THE PLACE AND DEFINITION OF FIBROUS ASTROSIDES IN THE STUDIES

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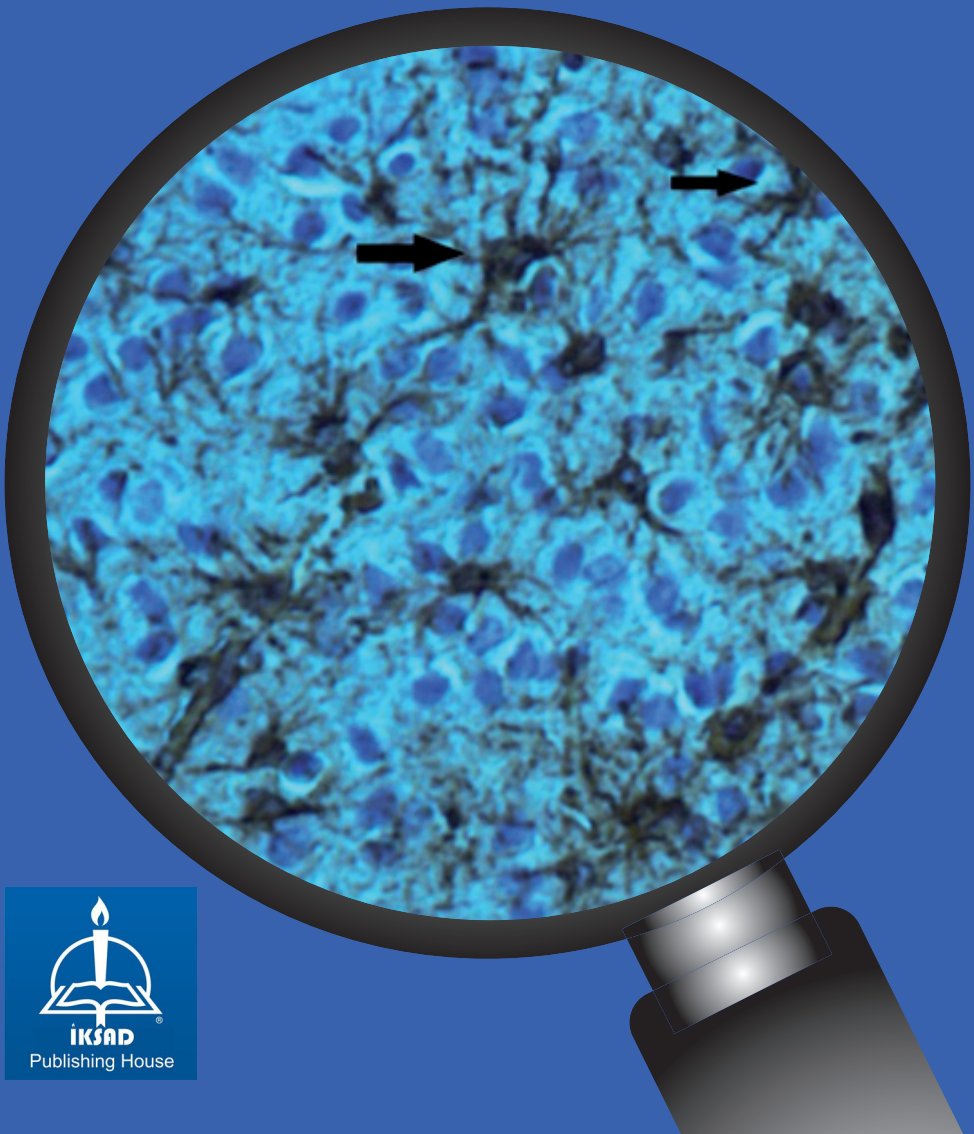

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INTRODUCTION

Astrocytes are among the most abundant cell types in the adult brain, where they play an important role in many functions. Although astrocytes play an important role in brain homeostasis, they provide vital metabolites to neurons and also buffer water, ions and glutamate outside the cell. Astrocytes, one of the three parts of the synapse, are an integral part. However, it plays an important role in the formation, cleaning and maintenance of synapses. To accomplish these important events, astrocytes communicate with each other and with other glial cells, neurons, cerebral vasculature, and the extracellular environment through numerous specialized membrane proteins, including cell adhesion molecules, aquaporins, ion channels, neurotransmitter transporters, and cavity. Astrocytes, like neurons, rely on intracellular transport to be well-co-ordinated tightly and regularly to support dynamic flow. Heavy traffic inside the cell

Few studies have been done to understand microtubule-based transport in astrocytes, unlike neurons, which has been described more extensively. In addition, proteins in the cell membrane and the exo- and endocytic trade of intracellular organelle

transplantation regulate and these processes are often severely affected by disease or injury [1].

Firstly, astrocytes are considered an important building block of the CNS (Central Nervous System) and are the most dynamic of the various CNS cells. Astrocytes join together with other astrocytes through connections in the space and astrocytes show increases in calcium in the secondary cell due to activation in neighboring neurons [2]. The neuroglial relationship is so complex that human protoplasmic astrocytes each contain close to two million synapses [3]. Astrocytes are extremely sensitive to many harmful stimuli from outside and have the ability to easily transform themselves into reactive cells after stimulation. This feature mediates the release of gliotransmitter accompanied by a slightly increased intracytoplasmic Ca + 2 concentration [4]. These events may indicate that they may be the harbinger of neurodegeneration, which is also seen in hyper excitability and excitotoxicity [5]. During astrocytic activation, calpain, a protease bound to calcium, can be triggered to participate in this reactive process. Proteins and cellular enzymes in Calpain's other cytoskeleton are also targets [6].

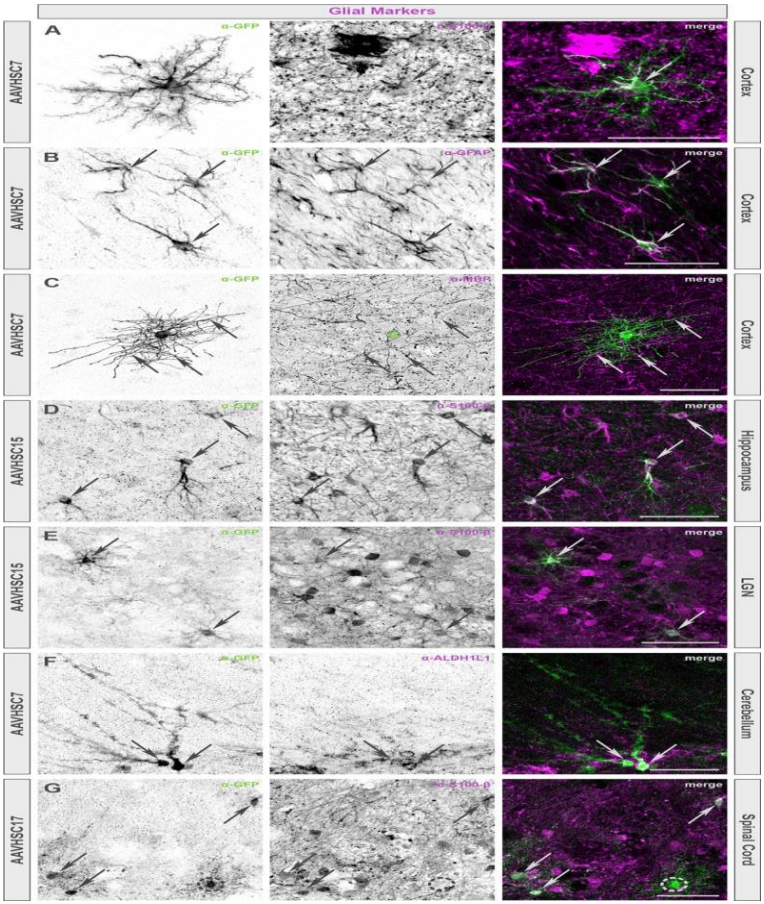


Figure 1: When eGFP immunofluorescence was examined in different brain regions in non-human animals treated with IV doses of scAAVHSC-CBA-eGFP, the animals were given the dose of scAAVHSC7-CBA-eGFP in colocalization with glial markers (A, B, C, F). (D, E) Animals were dosed with

scAAVHSC15-CBA-eGFP. (G) The animal was dosed with scAAVHSC17-CBA-eGFP. EGFP-positive cells were found to contain protoplasmic and fibrous astrocytes (A, B and DG, respectively), similar to glial cells. [7].

