate cellular migration and axonal growth and thus, actively participate in the development and maturation of the nervous system; an aspect which has in recent years gained rapidly expanding experimental support.

Recent data highlight the importance of extracellular matrix molecules as synaptic and perisynaptic scaffolds that direct the clustering of neurotransmitter receptors in the postsynaptic compartment, thus presenting barriers to inhibit the lateral diffusion of membrane proteins away from synapses, likely impacting long term potentiation.

Chondroitin sulfate proteoglycans also inhibit axonal growth. Application of chondoitinase enzyme after unilateral nigrostriatal axotomy in rat brains promote long-distance regeneration of interrupted dopaminergic nigral axons. In other experiments injection of chondroitinase into the spinal cord in the vicinity of a lesion site degrades chondroitin sulfate proteoglycans and promotes sprouting of injured dorsal column axons and causes functional recovery.

Although matrix molecules are diffusely spread all over the brain, there are two specialized forms: the well known perineuronal nets surrounding the cell

bodies and the proximal neurites, and the so called axonal coats ensheating the synaptic and perisynaptic axonal compartments.

The existence of perineuronal nets has been implicated by Golgi, Lugaro, Donaggio, Martinotti, Ramón y Cajal and Meyer. However, Ramón y Cajal credits Golgi with the discovery of perineuronal nets because he was the first to draw attention to them and gave the first precise description in 1893. Today perineuronal nets are kown to be the essential components of the developing and mature central nervous system of mammals, including human.

The structure differences of proteins and carbohydrate components of chondroitinsulphate proteoglycans suggest that they may envelope different types of neurons. The highly charged perineuronal net structure creates a defined and stable microenvironment around neurons in the adult central nervous system. In the rat neocortex, staining with *Wisteria Floribunda Agglutinin* reveals three types of neurons. Most of the perineuronal nets surround a non-pyramidal subset of neurons which express markers specific for inhibitory GABAergic (γ-aminobutyric acid-ergic) interneurons. Perineuronal nets stained with WFA were associated rather rarely to pyramidal cells compared to interneurons in layers II/III and V/VI of the rat neocortex. However, their frequency was considerably different between various cortical areas with a maximum in visual cortex and with a minimum in secondary motor cortices.

Lecticans are the most prominent components of perineuronal nets, produced by neurons and glial cells. Compositions of the perineuronal nets change during development; thus, in murines, they are present with low expression levels in embryos with a later onset during postnatal dvelopment. In the rat cerebellum, proteoglycans appear at the same time as other components of perineuronal nets: aggrecan, hyaluronan, and cartilage link protein (CRTL-1). Up-regulation of mRNAs of these three components, when the nets start to form, indicates that they may be the most important molecules for the condensation of perineuronal nets around neurons.

Perineuronal nets become more complex and established around neurons that block the access of approaching neurites, hence, the formation of novel synapses. Maturation of perineuronal nets can effectively reduce the plastic potential of neurons which suggest a role of perineuronal nets in the stabilization of synaptic contacts. Mature forms of perineuronal nets occur rather late during postnatal life and their appearance coincides with the end of experience-dependent plasticity, i.e., the onset of some critical periods. To elevate plastic properties within the central nervous system, chondroitinase, which degrades perineuronal nets and therefore reduces inhibitory chondroitin sulfates proteoglycans features, was used in different experimental models. Studies by Pizzorusso and colleagues (2002) demonstrate that treating the mature rat visual cortex with chondroitinase restores ocular dominance plasticity, and this implies that the maturation of perineuronal nets inhibits neuronal plasticity in the visual cortex.

In the barrel cortex, a part of the primary somatosensory cortex of rodents, appearance of perineuronal nets at the third postnatal week around interneurons

in the interbarrel space can create compartments and stabilizes connections formed earlier, and therefore can limit plasticity. Unilateral vibrissectomy (removal of whiskers) in rats at early postnatal age leads to diffuse matrix patterning with restricted sensory inputs. Cells with perineuronal nets were rarely seen, moreover the barrel field pattern was also disturbed. Thus, there is an interaction between extrinsic, sensory activity, and architectural aspects of perineuronal nets formation during development.

