Quantitative, structural and molecular changes in neuroglia of aging mammals: A review

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ABSTRACT

The neuroglia of the central and peripheral nervous systems undergo numerous changes during normal aging. Astrocytes become hypertrophic and accumulate intermediate filaments. Oligodendrocytes and Schwann cells undergo alterations that are often accompanied by degenerative changes to the myelin sheath. In microglia, proliferation in response to injury, motility of cell processes, ability to migrate to sites of neural injury, and phagocytic and autophagic capabilities are reduced. In sensory ganglia, the number and extent of gaps between perineuronal satellite cells – that leave the surfaces of sensory ganglion neurons directly exposed to basal lamina – increase significantly. The molecular profiles of neuroglia also change in old age, which, in view of the interactions between neurons and neuroglia, have negative consequences for important physiological processes in the nervous system. Since neuroglia actively participate in numerous nervous system processes, it is likely that not only neurons but also neuroglia will prove to be useful targets for interventions to prevent, reverse or slow the behavioral changes and cognitive decline that often accompany senescence.

Key words: Aging; astrocytes; microglia; neuroglia; oligodendrocytes; satellite cells; Schwann cells.

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Introduction

The human population has aged markedly over recent decades, and this has been accompanied by increased interest in understanding the aging process. Many studies have focused on nervous system aging and the aging of neurons in particular. By contrast, the aging of neuroglia cells has received somewhat less attention, probably in part because these cells were long considered to play a passive role in nervous system function, serving only to fill the gaps between neurons and hold them in place. However, more recent research has shown that neuroglia cells perform an extensive set of functions; for example, in the central nervous system they regulate homeostasis in the extracellular environment, provide metabolic support to neurons, modulate neuronal activity, support the long-term integrity of myelinated axons, are involved in the formation, function and plasticity of synapses, and in the peripheral nervous system they carry out neuroprotective functions and influence neuronal shape (*e.g.,* see the following reviews: [1-8]). The aim of the present review is to survey the quantitative, structural and molecular changes that occur to the neuroglia of humans and other mammals during normal aging.

Astrocytes

With age, astrocytes undergo changes in morphology, structure, number, molecular profile and function. In aged humans, astrocytes have enlarged bodies, and more numerous, shorter and thicker processes, than in young adults. Astrocyte hypertrophy is more prominent in the white matter than gray matter, and its extent varies across nervous system regions.[9] Hypertrophic astrocytes have been reported at the following sites: rat hippocampus;[10-12] areas of the cerebral cortex,[13,14] subcortical white matter,[15] and optic nerve[16] of monkey, and human cerebellum.[17] The astrocytic processes that form the glia limiting membrane (glia limitans) are much more numerous in old than young monkeys, so the glia limitans is much thicker in older animals.[13,18]

One of the most prominent changes observed in astrocytes during aging is increase in number of intermediate filaments, which has been observed, for example, in rat hippocampus;[10-12] and in cerebral cortex,[13,18] subcortical white matter,[15] optic nerve,[16] and anterior commissure[19] of monkey. Increased number of intermediate filaments is paralleled by enhanced expression of glial fibrillary acidic protein, and its mRNA (see the references in Table 1).

With advancing age, astrocytes also accumulate dense inclusions within their cytoplasm, presumably through phagocytosis.[13,20] Sometimes these inclusions are derived from the degeneration of axon terminals and dendritic processes that occurs during aging. In other cases components of these inclusions are labeled with antibodies to myelin basic protein; it has therefore been suggested that, in old age, astrocytes participate in the phagocytosis of degenerating myelin.[21] Astrocytes also accumulate lipofuscin with age (*e.g.*, see [18,20,22]). Age-related changes to the nuclear morphology of astrocytes have been observed in mouse neostriatum,[22] rat neurohypophysis (pituicytes),[23] and rat supraoptic nucleus.[24]