Astrocytes are known to be responsible for extracellular ion homeostasis in the central nervous system, including the H + ion. Astrocytes are known to have profound effects on many responses such as pH regulation, proper neurotransmission, and injury, and have been studied in detail before. In the central nervous system, the intracellular pH balance is determined by two main factors: (i) the buffering power inside the nerve cells and (ii) the important factor such as extrusion or acid loading by the activity of membrane transporters that occur with acid in the cell by moving H^+ equivalents across cell membranes contains. Also, acid extruders can directly extract H^+ ions from cells or import HCO_3 and acid loaders are suggested to remove only HCO^3. Two HCO^3 bonded carriers, Na-HCO_3 co-carrier Na + exchanger, which are HCO^3 exchangers in addition to an electro-neutral HCO exchanger (astrocytes). Carriers that are HCO^{3-} independent can bind the H^{+} + ion directly to the ionic gradient or maintain intracellular pH by other means of transport. Studies

of astrocytes used in culture practices show that the Na-H exchanger (NHE) 2 is the main basic HCO. In the CNS, 3 independent H^+ extrusion proteins connect the H^+ extrusion to the inward gradient while Na^+ [8]. Astrocytes also refer to a V-Type H-ATPase that can be blocked by baphilomycin, but the involvement of this pump in PH maintenance and recovery after acid charge is limited in cultured cells. Most of the available information on H^+ extrusion from astrocytes has been obtained from culture preparations. They have the advantage of low background signal and ease of use, but the disadvantage is that the cells can behave differently than in-situ cells, where they integrate into complex neural networks. Using mouse optic nerves 0-4 days postnatal (P0-P4), we are now studying the role of v-ATPase and NHE in maintaining stable state pH and pH recovery after acid charge in astrocytes. This white matter pathway allows high contrast imaging of ion-sensitive intracellular dyes and includes a population of early maturing fibrous astrocytes. The nerve was severed at both ends and the cells were displayed in the central region and therefore in a natural, effectively undamaged environment.

In contrast to cultured astrocytes, we report that V-ATPase is the dominant HCO^{3-}independent H^{+} extrusion mechanism in this in situ astrocyte population.

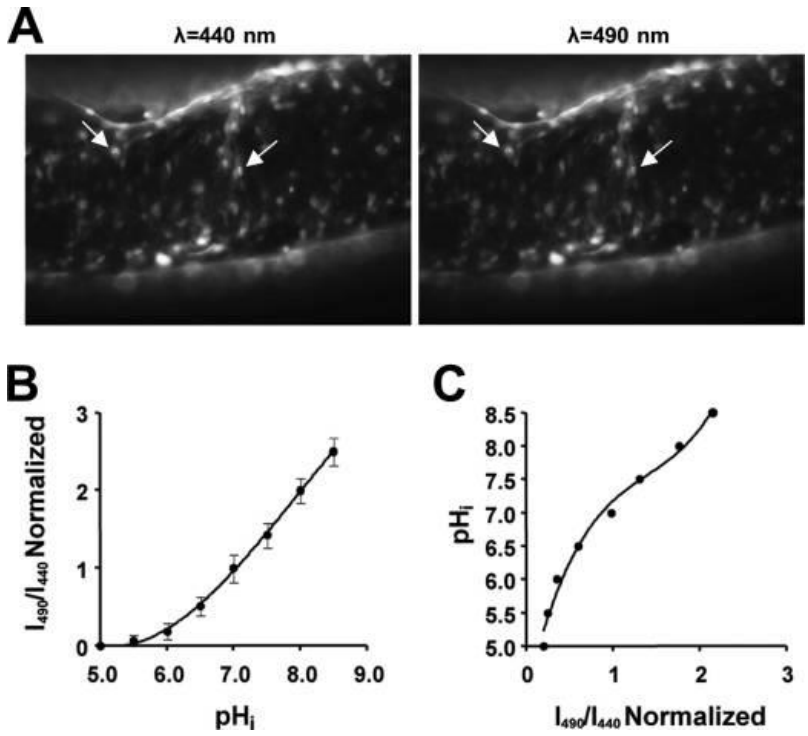


Figure 2: Cell loading of BCECF-AM and pH calibration in optic nerve astrocytes. It shows cell loading in the regulation of BCECF-AM and pH in astrocytes in the optic nerve. A reveals images of BCECF-AM loading in astrocytes in the optic nervous

system in the mouse. It appears to load in cells indicated by numerous arrows that occur during excitation at 440 and 490 nm. B is the graph of the calibration obtained from astrocytes in the optic nerve. The cells are usually exposed to high K + / nigeris calibration solutions at pH values between 5.5 and 8.5, resulting in ratios of 490/440. The 490/440 ratio was normalized to the ratio at pH 7.0. The values obtained are given as the mean ± SE C, the recovered calibration curve, but the data obtained are made available for a third order polynomial function. This is used to correlate pHi values with normalized ratios of 490/440 obtained from single point calibrations at the end of experiments [9].

Astrocytes, which play an important and critical role in brain functions, provide a functional interface between neurons and capillaries. It also modulates the brain system via the glial-neuron called 'vascular units' [10]. The astrocyte regulates the ionic and metabolic conditions in the brain environment by the release of a number of chemicals, and this regulation is carried out with chemicals such as ATP/adenosine, glutamate, D-serine. The findings showing that neural systems 'gliotransmitters' generally regulate CNS functions function as chemoreceptors in

the central region of astrocytes on the ventral surface of the oblongata located in the medulla. Changes in the partial pressures that occur trigger CO_2 or pH in the ventral medullary local center in chemorespiratory neurons and are activated by ATP generated from these cells that cannot be electrically stimulated. In addition, these neurons cause many changes in the central respiratory system. these changes are speed and volume [10]. In some studies, there are many studies supporting that astroglia play an important role in sodium channels and transporters, although most of them focus on Ca^{2+} metabolism [10]. When we look at the studies conducted, the first revealed are sodium channels in the epithelium located in the mullary glial cells of the retina. This statement proved that astrocytes belong anatomically to the subunit of ENaC, and it has been revealed that the inward flow of sodium in these cells can be stopped by amiloride. ENaC-expressing neurons have been observed in peripheral ventricular organs (CVOs) in the sensory regions [11], Studies have shown that an astrocyte group CVOs are located in the border regions. In these areas, it has been extensively immuno-immunized against its protein by the antibody in subunits of ENaC. In addition, astrocytes representing ENaC contained in the pia mater are intensively

immunostained. Fibrous processes have been demonstrated in the cardiovascular part of the brain stem in the last group of astrocytes in the area that functions as respiratory functions. In some studies, ENaC expresses the astrocytes in the γ-subunit and shows its location, and discusses the important roles it plays in sodium functions in the brain. ENaCs (Scnn1) are sodium channels that allow sodium to be transported across the apical membrane of epithelial cells, which enables salt reabsorption in the airways of the distal nephron and the distal colon part. Most of the studies have focused on ENaCs found in the kidneys and airways, but it has been revealed that ENaCs are in the brain. Thus, ENaCs have been intensely observed in astrocytes, ependymal cells of the choroid plexus, endothelial cells and neurons in the brain, and these channels adversely affect many functions. Some studies have been making the definition of the sub-units of ENaCs. When we look at the general definition of neurons and astrocytes shown immunoreactive by ENaCs in peripheral organs (CVOs), white region and pia mater;

Neurons representing ENaC are found in sensory CVOs. As stated in the studies conducted, the location of ENaC α-immunoreactive neurons is closely related to the information

obtained in in situ hybridization studies. Antisera in contrast to the ENaC subunit with the immune staining pattern expressed as the ENaC a-subunit antibody were similar to the results. However, in one study, the ENaC γ-immune staining pattern differed, and much less neuronal staining was achieved in CVO in three sensory regions: AP, SFO, and OVLT. To illustrate an example of weak ENaC- γ immunoreactive neurons, Figure 1. Unlike the immunostaining caused by antibodies in the α- and β subunit of ENaC, the ENaC caused excellent staining of these three CVOs surrounded by astrocytes in the γ-subunit (Figure 1). In addition, astrocytes showing ENaC γ-immunoreactive are in the optic chiasm (Figures 1 and 2) and in the pyramidal path (Figure 6) and the pia mater (Figures 1, 2) shown. It was stained immunohistochemically with antibodies against ENaC a and its subunits in the pia mater. Also, immunoreactivity was observed in the subunit of ENaC inde found in GFAP pial fibers (Figures 2A and 5A. In addition, all of the antibody of the ependymal lining of the brain was stained but, as previously known, no GFAP immunoreactivity was observed in this tissue.

