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Localization of Calretinin, Parvalbumin, and S100 Protein in *Nothobranchius guentheri* Retina: A Suitable Model for the Retina Aging

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Abstract: Calcium-binding proteins (CaBPs) are members of a heterogeneous family of proteins able to buffer intracellular Ca^{2+} ion concentration. CaBPs are expressed in the central and peripheral nervous system, including a subpopulation of retinal neurons. Since neurons expressing different CaBPs show different susceptibility to degeneration, it could be hypothesized that they are not just markers of different neuronal subpopulations, but that they might be crucial in survival. CaBPs' ability to buffer Ca^{2+} cytoplasmatic concentration makes them able to defend against a toxic increase in intracellular calcium that can lead to neurodegenerative processes, including those related to aging. An emergent model for aging studies is the annual killifish belonging to the Nothobranchius genus, thanks to its short lifespan. Members of this genus, such as *Nothobranchius guentheri*, show a retinal stratigraphy similar to that of other actinopterygian fishes and humans. However, according to our knowledge, CaBPs' occurrence and distribution in the retina of *N. guentheri* have never been investigated before. Therefore, the present study aimed to localize Calretinin N-18, Parvalbumin, and S100 protein (S100p) in the *N. guentheri* retina with immunohistochemistry methods. The results of the present investigation demonstrate for the first time the occurrence of Calretinin N-18, Parvalbumin, and S100p in *N. guentheri* retina and, consequently, the potential key role of these CaBPs in the biology of the retinal cells. Hence, the suitability of *N. guentheri* as a model to study the changes in CaBPs' expression patterns during neurodegenerative processes affecting the retina related both to disease and aging can be assumed.

Keywords: CaBPs; retina; aging; *N. guentheri*

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1. Introduction

Ca^{2+} ions can regulate a wide range of intracellular mechanisms. For instance, at the synaptic level, the transmission of a chemical stimulus in neurons depends on calcium concentration. When a transmembrane flow of Ca^{2+} ions is generated, a local increase in the intracellular concentration of the ion at the presynaptic termination regulates the fusion of vesicles containing neurotransmitters with the plasma membrane [1–4] and the release of their contents into the synaptic fissure [3,5,6]. Intracellular Ca^{2+} mobilization is involved in several downstream mechanisms induced by the activation of the GPCRs that evoke slow synaptic transmission [7,8]. The calcium level within cells is regulated by many proteins such as channels, transporters, pumps, and CaBPs. Calcium efficacy as a signaling agent depends on the level of sequestration of cytoplasmic calcium. In

particular, some CaBPs are proteins that can act like buffers [9] establishing gradients of free Ca^{2+} near a Ca^{2+} source, like a membrane ion channel [10,11]. CaBPs' ability to bind Ca^{2+} is relevant in the context of aging and neurodegeneration, because according to the so-called "Ca^{2+} aging hypothesis", intracellular Ca^{2+}-concentration is involved in age-related neurodegeneration [12,13]. Distinct studies showed the link between senescence decline and progressive increases in Ca^{2+} influx in cerebral cells [14–16]. In this context, the action of the calcium protein family ligands (CaBPs) can act as neuroprotective factors containing age-related changes. Calcium binding proteins are involved in calcium signaling regulation and neuronal excitability modulation for the long-term [17]. Calretinin, parvalbumin, and the S-100 protein are often considered histological markers due to their distribution in neuronal subclasses [14,18]. CaBPs are extensively disseminated in the peripheral and central nervous system, including the retina [14–16]. Since the retina is a crucial component of the central nervous system (CNS), disease processes in the retina could indicate a similar process elsewhere in the CNS and vice versa. In addition, scientific evidence [19–22] has shown that retinopathies appear concurrently with neurodegenerative diseases.