Round bodies of varying size (5-20 μm or more in diameter), called corpora amylacea, may sometimes be present in astrocyte cytoplasm and as extracellular deposits in normal aged humans. These bodies, which are basophilic and periodic-acid-Schiff-positive, have no limiting membrane, and consist of randomly arranged filaments, among which a dense, flocculent material is interspersed; they are made up of a glucose polymer and small amounts of proteins. The origin of corpora amylacea is unclear, and it is unknown whether they are harmful to astrocytes or neurons.[25-27]

With regard to the question as to whether astrocyte number changes with aging, no significant changes were found in rat and mouse hippocampus,[12,28-30] rat supraoptic nucleus,[24] rat auditory cortex,[20] human neocortex,[31,32] or visual cortex,[13,14,33] prefrontal cortex,[18] optic nerve,[16] anterior commissure,[19] and fornix [34] of monkey. However, age-related increases in astrocyte number have been reported in human cerebral cortex,[35] the molecular layer of rat dentate gyrus,[36] rat parietal cortex,[37] female mouse hippocampal dentate gyrus,[38] and mouse basal ganglia.[39] Conversely an age-related decrease in astrocyte number has been reported in the fimbria and ventral commissure of mouse.[39] These contrasting findings might suggest that changes, if their occur, depend on species and brain region. However, some of these studies did not make allowance for the greater shrinkage of young nervous tissue, compared to old tissue, that occurs during preparation for examination,[40] so that sections from young animals show greater cell density than those from old animals. It is also noteworthy that the sophistication (and likely accuracy) of the methods used to count astrocytes varied considerably between studies. To complicate matters further, an in-depth study of circumscribed regions of mouse hippocampus found that astrocyte number increased with age in the stratum lacunosum-moleculare of the dorsal part of Ammon's horn but decreased with age in the stratum oriens of Ammon's horn. So, the total number of astrocytes in the whole area of the hippocampus did not change with age.[41] It is possible that such 'give-and-take' changes also occur in other regions of the nervous system. Astrocytes have also been reported to occur grouped in clusters in the hippocampus of old rats.[11]

In the aging central nervous system, astrocytes and microglia are involved in the formation of amyloid beta (Aß) plaques, formerly known as senile or neuritic plaques (for a review, see [42]). These plaques consist of extracellular aggregates of fibrillar or non-fibrillar Aß protein surrounded by degenerating axons and dendrites, astrocytes and microglia. They were found in the cortex and basal ganglia of several healthy aged mammals, including humans, dogs, cats, rats, and monkeys; they are particularly numerous in the brains of humans with neurodegenerative diseases.

A number of molecules upregulated or downregulated in the astrocytes of healthy aged animals are listed in Tables 1 and 2.

An important function of astrocytes is to clear glutamate from the extracellular space at synapses, by means of the glutamate transporters and ionotropic glutamate receptors, present on astrocyte cell surfaces. The functional expression of ionotropic glutamate receptors varies with age. In the mouse, receptor density increases several folds between 1 month and 3-6 months of age to then decline rapidly, so that in old mice (21 months) receptor density is similar to that in 1-month-old animals.[43]

Gap junction connections between astrocytes are important for signaling. The astrocytes of old mice continue to express high levels of gap junction proteins, although a tendency to reduced interastroglial coupling has been reported.[44,45] Also in old mice, astrocytes conserve their ability to express spontaneous and neurotransmitter-dependent intracellular Ca^{2+} signals. Gliotransmission resting levels, and astrocyte-neuron interactions are also largely conserved in old mice.[46] Antioxidant capacity and glutathione metabolism are preserved from mature adulthood into senescence in mouse astrocytes.[47]