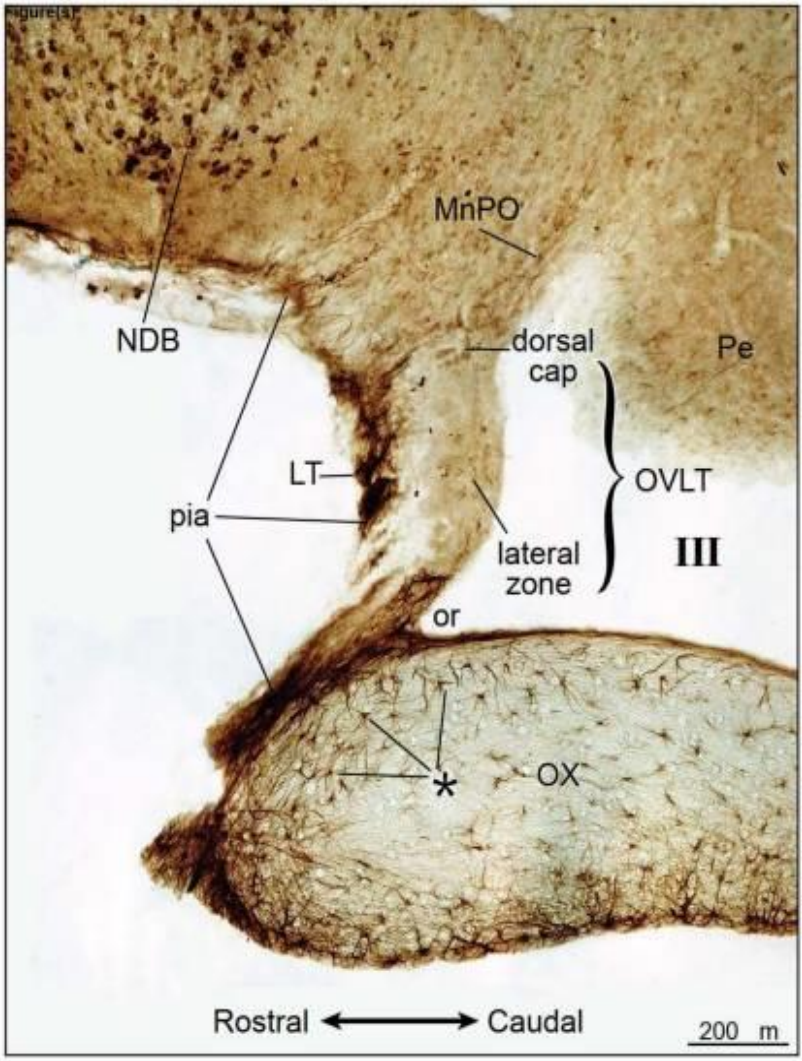


Figure 3: The demonstration of ENaC γ-subunit immunoreactivity is shown in the parasagittal cross section of

the forebrain of rats. ENaC γ-subunit immunoreactivity is extensively demonstrated in neurons in the nucleus of the diagonal band (NDB), found in the lamina terminalis (LT), pia mater. It is seen that the ENaC γ 'effect is very low in the neurons of the lamina terminalis (OVLT), the median preoptic nucleus (MnPO) and the periventricular hypothalamus region (Pe) and the lateral region of the organum vasculosum and also the dorsal valve. In the optic chiasm (OX), astrocytes have been shown to have very intense ENaC γ expression at the border of the fiber bundle and this area is indicated by asterisks (*). The ENaC γ-subunit expressing astrocytes is shown to be the region between NDB and LT [12].

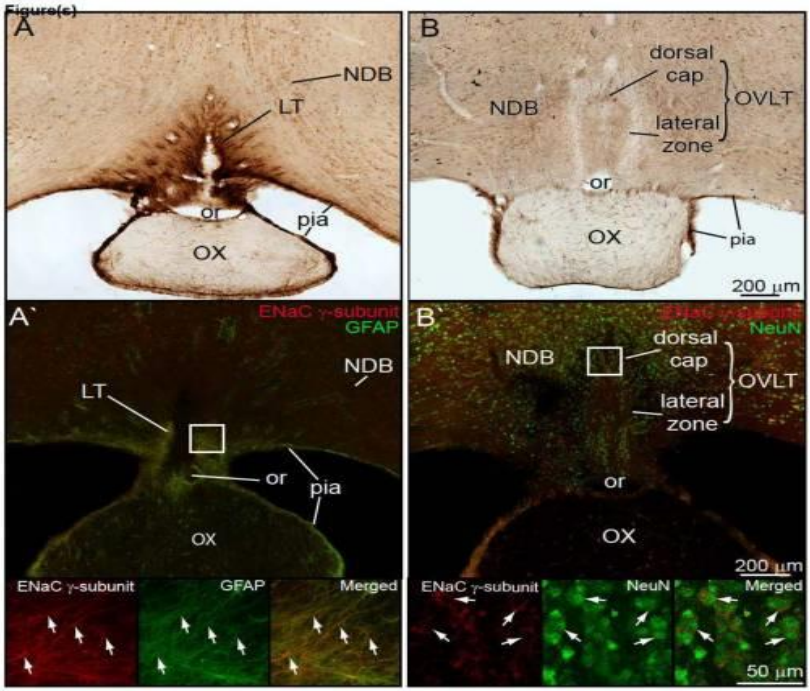


Figure 4: A. It is the bright areas in the longitudinal section of the forebrain where the astrocyte plexus is densely seen in the ENaC γ-subunit, which provides the formation of the lamina terminal (LT). This plexus continues with the pia mater located on the ventral surface of the brain and surrounding the optic chiasm (OX). ENaC γ-positive glial fibers are shown to be located in the most rostral part of the third ventricle. Co-expression of glial fibrillar acidic protein (GFAP) and ENaC-

subunit protein has been shown as immunofluorescence in Pia [12].

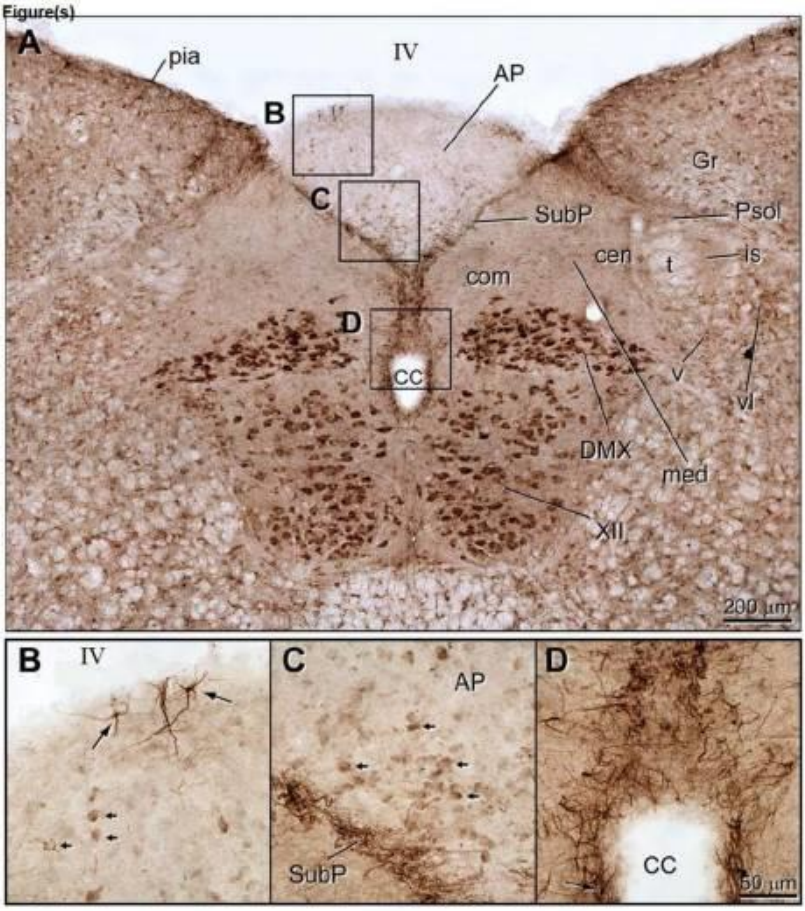


Figure 5: ENaC shows the intensity of γ-immunoreactivity in the medial medulla section of neurons and astrocytes in the

dorcele. A. Immunostaining in the most intense ENaC was observed in neurons in the dorsal motor vagal (DMX) and hypoglossal (XII) nuclei. In addition, it has been shown that more staining is shown in the subpostrema region (SubP), which elongates along the ventral border of the postrema region (AP) [12].