Perineuronal nets generate and maintain a polyanionic, ion-buffered microenvironment. As mentioned above, perineuronal nets surround predominantly GABAergic interneurons. These cells are so called fast-firing neurons which have specific electrophysiological properties. High activity of these neurons is possible due to cation channels, especially a subunit of voltage-gated potassium-channels, called Kv3.1b. Since the localization of these channels overlaps not only with interneurons in numerous rat brain regions but also with a distribution pattern of perineuronal nets, it has been hypothesised that the strongly anionic microenvironment can be involved in cation turnover.

Perineuronal nets may also have roles in the pathogenesis of neurodegenerative diseases. In Alzheimer's disease transgenic mouse models, aggrecan-expressing neurons are not affected by formation of amyloid plaques. Moreover, neurons surrounded by perineuronal nets are less sensitive to cytoskeleton changes in Alzheimer's disease. Double stained sections from human brains show that pyramidal and non-pyramidal neurons surrounded by perineuronal nets are unaffected by the formation of neurofibrillary tangles even in the severely damaged areas.

AIMS

This thesis investigates different aspects of distribution and plasticity dependence of perineuronal and perisynaptic matrix in animal models.

1. In the rat, cortical regions exhibit diverse matrix patterns. We asked if matrix establishment and patterning are concisely present within systems. In other words, nuclei and regions which project to each other within an ascending or descending system show similar matrix properties. We focused on interrelating field of the thalamus and cortex, surveying plastic and less plastic systems and territories.
2. Axonal coats were recently described around inhibitory synapses in the brain. We investigated this special type of matrix aggregates int he rat thalamus, its distribution int he different nuclei. Moreover, we challanged the hypothesis that, in contrast to previous assumptions about perineuronal nets, these individual perisynaptic matrix aggregates are formed not by the post-, but the praesynaptic neuron.
3. In rats and mice, perineuronal nets are formed by the end of the third week when synapses are establsihed. We asked, how perineuronal matrix develops in animals which come to daylight with a largely differentiated central

nervous system. For this, we have used the chicken (Gallus domesticus) as an animal model.

4. Perineuronal nets show activity dependence during their development. We performed unilateral light deprivation in chicken to understand if extracellular matrix development is dependent upon afferent activity in a differentiated nervous system.

METHODS

Animals, treatment, tissue aquisition

Treatment of animals was in accordance with the Ethical guideline of SOTE, the European Communities Council Directive (86/609/EEC; 24. November, 1996), and the NIH Guide for the care and use of laboratory animals (1985). Animals (rats and chicken) were kept in standard cages under normal housing conditions. Fixed brain tissues were acquired by transcardial fixation using 4% paraformaldehyde (PFA) as fixative solution. Removed brains were cut on a cryostat or vibratome at 40μm after cryoprotection in 30% sacharose solution, and subsequently processed for immunohistochemistry.

Distribution and classification of the extracellular matrix in the thalamus of the rat

Sixteen 5-month-old Wistar rats of both sexes were used. For the mapping of the extracellular matrix of the thalamus of the rat we used immuno- and lectinhistochemistry. We immunostained extracellular matrix for aggrecan core protein using the antibody HAG7D4 in addition to another well-established marker, the N-acetylgalactosamine-binding lectin Wisteria floribunda agglutinin (WFA), that stains glycosaminoglycan chains of chondroitin sulfate proteoglycans. The precipitate was visualized by using DAB (Sigma; 0.025%) intensified with nickel-ammonium sulfate.

Sections destined for electronmicroscopic analysis were developed for HAG7D4 immunohistochemistry and the ventral posterior thalamic nucleus was selected for further analysis.

For triple labelling experiments for confocal laser scanning microscopy we performed anterograde labelling with biotinylated BDA combined with HAG7D4 immunohistochemistry and glutamate-decarboxylase (GAD) immunohistochemistry to show the spacial relationship between the agrecan immunoreactive perineuronal nets, the afferent endings, and the inhibitory terminals. Visualization was achieved by using fluorescently conjugated secondary antibodies.

Development and distribution of the extracellular matrx in the central nervous system of the chick; dependence on light deprivation

To follow the development of the extracellular matrix int he chicken, six hatchlings, six thirteen-days old and three three months old chicken were used. Brains were perfused and processed for immunohistochemistry.