Astrocytes are important synthesizers of cholesterol within the central nervous system. However, cholesterol synthesis declines with age in astrocytes and this may adversely affect neurons, which rely on cholesterol from astrocytes (*e.g.*, see [48]). This decline also has negative effects on myelin production by oligodendrocytes resulting in changes in peri-axonal myelin sheaths (see para-

grapgh *Oligodendrocytes and myelin*). These changes are in turn responsible for reduced conduction velocities along axons, which may contribute to cognitive decline in aging. As noted previously, the expression of glial fibrillary acidic protein is increased in aged astrocytes (see also references in Table 1). Since increased expression of this protein is a characteristic of reactive astrocytes, aging astrocytes partially resemble reactive astrocytes – as also suggested by studies which found that aging astrocytes have a gene expression profile partially resembling that of reactive astrocytes.[49,50]

Astrocytes supply neurons with lactate as an additional energy substrate.[51] The astrocytic genes involved in lactate regulation are unaltered with age[49] suggesting that astrocytes are still capable to perform this function during aging. At the end of the 19th century, astrocytes were classified by morphology and location into protoplasmic and fibrous types, found mainly in gray and white matter, respectively.[52] Recent studies show that astrocytes also vary in terms of molecular profile, physiology and metabolism, and are hence far more heterogeneous than once suspected (*e.g.*, see [53-56]). It is possible that the various subtypes of astrocytes change in different ways with aging, and this might contribute to explaining the markedly heterogeneous picture that emerges from studies on astrocyte aging. Future studies which take account of the different subtypes of astrocytes, may be expected to produce a more coherent picture of senescent changes in these cells.

Oligodendrocytes and myelin

It has been estimated that the plasma membrane of a myelinating oligodendrocyte may reach a surface area of 20×10^5 μm^2. The production and support of so much membrane require enormous metabolic load and imply the production of abundant toxic byproducts. Furthermore, since iron is a cofactor for many of the enzymes involved in myelin synthesis, oligodendrocytes have large iron stores which are a potential source of free radicals. Oligodendrocytes are, in fact, much more vulnerable to oxidative damage than other nervous system cells (for a review, see[57]) and are strongly affected by aging.

In old age, some oligodendrocytes develop thick processes with bulbous enlargements. Dense inclusions are often present in the cell body and in the bulbous enlargements.[16,58] These inclusions have irregular shapes and can be as large as 1 μm in diameter. Some are composed of homogeneously dense material; others contain patches of a lower density component embedded in the dense material. Sometimes the lower density component appears to consist of stacks of thin lamellae. Oligodendrocytes are not generally thought to have phagocytic activity, so those containing such inclusions are likely to be breaking down and resorbing their own myelin sheaths.[59] Some oligodendrocytes degenerate during

Table 1. A list of molecules that are upregulated in the astrocytes of healthy aged animals.

Astrocyte marker	Species	References
Glial fibrillary acidic protein (GFAP)	Mouse and rat	137
	Mouse (female)	138
	Rat	24,87,139,140
	Human	141
GFAP mRNA	Rat and human	142
	Mouse (female)	138
	Rat	143
S100β (Calcium binding protein)	Human	144
Vimentin	Rat	24
	Human	141
Apolipoprotein E, apolipoprotein J (clusterin), Complement 3 receptor (OX42), heme oxygenase-1, Major histocompatibility complex II antigen (OX6), Transforming growth factor-β1	Rat	87
Components C3 and C4B of the complement system	Mouse	49,50
Cytokines		
CXCL10/inducible protein-10 (IP-10)	Mouse	50
CXCL5	Mouse	49
Serpina 3 (serine protease inhibitor)	Mouse	49,50
Cholesterol-transporting proteins	Mouse	49

Table 2. A list of molecules that are downregulated in the astrocytes of healthy aged animals.