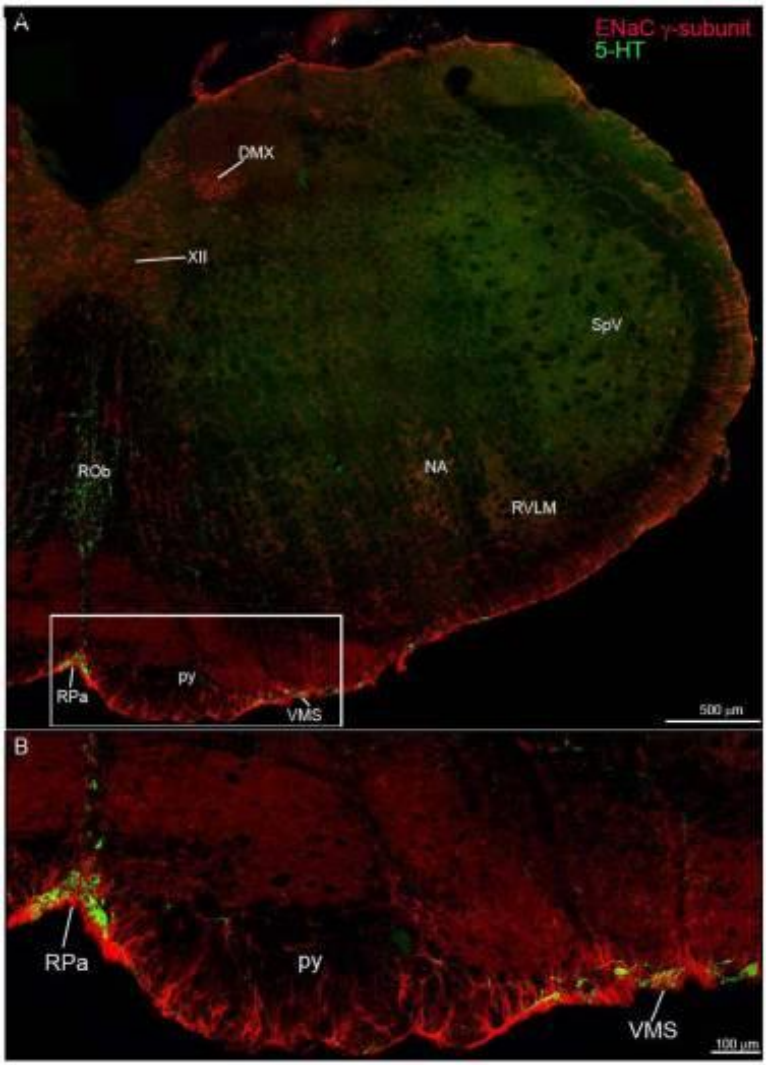


Figure 6: Reveals low power photographic image of medulla oblongata. When we examine the immunofluorescent

preparation, ENaC shows the γ-subunit and 5-HT immunoreactivity. A. shows the protein of the ENaC γ-subunit extensively seen in Pia mater. It indicates the interlocking of ENaC γ expressing astrocytes in the ventral medulla, raphe pallidus (RPa) and 5-HT neurons on the ventral medullary surface (VMS). reveals an intense appearance on the surface [12].

Bergmann glial cells extensively express NDRG2 (Figure 6). In the cerebellar granule cell layer, astrocytes were observed in the vicinity of the fiber terminals against the vesicular glutamate transporter 1 (VGLUT1), which is seen as immunoreactive (Figure 6b). In a similar situation, NDRG2, which includes astrocytic processes, was found to be associated with glutamatergic nerve terminals in the hippocampal stratum lucidum (Figure 6c).

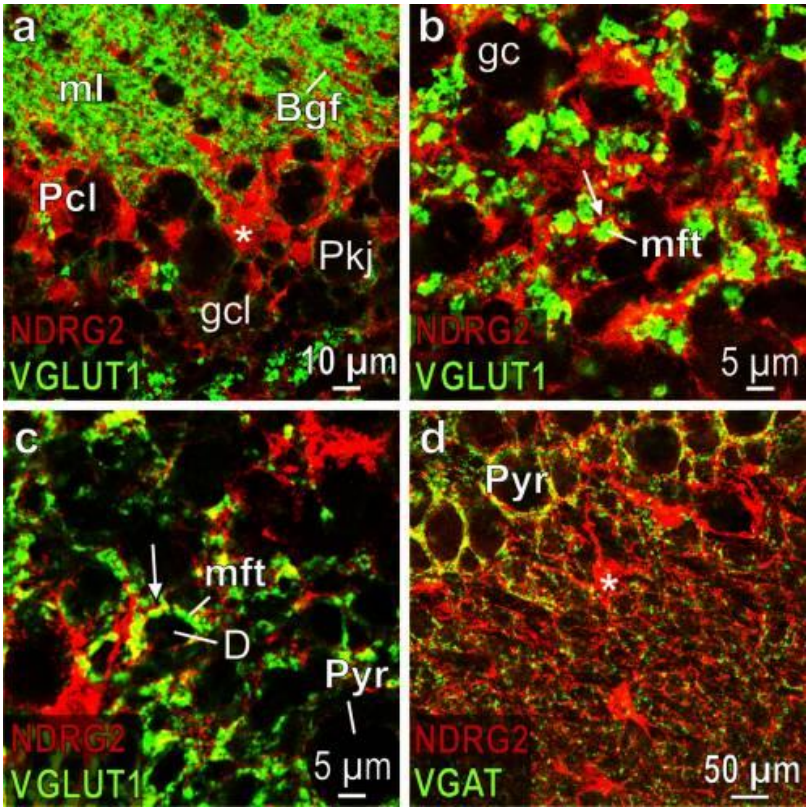


Figure 7: Glia cells in the hippocampus in the rat's cerebellum are fused to the cerebellar Purkinje cell layer (Pcl); The intensive NDRG2 immunoreactive Bergmann glia cell bodies found among Purkinje neurons (Pkj), which are not shown, are indicated by an asterisk; Bergmann glial fibers in the molecular layer are shown in red, while glutamatergic parallel fibers are

shown in green; gcl granule cell layer. Granules appear in the b (consolidated) cell layer located in the cerebellum (gc); It is indicated by the arrow that it reveals the NDRG2 process associated with the fiber terminal (mft) in the VGLUT1 immunoreactive region. c (combined) Hippocampal stratum lucidum; The arrow shows the NDRG2 positive process associated with the giant VGLUT1 immunoreactive mossy fiber terminal (mft) synapsing on the dendrites of pyramidal neurons (D). d (combined) In hippocampal stratum lucidum, fine NDRG2 positive processes are associated in VGAT immunoreactive nerve regions and the immunoreactive cell body in NDRG2 is indicated by an asterisk [13].

The layer in the multilaminar medullary epithelium has been suggested as the main source of differentiation in ocular medulloepitheliomas without a definite finding. It is seen that very early stages in cytological differentiation are erased in large lesions. Small lesions appear to offer great opportunities to solve the problem of different cell types. When the morphological evaluation was made, when we examined by immunohistochemical methods, it was revealed that neuroblasts and fibrous astrocytes appeared directly and separately from

each of them in the medullary epithelium. When we look specifically, some immunohistochemically defined biomarkers are seen as analytical in many cases [14]; In a neuronal differentiation, astrocytes glial fibril acidic protein (GFAP) for photoreceptor differentiation in neurofilament protein for neuronal cell bodies and axons, CD99 precursor neuroepithelium for premature and S100 (including dendrites and axons) for astrocytes and neurons appear to be involved in this differentiation. It has been revealed that astrocytes and neurons develop separately from the medullary epithelium and develop respectively.