The brain and retina share this common aging mechanism. Even if retina aging and its related neurodegenerative process are complex due to the combination of multiple genes, cell processes and death, biochemical alterations, and environmental risk factors [14–18] to study the role of Calcium and CaBPs are intriguing. Indeed, it has been demonstrated that during retinal aging, a higher level of intracellular calcium promotes the weakening of synapses and the degradation of visual performance, as demonstrated by Berkowitz et al. [23]. Likewise, age-related changes in calcium-binding proteins and its different trends in the SNC and in the retina have been reported in several species [18,24–39]. Different CaBPs, like calretinin and parvalbumin, can be used as cellular markers in retinal aging studies to monitor these changes over a lifetime [40]. It has been demonstrated that vertebrates from fish to mammals express CaBPs both in the central and peripheral nervous systems [4–7,41–44], and it is intriguing in the translational medicine field. Aging studies have been impaired because of the lack of a suitable model. However, *Nothobranchius* spp. is being established as a suitable model in this research area. For instance, *Nothobranchius guentheri* (*N. guentheri*) retina shows the typical retinal stratigraphy of vertebrates including humans: ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), inner segment/outer segment of photoreceptor cells (PRL), retinal pigment epithelium cells (RPE) [45]. The Nothobranchiidae family of fish is a large group, typical of North Africa where they mainly inhabit shallow ephemeral pools and seasonal swamps. The *Nothobranchius* spp. hold the record of the fastest maturing vertebrate with the briefest life in captivity and is a novel model organism in aging studies [46]. Further, *N. guentheri* and humans share some aging markers, for instance, the apolipoprotein E [26], the insulin growth factor [16,26,27], and isthmin [28]. It has also been demonstrated that the expression of senescence-associated β-galactosidase and the accumulation of lipofuscin increased with age both in Nothobranchius and humans [29,30]. In the aging retina of both in Nothobranchius and humans, a decreased effectiveness of the antioxidant defense system occurs [30,31], so the activities of catalase, glutathione peroxidase, and superoxide dismutase decreased with age. For all the abovementioned reasons, this work aimed to show the localization of calcium-binding proteins in the retina of the annual killifish (*N. guentheri*) as a possible model for retinal aging studies.

2. Materials and Methods

2.1. Fish and Tissue Treatment

In this investigation, we used paraffin-embedded tissue of 1-year-old *N. guentheri* from earlier studies [32]. One-year-old, male, and female adult *N. guentheri* specimens from ornamental aquariums were employed. They were found dead of unexplained causes. The heads were rapidly removed and stored in 4% paraformaldehyde (Sigma-Aldrich, Inc., St. Louis, MO, USA, #158127) in 0.1 m (pH = 7.4) of phosphate-buffered saline (PBS,

Sigma-Aldrich, Inc., St. Louis, MO, USA, # P4417) for 12–18 h, dehydrated by graded ethanol series, clarified in xylene, and used for paraffin wax (Bio-Optica S.p.a. Milano, Italy, # 08–7910) embedding. The included tissues were then cut into serial sections that were 7 µm thick and collected on gelatin-coated microscope slides [47]. Later, deparaffinized and rehydrated serial slices were washed in distilled water, processed with Masson trichrome with aniline blue (Bio-Optica S.p.a Milano, Italy, cat. #04-010802) [33]. At the end, stained sections were examined under a Leica DMRB light microscope equipped with Leica MC 120 HD camera (Leica Application Suite LAS V4.7).