Astrocyte marker	Species	References
Aquaporin-4	Mouse	145,146
Ampa receptors	Mouse	43
ATP	Mouse	147
Fibroblast growth factor 2 (FGF2)	Rat	148
Vascular endothelial growth factor (VEGF)	Rat	148
Brain derived neurotrophic factor (BDNF); Glial derived neurotrophic factor (GDNF)	Rat (in culture)	149
Cholesterol synthesis enzymes	Mouse	49

aging, and new oligodendrocytes are produced. If these two processes are balanced, cell number remains constant, while imbalance may lead to an increase or decrease in oligodendrocyte number. Available findings are that oligodendrocyte number does not change significantly with age in the auditory[20] and prefrontal[18] cortices of rat, and anterior commissure[19] of monkey; but it increases in the optic nerve,[16] visual cortex,[14,33] and fornix[34] of monkey, and visual and auditory cortices of the mouse;[60] and decreases in human neocortex[31,32] and rat subcortical white matter.[61] These findings suggest that the age-related changes to the oligodendrocyte number vary with species and brain region. However, as was the case for astrocytes (see paragraph *Astrocytes*), the large methodological variation among studies precludes definitive conclusions.

As regards the origin of new oligodendrocytes, the prevailing view is that mature oligodendrocytes do not divide,[62] and that new oligodendrocytes originate from progenitor cells present in white and gray matter. Whereas in young age oligodendrocytes usually occur singly, in old age they often occur in pairs, rows or clusters,[33,59] interpreted as the result of recent cell division.

Alterations to oligodendrocytes are often accompanied by degenerative changes to associated myelin sheaths.[63] A common age-related degenerative change to myelin is local splitting of the major dense line with enclosure of a pocket of cytoplasm within the split.[64] This pocket of cytoplasm, which probably belongs to the oligodendrocyte that formed the sheath, appears to be degenerating, as it is dense and often contains amorphous dense bodies.[64] Bleb formation is another type of age-related degenerative change to myelin sheaths. Blebs, which have round profiles and may be up to 10 μm in diameter,[65] are produced by splitting of the intraperiod line of compact myelin. Changes to myelin contribute to a decrease in white matter volume that occurs in advanced age.[66,67] Other age-related changes to myelin are occurrence of sheaths of redundant myelin,[68] appearance of circumferential splits in thick sheaths,[64] and increased percentage of thin sheaths (*e.g.*, see[21]). These changes indicate that myelin continues to form in old age. In fact, degeneration of myelin internodes is followed by remyelination.[21] However, remyelination becomes less efficient with advancing age[69,70] because the regenerative capacity of oligodendrocyte progenitor cells decreases,[71] the ability of oligodendrocytes to produce myelin declines, and also because they may not receive sufficient cholesterol from astrocytes. Degenerated myelin internodes are replaced by internodes which are shorter than pre-existing ones. Since myelin insulates axons and ensures rapid propagation of axon potentials, formation of shorter internodes, in combination with alterations to the myelin sheath, lead to reduced conduction velocities along the involved axons (*e.g.*, see[72]). Velocity reductions have been recorded in the central nervous system of old humans and other animals.[73-76] It is likely that reduced conduction velocity contributes to the cognitive decline often observed in old age[70,77]

Much like astrocytes, oligodendrocytes are a heterogeneous cell population[78] but whether the various subtypes of oligodendrocytes change in different ways with aging is not known.

Microglia

Notwithstanding reports to the contrary (*e.g.*, see[79]), the prevailing opinion is that in healthy animals microglia are long-lived and have a low turnover rate. In mice, approximately half the microglia survive the entire animal lifespan.[80] In humans, microglia renew slowly and some last for over two decades.[81] The long lifespan of microglia increases the probability that they will be affected by aging. Aging is accompanied by morphological,

molecular, and functional changes to microglia. Thus, microglia in normal aged animals have enlarged and rounded cell bodies, and less branched processes, than those in young adults (*e.g.*, see[60,82]). Further, microglia with abnormally twisted, tortuous, and beading cytoplasmic processes have been found intermingled with microglia of normal aspect in the aged human brain.[83] Finally, heterogeneous inclusions, including lipofuscin granules, accumulate with age in microglia;[13,16,20,84,85] and in extremely advanced age, nearly all microglia contain perikaryal inclusions.[60]