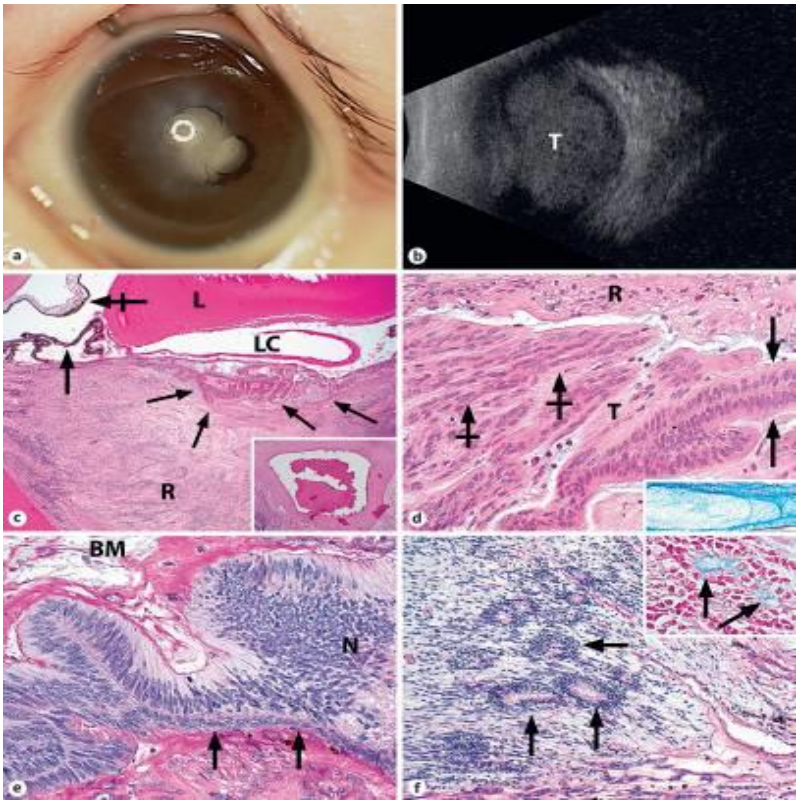


Figure 8: Small intraocular medulloepithelioma. a, 3-week-old girl was found to have left leukocoria by her grandmother and father. b, B-reveal the intraocular tumor by scanning ultrasonography. No funnel-shaped retinal detachment was seen in the ultrasonographic image. c The loci is attached to a retrolental (L) mass, and the cords and strands connected together in the medullary epithelium indicated by arrows

indicate the boundaries in the medulloepithelioma. When we examined the mass, it was revealed that most of it consists of irregular and compressed retinal tissue (R). The arrows showing the torn lens capsule show long ciliary processes, and the crossed arrows reveal the iris leaflet. d, Dysplastic retina / medulloepitheliomatous mass at the base of the tumor (T) has been shown to be formed by the formation of the longitudinal pseudopapilla and strip of the medullary epithelium. Less prominent medullary cells are visible in the immediate vicinity, and these are indicated by crossed arrows. e, The single layer (arrows) of the premedullary epithelium at the base of the tumor enters the left medullary epithelium [15].

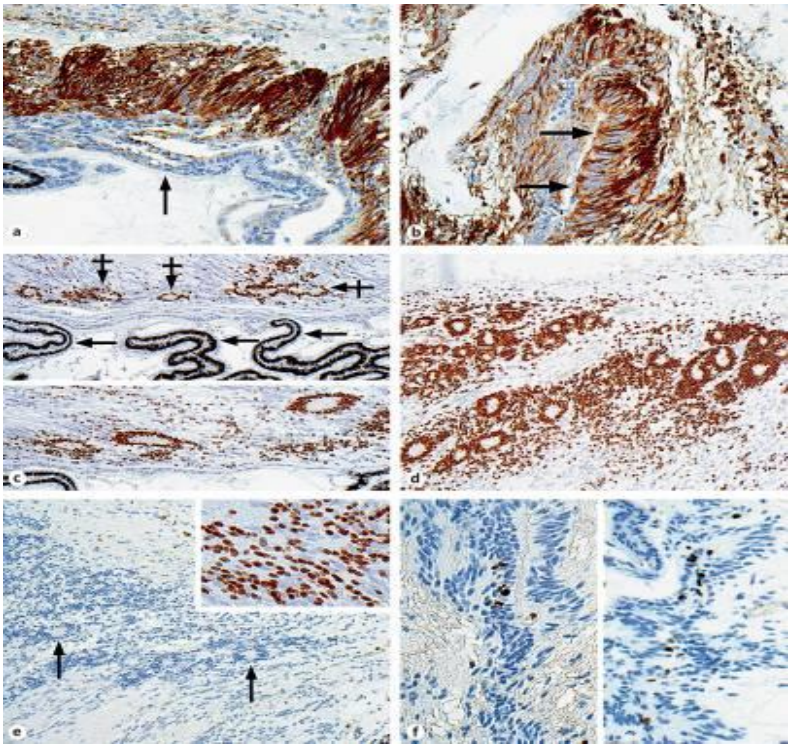


Figure 9: Medulloepithelioma in the eye is demonstrated by immunohistochemical staining. Acidic proteins in glial fibrils are followed by many fibrous astrocytic processes at the level of the medullary epithelium located at the base of the mass. The arrow indicates that there is a, single premedullary epithelial layer under the medullary epithelium. The emergence of fibrous astrocytes in the b, medullary leaf is shown by the arrows. c, Upper: The positivity in CRX has a normal appearance, but the

ones in the long ciliary process (uncrossed arrows) and the medullary grooves just above it are demonstrated by crossed arrows. When we examined the bottom: cross section, the formation of the CRX + medullary epithelium was observed very densely. dCRX, retinal mass irregularly covers the neoplasm and is manifested in dysplastic rosettes. e, Small neuroblasts NeuN reveals that it surrounds in dysplastic rosettes as shown by arrows. The f, Ki-67 protein appears to react as dark brown and is limited to the leaves of the medullary epithelium found in its cores [15].

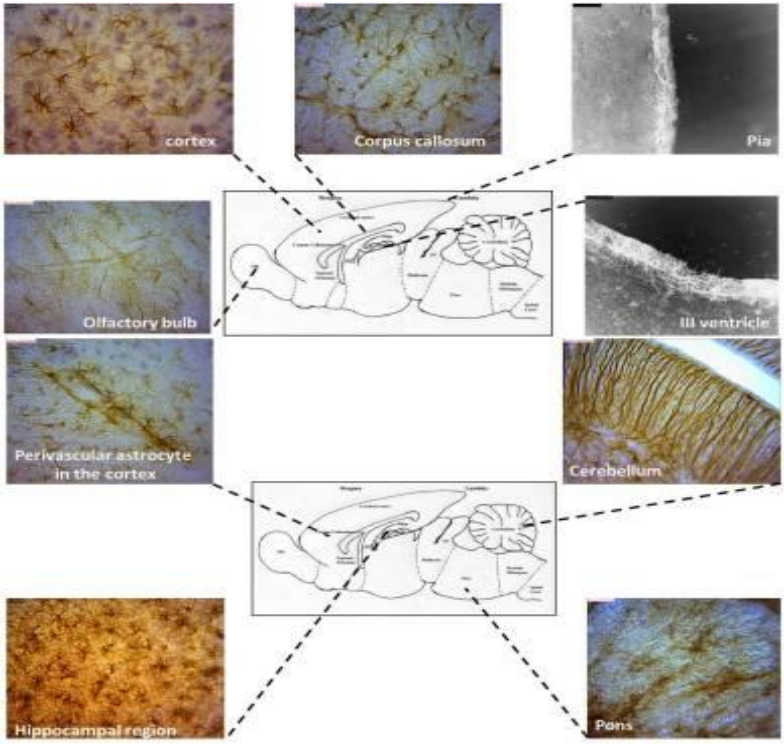


Figure 10: Astrocyte morphological images representing specific regions of the AGR brain were obtained from sagittal sections and displayed immunohistochemically with GFAP [16].

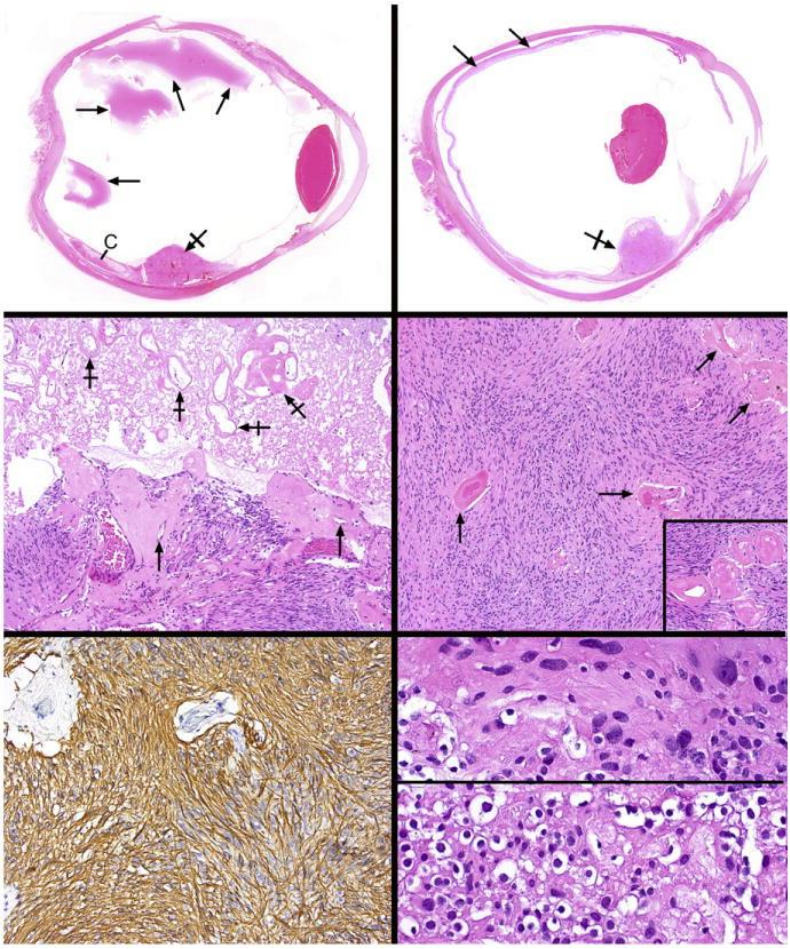


Figure 11: It reveals the histopaological features in astrocytic tumors showing reactive in the retinal region. The eosinophilic exudate arrow in the vitreous cavity in the upper left picture shows a high level of tumor in the inferotemporal region and is

shown with a cross arrow. It is demonstrated that there is a large intraretinal cyst located just behind the mass (C). It reveals the pattern of a reactive astrocytic tumor formed in the area of apical necrosis in the upper right and indicated by crossed arrows [17].