2.2. Immunohistochemistry

To analyze the localization of CaBPs in *N. guentheri* retina, some serial slides were deparaffinized and rehydrated, finally in phosphate-buffered saline (PBS Sigma-Aldrich, Inc., St. Louis, MO, USA cat. # P4417). The sections were incubated in 0.1% Triton X100 (Sigma-Aldrich, Inc., St. Louis, MO, USA, cat. #X100) PBS solution to permeate the membranes, after incubation in a 0.3% hydrogen peroxide solution (H_2O_2 Sigma-Aldrich, Inc., St. Louis, MO, USA, cat. #1085971000) to prevent the activity of endogenous peroxidase. The 25% fetal bovine serum (Sigma-Aldrich, Inc., St. Louis, MO, USA, cat. #F7524) solution was then added to the rinsed sections. Sections were incubated overnight at 4 °C in a humid chamber with antibodies ant-Calretinin N-18 and anti-Parvalbumin antibodies (see Table 1). Some representative sections were incubated with anti-Opsin and anti-Chat antibodies, recognized as specific markers for rods and amacrine cells, respectively (see Table 1). Some representative serial sections were used to detect anti-S100 protein that recognizes a mixture of both S100A and S100B proteins subunit by the immunohistochemistry peroxidase method. As mentioned above, sections were incubated overnight with anti-S100 protein (see Table 1). After rinsing in PBS, the sections were incubated for 1 h at 4 °C with a fluorescent secondary antibody (see Table 1) at room temperature in a dark humid chamber. Washing and mounting using Fluoromount Aqueous Mounting Medium (Sigma-Aldrich, Inc., St. Louis, MO, USA, cat. #F4680) were the final steps. A Zeiss LSMDUO confocal laser scanning microscope with META module (Carl Zeiss MicroImaging, Carl Zeiss Microscopy GmbH Strasse 22 73447 Oberkochen Deutschland) was used to detect the immunofluorescence, and Zen 2011 (LSM 700 Zeiss software) was employed to process the images [34–36]. Each image was rapidly acquired to minimize photodegradation. The sections treated with the anti-S100 protein after incubation were washed in the same buffer and incubated for 1.5 h at room temperature with secondary antibody-peroxidase conjugate (see Table 1). The immunoreaction was visualized using 3-30-diaminobenzidine as a chromogen (DAB, Sigma-Aldrich, Inc., St. Louis, MO, USA, cat. #D5905) [37]. After rinsing in freshwater, sections were dehydrated, mounted, and examined under Leica DMRB light microscope. Representative sections were incubated with appropriately preabsorbed antisera as mentioned above to provide negative controls. In these circumstances, there was no evidence of positive immunostaining.

Table 1. Antibodies used in this study.

Primary Antibodies	Supplier	Catalog Number	Source	Dilution	Antibody ID
Calretinin-N18	Santa Cruz Biotechnology, Inc., Dallas, TX, USA	sc-11644	goat	1:100	AB_634545
Parvalbumin clone PA235	Sigma-Aldrich, Inc., St. Louis, MO, USA	P-3171	mouse	1:1000	AB_2313693
S100	Dako Agilent, Santa Clara, CA, USA	Z0311	rabbit	1:100	AB_10013383
Anti-Opsina Clone RET-P1	Sigma-Aldrich, Inc., St. Louis, MO, USA	O4886	mouse	1:100	AB_260838
Anti-Chat	Sigma-Aldrich, Inc., St. Louis, MO, USA	AMAB91130	mouse	1:100	AB_2665812

Table 1. *Cont.*

Secondary Antibodies	Supplier	Catalog Number	Source	Dilution	Antibody ID
Antigoat IgG (H + L) Alexa Fluor 594	Molecular Probes, Invitrogen, Waltham, MA, USA	A-11058	donkey	1:300	AB_2534105
Antimouse IgG (H + L) Alexa Fluor 488	Molecular Probes, Invitrogen, Waltham, MA, USA	A-11001	goat	1:300	AB_2534069
Antirabbit IgG peroxidase conjugate	Amersham Bioscences, Amersham, United Kingdom	NA934	donkey	1:100	AB_772206

2.3. Statistical Analysis

ImageJ software (Version 1.53t) was used to evaluate microscope fields collected randomly. One-way ANOVA was used to examine the statistical significance of the quantity of retinal pigment epithelium (RPE), photoreceptor layer (PRL), outer plexiform layer (OPL), amacrine cells (ACs), inner plexiform layer (IPL), bipolar cells (BCs), and ganglion cells (GCs) detected by Calretinin N-18, Parvalbumin and S100 protein. SigmaPlot version 14.0 (Systat Software, San Jose, CA, USA) was used to conduct the statistical analysis. An unpaired Z test was also performed. The information was given as median values with standard deviations ($\Delta\sigma$). Values of p below 0.05 were considered statistically significant in the following order *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

3. Results

In order to analyze the localization of the calcium-binding proteins (CaBPs) Calretinin N-18, Parvalbumin, and S100, an immunohistochemistry study was conducted. The cells immunoreactive to CaBPs were identified by the topographic approach and using the specificity of anti-Calretinin N-18 and anti-Parvalbumin antibodies for retinal neurons. The morphological investigation of *N. guentheri* retina showed a similar organization to other vertebrates. The retina of *N. guentheri* was formed in seven layers: retinal pigment epithelium (RPE), photoreceptor layer (PRL) containing cones and rods, outer nuclear layer (ONL), inner nuclear layer (INL), ganglion cell layer (GCL), the outer plexiform layer (OPL) between ONL and INL, and the inner plexiform layer (IPL) between INL and GCL (Figure 1).