It has been reported that the mean number of microglia does not change significantly with age in rat cortical area 2 of Krieg,[86] rat dentate gyrus,[87,88] rat olfactory bulb and cerebellum,[89] and monkey visual cortex,[14] and fornix.[34] By contrast, microglia number is reported to increase significantly with age in rat auditory cortex,[20] monkey optic nerve,[16] mouse visual and auditory cortices,[60] mouse fimbria and ventral commissure,[39] female mouse hippocampus,[38] and human female neocortex.[32] These findings suggest that age-related changes to microglia number vary markedly with brain region and species. However, the caveats regarding data on age-related changes to astrocyte number (see paragraph *Astrocytes*) also apply to data on microglia. To complicate matters, age-related changes to microglia may also depend on gender. Thus, in two studies that used the same tissue processing and stereological methods, it was found that microglia number did not change with age in the hippocampus of male mice[30] but increased significantly in the hippocampus of females.[38]

Microglia cells are closer to each other and less evenly distributed in aged than in young animals (*e.g.*.[20,38,60,90]). Once again, however, tissue shrinkage during sample preparation differs between old and young adult animals and could have contributed to reported differences in microglia distribution.

Proliferation in response to injury,[91] motility of cell processes,[82] ability to migrate to sites of neural injury,[82] and phagocytic and autophagic capabilities[92,93] are all reduced in the microglia of aged animals compared with young adults. Reduced dynamic behavior with age has been observed in microglia cultures.[94] As noted in the paragraph *Astrocytes*, microglia are involved with astrocytes in the formation of Aß plaques during aging. A number of molecules that are upregulated or downregulated in the microglia of healthy aged animals are listed in Tables 3 and 4. From these tables it is evident that some findings are conflicting. Thus, in aged mice the expression of Toll-like receptors TLR2 and TLR4 is upregulated according to Letiembre *et al.*[95] but downregulated according to Caldeira *et al.*[94] Similarly, the expression of anti-inflammatory cytokines in mice is upregulated according to Sierra *et al.*[84] and Henry *et al.*[96] and downregulated according to Ye and Johnson.[97]

The decreased length and branching of processes, and the increased expression of inflammatory markers and cytokines, observed in aged microglia, are reminiscent of changes observed in activated microglia. Thus, it was once thought that microglia activation state increased with age (for reviews, see[93,98,99]). However, other changes that occur in microglia during normal aging (*e.g.*, changed cytoplasmic structure, reduced ability to phagocytose and to migrate, decreased process motility, and changes in receptor expression) are not characteristic of activation and have been interpreted as an intrinsic expression of microglia aging[83,91,100] that is accompanied by a decline in cell function.

Age-related decline in microglia function adversely affects neurons. In younger mice, microglia clear pathogens, aberrant proteins, and debris from the central nervous system by phagocytosis. Age-related decline in phagocytosis results in a more toxic environment which eventually impairs neuronal activity. Microglia processes are dynamic structures whose direct contact with neurons effects homeostatic regulation of neuronal activity. Highly

active neurons release ATP, which induces microglia to migrate towards – and polarize their processes towards – these neurons. Microglia contact downregulates neuronal activity. The age-related reduction in microglia migration, process branching, and process motility, results in impaired homeostatic regulation of neuronal activity. Aging also results in imbalanced expression of receptors on microglia surfaces, which in turn may alter responses to environmental cues. Microglia responses to central nervous system injury, infection, disease or other perturbation can therefore become dysregulated with aging, and result in more severe neurodegeneration and functional impairment than would occur (due to perturbation) in younger animals.[99]

Ependymal cells, tanycytes, and choroid epithelium cells

The age-related changes of these cells have been far less investigated compared to other neuroglia cells.