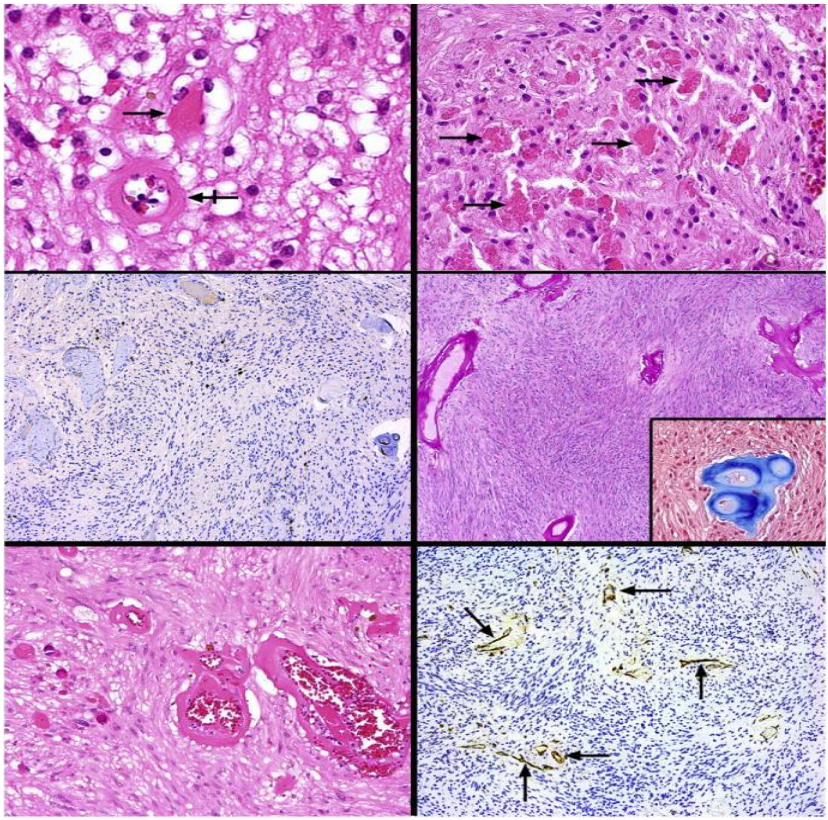


Figure 12: Histopathological view of astrocytic tumors occurring in the reactive retinal region is presented [17].

Investigation of the Diversity of Astrocytes in the Brain Regions;

Astrocytes have been demonstrated to be non-neuronal cells that maintain precise environmental conditions for their connections with neurons in the central nervous system. The structures of astrocytes are complex and when we examine their molecular properties, it has been shown in many studies that bastrocytes have important roles in the regulation of ion flow outside the cell, recovery of neurotransmitter and regulation of cerebrovasculature. When we look at protoplasmic astrocytes, it is characterized by the fact that it is significantly complex and also envelops neuronal cell bodies, but also very thinly enveloping blood vessels with synapses and feet. In the continuation of these processes, it has been suggested in many studies that cells are loaded with special molecules to remove neurotransmitters and ions, as well as secrete neuroactive substances that regulate synapses, regulate energy substrates and change nutrients in the vascular system to fulfill these functions [18].

Astrocytes were first suggested to have star-shaped morphologies in the 19th century. However, studies conducted today reveal that astrocytes exhibit morphological and functional properties in many events that reflect the brain circuits around them. When we look at the astrocyte morphology in some regions of the CNS, it shows many differences to reveal the anatomical regions [19]. When we look at recent studies, it has revealed that it goes beyond the morphological differences between astrocytes and revealed different molecular and functional properties of some CNS astrocytes, which are quite suitable for the function of neighboring neurons. If we explain this with a picture, different astrocyte samples with different adaptation properties and structural and functional properties are shown in the CNS regions.

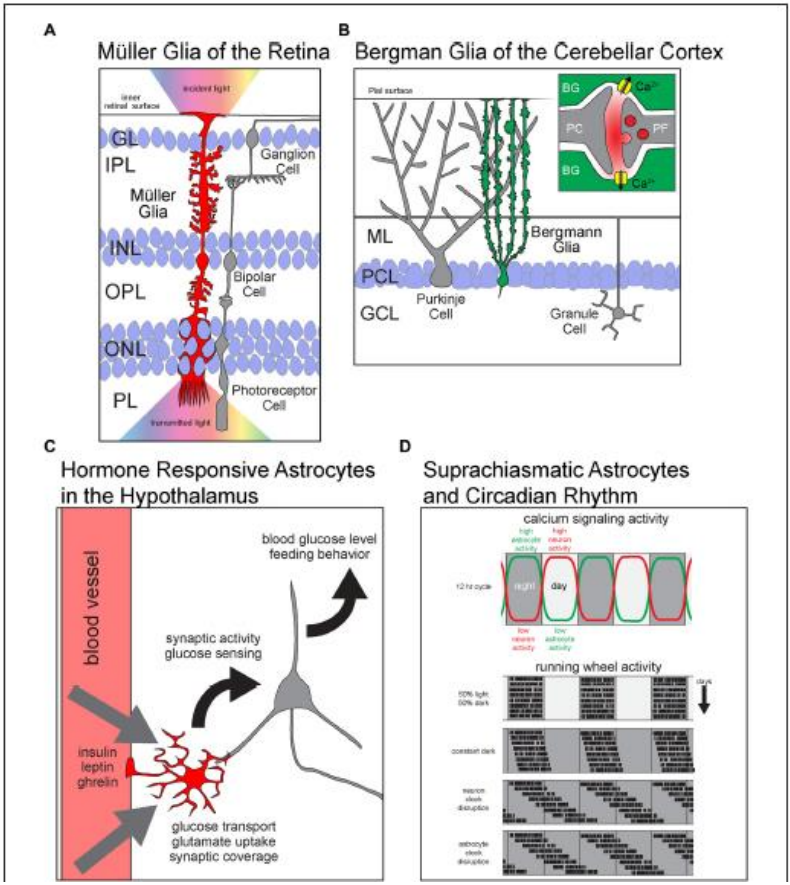


Figure 13. When we look at the variety of astrocytes in the regions of the brain, diagrams showing the region-specific features and functions of different astrocyte types are presented. (A) Shows the presence of radially polarized astrocytes covering the retinal layers located in the Müller glia region of the retina.

(B) BG reveals radially polarized astrocytes that direct glutamatergically synapse-rich neuropilin in the cerebellar cortex. (C) Astrocytes have been observed in the curved nucleus of the hypothalamus and are also shown to be among the critical regulators of energy homeostasis [20].

Astrocyte Heterogeneity

Looking at the middle of the 19th century, Rudolph Virchow is known as the first person to reveal a particular type of cell in the brain that we know today as astrocytes. At that time, the excellent functional functions and complexity of these cells and how they contributed to brain function were not yet known. In histological studies, many features and protoplasmic and fibrous astrocytes according to their anatomical positions are shown as figures [21]. Protoplasmic astrocytes, a common type of astrocyte, are seen distributed in the gray matter (GM) of the brain. This type of astrocyte is larger, rounded and has numerous branching and appears to be thick and short. In contrast to these astrocytes, the cell bodies of fibrous astrocytes in the white zone (BM) generally show longer, thinner and less branching [22]. The reason for these morphological differences is due to the specific features and functions of different brain regions. When

we look at its most important role, it reveals that it is of great importance in controlling neuronal synapses in GM to perform important activities in the brain [23]. In addition, when we look at another important task, it has the ability to synapse and reveals that it has great contributions to neurotransmitter, ion and energy homeostasis. Contrary to these events, the electrical information that occurs in the UN significantly shows that most of it is spread by myelinated axons with much less information processing. Thus, it accelerates the processes carried out by fibrous astrocytes together with the axons along the WM and reveals that at least in myelinated fibers, only the axons are in contact with the Ranvier node. A large number of somatas, which are quite large and round, have been found to have thin branches during this process, resulting in their thick and short processes.