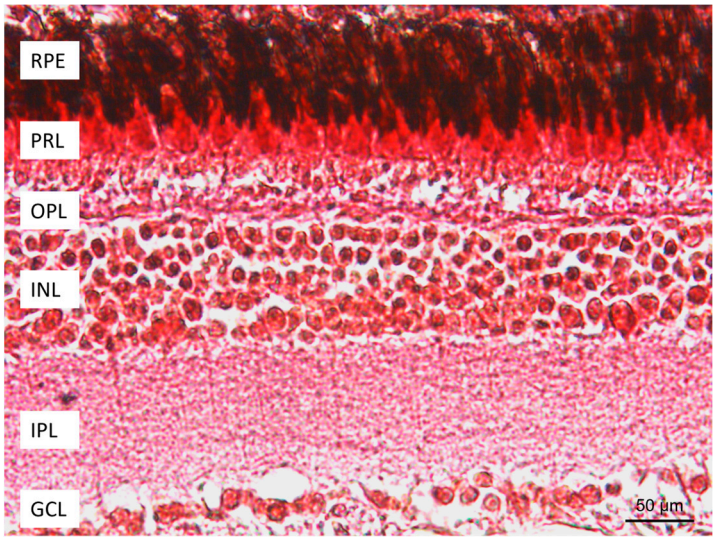

Figure 1. Retina of *N. guentheri*: RPE, retinal pigment epithelium; PRL, photoreceptor layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; Masson trichrome with aniline blue method. Magnification 40×.

In the retina of *N. guentheri*, Calretinin N-18 and Parvalbumin were immunolocalized in the cytoplasmatic prolongation of the retinal pigment epithelium (RPE) and in the photoreceptor layer (PRL). A subpopulation of amacrine cells in the outer plexiform layer (OPL) and ganglion cells showed immunopositivity to Calretinin N-18 and Parvalbumin (Figures 2 and 3). In addition, the optic nerve of *N. guentheri* showed Calretinin-N18 immunostained (Figure 2e) but not immunoreactivity to Parvalbumin (Figure 3e).