In aged mammals, ependymal cells are flattened and contain high numbers of intermediate filaments, dense bodies, large lipid droplets, and sometimes sparse Biondi bodies. Cilia are reduced in density and concentrated on a limited area of the apical surface (for a review, see[101]). With increasing age, tanycytes accumulate lipid droplets and bodies consisting of dense material and myelin figures (e.g., see[102]). Choroid epithelium cells become flattened and accumulate iron-positive inclusions, amyloid, and Biondi bodies with age.[103,104] Biondi bodies are cytoplasmic inclusions consisting of filaments, 8-10 nm in thickness, among which small lipid droplets and dense granules are interspersed.[105-107] Biondi bodies are characteristic of aged humans; however, inclusions resembling Biondi bodies have been identified in the choroid epithelium of an aged chimpanzee.[108] The origin and significance of these bodies are unclear. The age-related structural changes of choroid epithelium cells go together with a general reduction in the rate of cerebrospinal fluid turnover.[109,110]

Table 3. A list of molecules that are upregulated in the microglia of healthy aged animals.

Microglial marker	Species	References
Major histocompatibility complex class ll (MHC ll) antigens	Human Rat Monkey	150,151 88,89 152
Macrophage antigen (ED$_1$)	Rat	88,153
Leukocyte common antigen (LCA)	Rat	88
Antibody OX6	Rat	89
Surface markers CD4, CD40 and CD86	Rat	87,88,154,155
Surface markers CD11b (=complement receptor 3, CR3 and MAC1), CD11c and CD68 (=Macrosialin)	Mouse	156-158
Toll-like receptors (TLRs) and CD14	Mouse Rat	95 159
Galectin-3 (=MAC-2)	Mouse	160
Senescence-associated β-galactosidase (SA-β-GAL)	Mouse (in culture)	94
Proinflammatory cytokines (IL1α, IL1β, IL6, IL18, TNF α)	Human Rat Rat (in culture) Mouse Mouse (in culture)	161 155,162,163 164 84,96 97,165,166
Interferon-ϒ (IFNϒ)	Rat	154,155
Anti-inflammatory cytokines (IL10, TGFβ1)	Mouse	84,96
Calpain-1	Monkey	167,168
Intercellular adhesion molecules (ICAM)	Rat	155
Clusterin	Rat	153

Table 4. A list of molecules that are downregulated in the microglia of healthy aged animals.

Microglial marker	Species	References
Fractalkine receptor (CX3CR1)	Mouse (after lipopolysaccharide [LPS] challenge)	169
Anti-inflammatory cytokines (IL4, IL10)	Mouse (in culture) Rat	97 (however, see 84,96) 162,170
Glutathione	Mouse	165
Toll-like receptors	Mouse (in culture)	94 (however, see 58,95)
Nuclear factor NF-kB	Mouse (in culture)	94
microRNA (miR-124 and miR-155)	Mouse (in culture)	94

Schwann cells and their myelin sheaths

The following age-related changes have been observed in Schwann cells: adaxonal cell processes sequestering portions of axoplasm,[111] presence of residual bodies and myelin debris,[112] and significant decrease in the mean percentage of cytoplasmic volume occupied by mitochondria.[113] The latter change could lead to reduced energy availability in Schwann cells and to myelin alterations. Finally, in fowl Schwann cells, intranuclear inclusions are rare in young animals but common in old animals.[114]

Myelin alterations reported in the peripheral nervous system of aged individuals are similar to those observed in the central nervous system. They include segmental demyelination followed by remyelination (*e.g.*[115-120]), loss of myelin tightness (decompaction) due to the development of splits between lamellae, and presence of wide incisures and myelin loops.[116,118] As in the central nervous system (see paragraph *Astrocytes*), these alterations may lead to reduced nerve conduction velocities. Such reductions have been observed in the peripheral nervous system of aged humans (*e.g.*[74,121-125]).