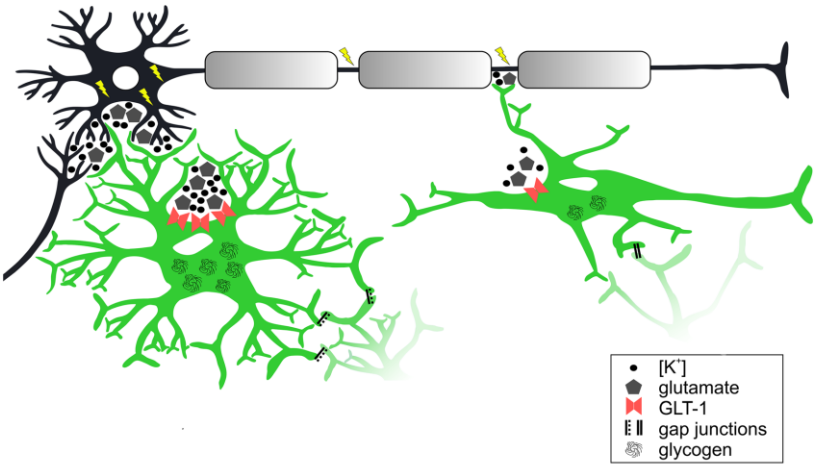
Thus, besides these morphological differences between protoplasmic and fibrous astrocytes in GM and BM, many differences occur in these cell populations. As an example, the fibrous astrocytes show very high levels of intermediate filament GFAP from protoplasmic astrocytes with GM, and also reveal differential expression of calcium binding proteins such as S100p or S100A4 (Mts1) [24]. These demonstrated features

have been used in several subpopulations to develop astrocytic markers, but this distinction is not exclusive. In addition, the expression Aldh1l1 is accepted as a general indicator for all astrocytes [25]. Generally speaking, gene expression profiles in astrocytes differ greatly between GM and BM, suggesting that the tissue environment and astrocytes in some parts of the brain likely reflect an adaptation with different functions and functions [26].

Studies show that astrocytes originating from a few precursor cells fill the brain from the 16th day of the embryonal period in mice. There have been many studies proving that protoplasmic and fibrous astrocytes are produced from different cell parts [27]. It has been revealed that the different number and distribution of astrocytes in the GM and WM regions depends on the different factors in the transcription regions [28], Apart from these, external signals that perform an important activity such as neuronal activity also provide great support for their maturation [29]. It has been shown in many studies that the development of astrocytes specific to the region where they are located has a great effect on neurogenesis [30].

Looking at Heterogeneity in Glutamate Metabolism

The most important definition of glutamate has been demonstrated to be the main stimulating neurotransmitter in the mammalian brain. Studies show that glutamate contained in GM is released at the neuronal synapse in order to provide information to postsynaptic cells. These glutamergic synaptic signals are terminated by the advent of glutamate in the astrocytic process surrounding synapses. Thus, it has been revealed that it forms the structure of the triple synapse. Contrary to these events, many studies have suggested that glutamate, which is composed of axons, probably synapses in GM [31] released in much smaller amounts and provides support by coordinating metabolic events from myelin to axon, as well as signaling NMDA receptors oligodendroglially [32]: Moreover, astrocytes can reach the axons at the Ranvier nodes of unmyelinated and myelinated axons. As a result, it is suggested that the glutamate required by astrocytes is very different in GM and BM.



	Protoplasmic astrocytes	Fibrous astrocytes
Neurons	many contacts at synapses	contacts only at node of Ranvier
Glutamate metabolism	glutamate exposure high glutamate clearance high high GLT-1 expression	glutamate exposure low glutamate clearance low low GLT-1 expression
Glycogen	high glycogen content	low glycogen content
Gap junction coupling	intense coupling connexins 43 & 30	less coupling mainly connexin 43

Figure 14. The main main differences of astrocytes in gray and white matter are due to the heterogeneity found in Energy Metabolism.

Many studies show that one of the most important functions of astrocytes is to maintain energy homeostasis in the brain. This task performed by astrocytes contributes at many levels: First,

astrocytes come into contact with blood vessels located at the ends of the legs and appear to make an important contribution to the regulation of local blood flow. When we look at a second important task, astrocytes control by carrying substrate in and out of the parenchyma of the brain. The third task of astrocytes is that they take energy-source substrates such as glucose from capillaries and partially metabolize these energy substrates to other molecules such as lactate, and then have an important role in transferring them to other cells such as neurons and oligodendrocytes. In addition, astrocytes store glycogen as an energy in the brain and it has been suggested in many studies that they act to support brain function [34,35]

Although these general concepts have been valid for astrocytes in GM and UN, they exist with a few important criteria that have not yet been put forward systematically [36]. Initial studies reveal that energy metabolism varies significantly between GM and WM. When we look at the events taking place in BM, glucose uptake, glucose phosphorylation and local glucose utilization are much slower. In addition, studies have shown that it indicates not only astrocytes but also total tissue, according to the analyzes obtained. However, it is suggested in many studies

that some enzymes of the TCA cycle and glycolysis have a much lower activity than BM compared to GM, and that the activity in the respiratory chain is much lower than glycolytic activity. In line with this information obtained, it has been revealed that the capacity of astrocytes in the UN in ATP production is much lower [37,38]

Heterogeneity in the Blood-Brain Barrier (BBB)

Astrocytes are an important part of the interface of the blood-brain barrier and contact the blood capillaries with their end legs, so it has been demonstrated that they differ between GM and BM. The density in the capillaries is much higher in GM than in BM [39]. As shown in studies, the density of capillaries is higher in GM and when we look at glucose consumption rates, it is seen that glucose utilization rate is closely related. [40] Looking at another direction, deletion of GFAP preserves myelination for a long time, but causes failure. Astrocytes in the WM capillaries and oligodendrocytes have been placed in the oartum where there are significantly large relationships between them. Thus, it has been suggested that, due to the different properties of protoplasmic and fibrous astrocytes, gray and white matter are

likely to contribute significantly to the differences in BBB properties.

When we consider an important aspect of the BBB, we see that water is transmitted to the brain and allows it to be distributed from the brain to other cells. For example, it has been shown in studies that water homeostasis in ischemia is among the important examples that it will lead to death with the formation of edema, swelling of the cell, increased brain pressure [41]. The largest mediator of water transport is aquaporins (AQP) and therefore it has been suggested in many studies that they play an important role in controlling cell swelling [42,43]. In addition, if we consider the location of astrocytes, it has been shown in the studies that the astrocytes in GM AQP4 are mainly localized in the perivascular end legs, while the astrocytes in the BM are located in a common position in the entire plasma membrane. However, this localization may not be static, and studies show that the polarized positioning of the perivascular end legs over CNS damage continues through the plasmalemma, possibly contributing to protecting the brain from edema and swelling [44]. The AQP1 astrocyte variety represents WM astrocytes in the spinal cord of rats, and the regulatory task is milked during

spinal cord injury [45]. In addition, many studies have shown that AQP1 is involved in the processes and end legs of fibrous astrocytes in BM in primates and humans [46].

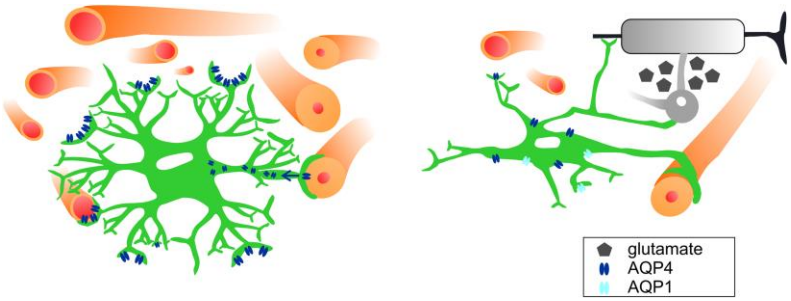


Figure 15. Ischemic damage in gray and white matter demonstrates the heterogeneity of astrocytic sensitivity. Left-sided astrocytes in GM indicate that AQP4 is mainly in the extremity limbs, and rearranges in the ischemia state. Astrocytes on the right side of the BM show us that they are AQP1 and AQP4, although their numbers are small and there are few localizations.