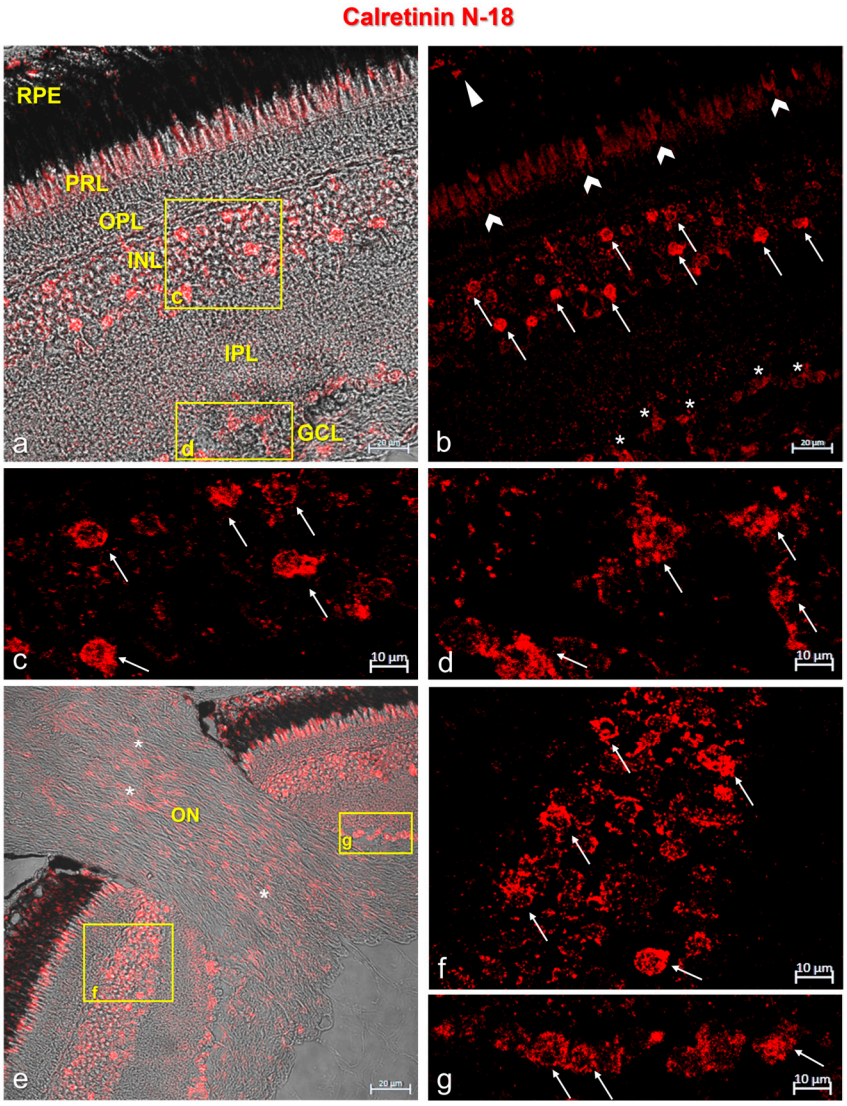

Figure 2. Calretinin N-18 immunostaining in *N. guentheri* retina. (**a**) Transmitted light of Calretinin N-18 immunostaining. This image shows the stratigraphy of the *N. guentheri* retina: RPE, retinal pigment epithelium; PRL, photoreceptor layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. (**b**) Calretinin-N18 immunoreactivity in the cytoplasmic prolongations of the cells of the retinal pigment epithelium (RPE) (arrowhead); in the cones and rods of the photoreceptors layer (PRL) (chevron arrows); in a subpopulation of amacrine cells in the inner nuclear layer (INL) (arrows); in the soma of ganglion cells (GCL) (asterisk). (**c**) High magnification of the inset in (**a**) showing a Calretinin-N18-immunopositive subpopulation of amacrine cells (arrows) in the INL. (**d**) High magnification of the inset in (**a**) showing Calretinin-N18 immunostained soma of the ganglion cells (GCL) (arrows). (**e**) Transmitted light of Calretinin-N18 immunostaining of optic nerve (ON, asterisk) in *N. guentheri* retina. (**f**) High magnification of inset in (**e**) showing a subpopulation of Calretinin -N18-immunoreactive amacrine cells (arrows) in the INL. (**g**) High magnification of inset in (**e**) showing the soma of Calretinin-N18-immunostained ganglion cells (GCL) (arrows). Magnification: 40× (**a**,**b**,**e**), 63× (**c**,**d**,**f**,**g**).