Satellite cells in sensory ganglia

In the sensory ganglia of adult vertebrates, each nerve cell body is usually enveloped by its own satellite cell sheath thus constituting a unit.[126] This organization does not change with age. However, both the mean volume of the satellite cell sheath, and the mean ratio of satellite cell sheath volume to related nerve cell body volume, are significantly lower in old animals than in young adults.[127,128] The reduction in satellite cell sheath volume is in part attributable to the significant decrease in satellite cell number that occurs in old age.[129]

With advancing age satellite cells undergo a number of changes (for a summary, see[130]). Thus, in rabbit spinal ganglia, both the total volume of the Golgi apparatus and the mean percentage of cytoplasmic volume occupied by this organelle decrease significantly – while the Golgi apparatus itself undergoes neither structural changes nor peripheral displacement. Furthermore, although mitochondrial structure does not change, mitochondrial size increases progressively and significantly with advancing age; while both mitochondrial mass and mean percentage of cytoplasmic volume occupied by mitochondria decrease progressively and significantly with age. Taken together, these findings suggest that the ability of satellite cells to produce energy metabolites decreases with age. The reduced ability of sensory neurons to respond to high energy demands in old age (*e.g.*, see[131]) may be in part due to the diminished contribution of perineuronal satellite cells. With age, satellite cells accumulate lipofuscin.[132] However, lipofuscin accumulation seems to have little or no effect on metabolism or functional activity of these cells.

Since satellite cells provide trophic and protective support to neurons, it is likely that the significant reduction in their number, mitochondrial mass, and ratio of satellite cell volume to nerve cell body volume, add up to reduced neuronal support, with negative consequences for neuronal activity. Furthermore, the number and extent of gaps between satellite cells, that leave the neuronal surface directly exposed to the basal lamina, significantly increase in old animals.[128] For example, in rabbit spinal ganglia, for comparable neuronal perimeters, these gaps occur more than twice as often in old compared to young animals. In addition, while in young adults these gaps are no longer than 0.75 µm, in old rabbits they may be up to 7.7 µm. Since the nerve cells in sensory ganglia lack the protection of a vascular barrier such as is present in the central

nervous system, only the satellite cell sheath controls the traffic of substances from the blood to the nerve cell body. Thus, the ganglionic nerve cells of old animals are more exposed, than those in young adults, to damage by harmful substances from the circulation.

In rabbit spinal ganglia, the gap junctions between perineuronal satellite cells – which are mainly composed of connexin43 – increase in number with age, whereas the mean size of individual gap junctions remains constant.[133] In spinal ganglia of the senescent mouse, both gap junction number and dye coupling between satellite cells increase,[134] whereas connexin43 expression decreases.[135] These contrasting changes in the senescent mouse could be related to the presence of connexin types other than connexin43, in the gap junctions between the satellite cells of these animals.

Closing remarks

Over the last few decades knowledge of the structural and dynamic behavior changes that occur in neuroglia during normal aging has increased markedly. Knowledge of changes in molecular profiles has also increased, although many questions remain. More than in other organs, the various cells of the nervous system interact intimately with each other, so that age-related functional impairment in one cell type almost always affects the functioning of other cell types. We have seen, for example, that impaired cholesterol synthesis in aging astrocytes has negative effects on neuronal activity and on myelin production by oligodendrocytes, and also that the age-related functional decline in microglia cells damage neuronal activity. We can anticipate that continued study of interactions between the various cell types within the nervous system will be important for improving understanding of nervous system aging; particularly when combined with new experimental approaches such as advanced cell culturing, use of viral vectors, *in situ* glial imaging, and high content molecular analysis (for a review, see[136]). Since neuroglia participate actively in numerous nervous system processes, it is likely that not only neurons but also neuroglia will prove to be useful targets for interventions to prevent, reverse or slow the behavioral changes and cognitive decline that often accompany senescence. But to develop glia-targeting therapies it will be necessary to further improve understanding of the changes neuroglia undergo during normal aging.

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