For light deprivation experiments, chickens at different ages (six four weeks old, six one-day old and six animals immediately after hatching) of both sexes were used. One-day old animals acquired from the distributor were immediately treated upon arrival of transport. These animals were kept and transported after hatching in paper boxes allowing very poor illumination. The exact age of animals was between 18 and 24 h after hatching. The newly hatched animals of the third group were incubated in our institute. Fertilized eggs were acquired from Bábolna. Eggs were kept in complete darkness in the incubator and hatched individuals stayed in the dark on the day of hatching until the eye patching treatment. Left or right eyes were covered alternatively on the animals for three weeks.

Components of the extracellular matrix were visualized by lectin histochemistry and anti-aggrecan immunohistochemistry.

IMAGING

The sections labelled with immunoperoxidase reaction were captured by light microscope. Immunofluorescent labellings were examined with a Nicon Eclipse E800 microscope attached to a Bio-Rad Radiance 2100 Rainbow confocal laser scanning system. Sections for ultrastructural analisys were studied under JEOL1200 EMX electronmicroscope.

RESULTS

Distribution of HAG7D4 immunoreactivity in the rat thalamus

Aggrecan immunoreactivity as detected by the HAG7D4 antibody showed different intensities in the various subdivisions of thalamus. In addition to the peculiar forms of extracellular matrix termed perineuronal nets, the aggrecan-based matrix appeared in a different phenotype as well. These were identified as 2–5μm large axonal coats that were clearly independent of somatic or proximal dendritic compartments of perineuronal nets. An individual appearance was less common, but they typically occurred in groups of three to eight, in which they were rather closely set or even attached to each other. In most thalamic nuclei, immunoreactivity appeared both as perineuronal nets and as axonal coats in addition to the stained neuropil, but differences were observable in the different divisions, nuclei, or subnuclei of thalamus. With regard to the major distribution, matrix immunoreactivity was strongest in the reticular and intralaminar nuclei; anterior and medial nuclei were poorly labelled, and dorsal

nuclei of thalamus showed equally low immunoreactivity; nevertheless, some nuclei exibited more distinct immunostaining regarding all investigated phenotypic appearances. The ventral nuclei of thalamus containing the principal relay nuclei differed mostly in their subdivisions. The anterior motor nuclei of ventral thalamus exibited both perineuronal nets and axonal coats as shown by HAG7D4 immunostaining, whereas ventral posterior nuclei, especially the medial division (VPM), were far richer in axonal coats than in the rather vaguely labelled perineuronal nets. Matrix immunoreactivity was evidently lower in the posterior thalamic nuclear group (PO nucleus of thalamus) than in VPL or VPM nuclei. Divisions of the lateral geniculate body also differed in their extracellular matrix immunoreactivity; whereas the dorsal division was completely devoid of stained structures, the ventral divisions contained labelled perineuronal nets in an immunostained neuropil. The medial geniculate body also showed matrix heterogenity; dorsal division was poorly labelled, but the ventral division showed axonal coats and perineuronal nets, too.

Distribution of WFA reactivity in the rat thalamus

The various nuclei and subnuclei of thalamus showed a similar pattern of matrix activity with WFA staining. Both perineuronal nets and axonal coats of similar size were observable in the corresponding nuclei, however, with some differences in their frequency. Anterior and medial thalamic nuclei were faintly labelled; only the dorsomedial part of anteroventral nucleus (AVDM) showed identifiable perineuronal nets and axonal coats, with a somewhat less intensively labelled neuropil. In contrast to HAG immunostaining, no labelling was seen in any divisions of the laterodorsal nucleus. The anterior and medial subdivisions of ventral motor nuclei were less intensively, although still observably, labelled, whereas matrix intesity was practically identical in sensory nuclei of thalamus, although with a stronger reactivity in the VPL. The relative staining intensity of geniculate bodies was similar to aggrecan immunoreactivity.

Electron Microscopy

HAG7D4-immunolabelled profiles were seen around various neuronal compartments in the ventrobasal complex of thalamus. Most typically, immunoreactivity was found around preterminal sections of axons that were frequently found in groups of five to ten. Dendritic sections were frequently seen associated with labelled matrix and in several cases with axodendritic connections, synapses with flat vesicles in the presynaptic side, too.