The adjustment and regulation of the nervous system must have a substantially large mechanism that provides extensive cellular diversity. When we look at the work done so surprising it has been suggested that astrocytes change even in a particular CNS region. To give an example of the most important heterogeneity

between regions, Bergmann glia (BG) and velate astrocytes (VAs), the two main astrocytes of the cerebellum, are significantly different. BG and VAs consist of the same progenitor pool [47]. When we look at different brain regions, it is obvious that astrocyte heterogeneity is much more complex [48,49]. The unicellular RNA seq of the striatum has been demonstrated in many studies, unlike other cells of the striatum, that astrocytes do not separate into different populations and therefore subunits that have not yet emerged are not formed [50]. It has been suggested in many studies that astrocytes are found in the cerebral cortex, and they reveal different expression patterns with layer-specific molecular heterogeneity capability [51].

Conditional Signaling and Expansion of Astrocyte Diversity

In line with the results of the studies, one of the questions that comes to mind is the question of how the differences occur in the region of astrocytes. Astrocytes have been shown in studies that various features are used in some parts of the brain. This excellent property of astrocytes allows astrocytes to match the circuits in their relationship with neighboring neurons, and to change the various functional and structural properties of

astrocytes in order to adapt to the different environmental conditions that occur. As a result of the researches, it has been revealed that the components of multiple signal pathways in the developing models of the CNS are rich in mature astrocytes [52]. In addition, when we look at a more important issue, when we look at the studies, it has been suggested that it is necessary to send permanent signals in the adult brain through certain signal pathways in order to preserve the properties of astrocytes. [53].

Sonic Hedgehog (Shh) in Astrocyte Regulation

When we look at the diversity in the cerebellum, cortex and hippocampus, these studies have revealed that the changes in the molecular structures of adult astrocytes depend on the neuron-derived Shh factor. Studies show that the most important role of Shh in ventralizing the developing CNS is due to morphogen [18,52,54]. In the cerebellum, it has been attempted to preserve the gene expression structure of persistent Shh signals from Bergmann glia (BG) purkinje cells (PC). In addition, activation of VAs in the Shh pathway has been suggested in studies that provide a transcriptional profile similar to BG. Therefore, it has been demonstrated that the main determinant of astrocytic gene expression in the cerebellum is provided by a certain neuron

population that is not endogenous [18]. The ability of the differential Shh signal to trigger such profound changes in mature astrocytes suggests that astrocytes are much more changeable than previously thought.

Notch Signal's Inhibition of Neurogenic Program

Studies have shown that Notch mediates the cell-cell contact pathway, which is necessary to regulate events throughout development. In the developing cerebellum, many studies have been carried out to ensure that Notch signal is properly located around PCs [55]. Astrocytes in the adult brain are highly enriched by Notch signal components [52]. As a result of the injury in the cortex, astrocytic blocks the Notch signal and causes astrocytes to become neurogenic. On the contrary, it has been shown in many studies that activation of Notch signal in astrocytes prevents neurogenesis when injury occurs [56]. Therefore, it has been suggested in many studies that the Notch pathway maintains permanent activation under certain conditions in order to remain immobile in mature astrocytes [53].

Fibroblast Growth Factor (FGF) Regulates Reagent-Like Phenotype Signal

Several studies have revealed many tasks, including the morphological evaluation of drosophila astrocytes and the differentiation of astrocytes in rodents, the signaling pathway called fibroblast growth factor (FGF) [57]. It has been demonstrated by studies that adult astrocytes maintain the expression of FGFR1, FGFR2 and FGFR3 [58,59]. When we examine adult astrocytes, many studies have shown that the restriction of FGF signals causes astrocytes to upregulate GFAP and astrocyte reactivity to display a hypertrophic morphology (Figure 16). Studies have suggested that the use of the FGF signal as a result of this injury prevents changes [60,61].

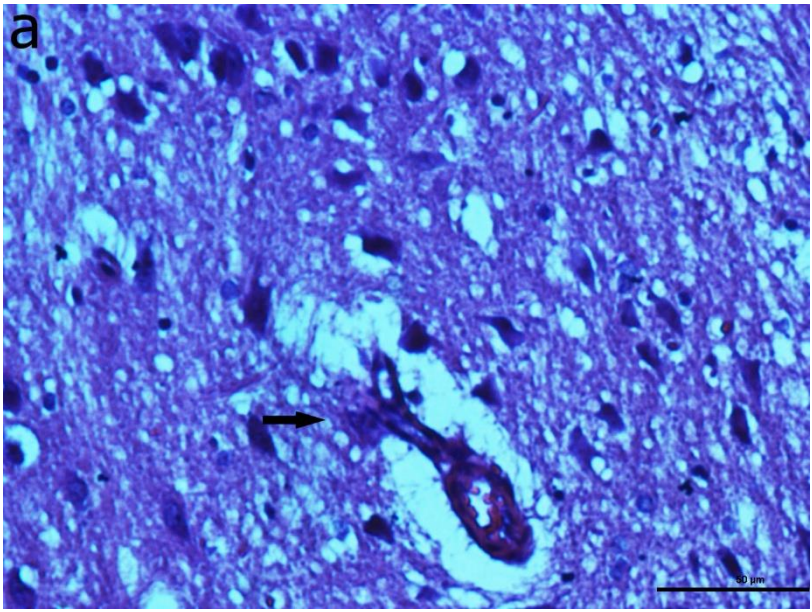


Figure 16. Astrocyte micrograph around the vessel in HE staining.

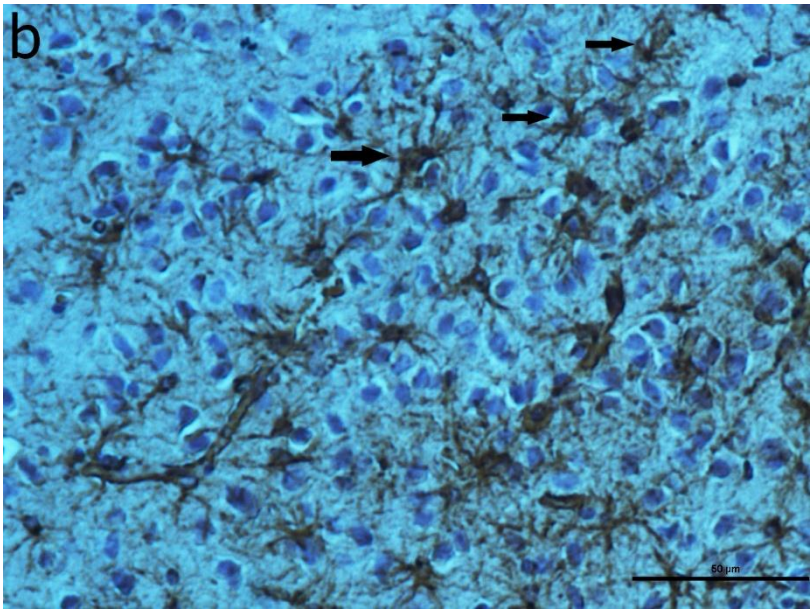


Figure 17. GFAP positive fibrous astrocyte micrograph.

CONCLUSION

Astrocytes are defined as a heterogeneous group of cells with many features found in certain and different parts of the brain. There are many differences in the morphology, gene expression and functional properties of astrocytes in GM and BM. Although these differences have many different functions in many areas of the brain, studies have shown that they result in different needs that occur in astrocytes by reflecting their adaptation. It should definitely not be forgotten that astrocytes in GM have the ability to form synapses directly at the main site of action. Therefore, studies show that the myelinated axons of oligodendrocytes in BM form the myelin sheath. In addition, when we look at another feature of oligodendrocytes, it has been stated in many studies that they have a very complex structure and have a heterogeneous feature. Until this time, it will be essential to reveal the heterogeneity of this triple relationship between neurons, oligodendrocytes and astrocytes, such as neuron-astrocyte or neuron / axon-oligodendrocyte, although many studies have focused on this issue.

Although there are many features as a result of these definitions, many studies are needed to reveal the steps to be followed and

new mechanisms from the presence of astrocytes to a healthy individual to the formation of the disease. However, in order to understand how astrocyte heterogeneity is produced, it would be more accurate to understand the basic properties of the CNS. In addition, many studies reveal that the injury or the occurrence of many diseases will allow us to possibly improve brain and spinal cord function.

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