Anterior tracing experiments combined with HAG7D4 immunostaining or HAG7D4/GAD double immunolabelling

We next asked the source of matrix-wrapped terminals int he thalamus. Because the immunoreactive axonal coats occurred most typically in ventral

nuclei of thalamus, nuclei projecting to motor (VA/VL) and sensory (VPL, VPM, PO) nuclei of thalamus were injected with the anterograde tracer to show an eventual relation between preterminal and terminal boutons of fibers and matrix immunoreactivity. Anterogradely labelled boutons traced from cerebellar nuclei were largely unrelated to matrix immunoreactivity in anterior nuclei (VA/VL) of ventral thalamus, except for a single and rather ambiguous case. Terminal or preterminal sections of labelled fibers arising from gracile and cuneate nuclei as well as from trigeminal nuclei were only sporadically associated with immunoreactive profiles in VPL or VPM of thalamus. The smaller terminal sections of fibers originating from the reticular nucleus of thalamus as well as terminal fibers arising from the primary somatosensory cortex were unrelated to matrix immunoreactivity.

Triple labellings revealed that axonal coats immunoreactive for HAG7D4 occurred occasionally around GAD-immunoreactive profiles. Similar observations were made in the red nucleus, too, where preterminal parts of cerebellar afferents as well as small GAD-immunoreactive profiles were in some instances surrounded by HAG-immunoreactive profiles; nevertheless, most of the small, delicate aggrecan-positive axonal coats were unrelated to the other labelled structures.

Extracelular matrix distribution in the brain of the chicken

Chondroitin sulphate proteoglycan-based extracellular matrix detected with Cat-315 and 1-B-5 immunohistochemistry showed almost identical cellular and regional patterns in all brain fields and appeared already on the first postnatal day (P1) around perikarya but at the same time throughout the neuropil as well. However, the staining intensity increased in the 13 days old chicken brains (P13 brains) and clearly contoured perineuronal nets were found only in adult animals. Since patterns gained with Cat-315 or 1-B-5 were similar, an overview in the adult chicken brain at representative coronal planes is shown only with Cat-315. Staining for 1-B-5 immunoreactivity is not shown. Distinct lectin (HAA, SBA, VVA and WFA) labelled perineuronal nets were only observed in some regions of the adult midbrain. No labelling was seen when sections were stained for aggrecan using HAG7D4 and AB1031 antibodies detecting human and rodent aggrecan core protein.

Chicken midbrain neurons stain intensely with lectins

The various areas of the chicken forebrain were poorly labelled when using WFA, VVA, HAA or SBA lectin staining. However, distinct fields of midbrain, i.e. the magnocellular part of the isthmic nucleus and the nucleus tegmenti pedunculopontinus stained intensively whereas the parvocellular part of nuclei isthmi (Ipc) was more moderately stained with HAA, SBA and VVA. Similarly, fusiform neurons in layer 10 of the optic tectum were selectively stained with SBA and VVA. However, none of these nuclei could be visualized

with WFA lectin staining. Actually, neurons with delicate WFA-labelled perineuronal nets could be identified only in the pons (nucleus reticularis pontis oralis, data not shown). In accordance to findings in mammals VVA and SBA lectin histochemistry visualized nodes of Ranvier in many fiber tracts.

CSPG immunoreactivity increases with age and becomes more contrastful around somata

The various areas of chicken forebrain, midbrain and cerebellum showed different intensity for Cat-315 immunostaining. In P1 brains, perineuronal nets were very delicate and in many cases incomplete i.e. they covered only part of the total perimeter of the perikarya or they showed a granular configuration. In the neuropil a homogenous immunostaining was visible, however with different intensity. Brain areas representing axonal pathways and thus containing few or no neuronal somata showed no or extremely low immunoreactivity. A unique staining pattern was seen in the pretectal nucleus. Whereas the neurons established delicate perineuronal nets and diffuse matrix staining was relatively weak in the inner part of the nucleus, an intensely labelled capsule-like structure was visible around the nucleus. Compared to P1 brains, immunoreactivity was only slightly increased in P13 brains and different brain areas preserved their relative staining intensities. At the same time, perineuronal nets were more characteristic and complete around neuronal cell bodies and could be better separated from the immunostained matrix of the neuropil. Cat-315 immunoreactivity was significantly higher both around perikarya and in the neuropil in the three months old chicken brain compared to the immunoreactivity found in P13 brain counterparts. At the same time, perineuronal nets became well-defined and their contrast to the surrounding immunostained matrix was higher than that in P1 or P13 brains. Perineuronal nets were typically present around the cell body but only occasionally around the proximal part of dendrites. In contrast to mammals, axon initial segments could be only exceptionally retrieved in the forebrain and midbrain of the chicken brain.

Extracellular matrix development could be clearly monitored in the cerebellar cortex. In P1 brains, Purkinje cells were surrounded by a delicate extracellular matrix that was thickened at P13 and became rather robust in adult animals, moreover, the pinceau could be distinguished in several casesas well. Dendrites of Purkinje cells became more expressed in the molecular layer during postnatal development. Similarly, nodes of Ranvier became clearly visible in the white matter of adult animals. Perineuronal nets of neurons in cerebellar nuclei appeared as contrastful profiles around perikarya.

Link-protein CRTL-1 (hHAPLN1) immunoreactivity

Link-protein-immunoreactivity was detectable already in the 1-day-old chicken, but increased in staining intensity at later ages. Midbrain nuclei

including isthmic nucleus (especially the magno- but also the parvocellular part), the nucleus tegmenti pedunculopontinus, neurons of layers 10–11 of the optic tectum, the pretectal, subpretectal and ovoid nucleus contained numerous neurons with perineuronal nets as well as the inferior colliculus. In diencephalic regions perineuronal nets were observed in the nucleus rotundus and subrotundus. Telencephalic regions were poorly labelled for link-protein, immunoreactivity was found only in the entopallium and in the globus pallidus. In the cerebellar cortex, stained matrix was visible in delicate vertical chords in the molecular layer but not around the cell body of Purkinje cells.

Cat-315 colocalizes with the potassium channel Kv3.1β but not with cholinergic or monoaminergic neurons

Perineuronal nets demonstrated by the Cat-315 antibody were found to colocalize with the potassium channel subunit Kv3.1β around neurons in the magnocellular part of nucleus isthmi (Imc) and neurons in layers 10–11 of the optic tectum already at P1–P14 although well-established perineuronal nets appeared only in the adult brain. Cat-315 showed similar colocalization with B-HABP. In contrast, no colocalization was found between Cat-315 and choline acetyltransferase inr egions known to contain cholinergic neurons, i.e. in the basal forebrain or between Cat-315 and tyrosine hydroxylase in brainstem nuclei.

Chondroitin sulphate proteoglycan-based perineuronal net establishment is largely activity-independent in chick visual system

In all three populations (monocular light deprivation at four weeks old chickens, one-day old chicks, hatchlings), the optic tectum and magnocellular isthmic nucleus (Imc) of mesencephalon, the nucleus rotundus of diencephalon and the entopallium of telencephalon of both sides were investigated for matrix establishment. Since the visual pathway is fully crossed at the optic chiasm in chicks, regions contralateral to the closed and covered eye were acknowledged as deprived whereas regions ipsilateral to treatment as spared areas with restrictions to diencephalon and mesencephalon. As shown previously, extracellular matrix as revealed by Cat-315 and CRTL-1-immunoreactivity accumulated around cell bodies of neurons forming perineuronal nets. Additionally, neuropil was immunostained as well, especially when using the Cat-315 antibody.

The immunostained neuropil was stained very similarly on deprived and spared sides. Slight intensity differences were occasional, occurred alternatively between sides in the investigated animals and were in no way comparable to the dramatic activity-induced development described in mammals. Perineuronal nets were established and well identifiable on both deprived and spared sides.

CONCLUSIONS

Our results in relation to the development and plastic properties of perineuronal matrix suggest that

(1) based on the findings in rat thalamus, the distribution of aggrecan-based extracellular matrix is dependent on the role and plastic properties of the target cortical region.

(2) The extracellular matrix molecules rarely accumulate as perineuronal nets in principal nuclei of rat thalamus but establish an ambiguous network that typically condenses around preterminal axons loosing their myelin sheath, axodendritic junctions, and some inhibitory terminals. We suggest that the core protein aggrecan of extracellular matrix may load from both pre- and postsynaptic sides.

(3) Chicken leave the egg with a well established perineuronal matrix which, however, shows further maturation during the first three months. This is due to the immediate functional performace of the chicken after hatching, and to the ongoing synaptogenesis during ageing, respectively.

(4) The results of the monocular deprivation suggest that chondroitin sulfate proteoglycan based typical matrix accumulations, i.e. formation of perineuronal nets is largely activity-independent in domestic chicken. Further studies need to investigate the factors which play major roles in the matrix establishment of the chick brain.

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