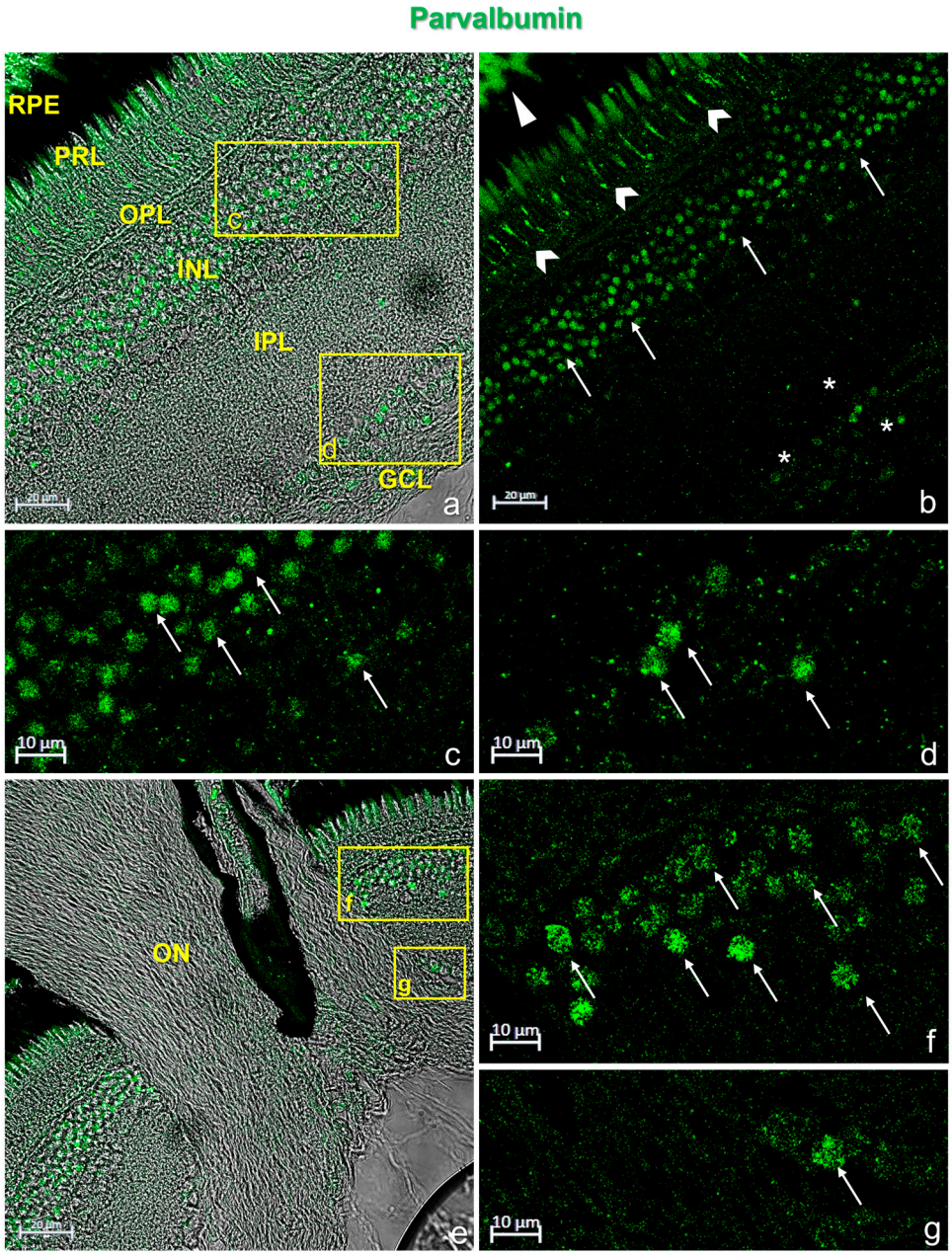

Figure 3. Parvalbumin immunostaining in *N. guentheri* retina. (**a**) Transmitted light of Parvalbumin immunostaining. Stratigraphy of the *N. guentheri* retina: RPE, retinal pigment epithelium; PRL, photoreceptor layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. (**b**) Parvalbumin immunoreactivity in the cytoplasmic prolongations of the cells of the retinal pigment epithelium (RPE) (arrowhead); in the cones and rods of the photoreceptors layer (PRL) (chevron arrows); in a subpopulation of amacrine cells in the inner nuclear layer (INL) (arrows); in the soma of ganglion cells (GCL) (asterisk). (**c**) High magnification of the inset in (**a**) showing a subpopulation of Calretinin-N18-immunoreactive amacrine cells in the INL (arrows). (**d**) High magnification of the inset in (**a**) showing the soma of the Parvalbumin-immunostained ganglion cells (GCL) (arrows). (**e**) Transmitted light of Parvalbumin immunostaining in *N. guentheri* retina. No immunoreaction to Parvalbumin was found in the optic nerve (ON). (**f**) High magnification of inset in (**e**) showing a subpopulation of Parvalbumin-immunoreactive amacrine cells (arrows) in the INL. (**g**) High magnification of inset in (**e**) showing the soma of Parvalbumin-immunostained ganglion cells (GCL) (arrows). Magnification: 40× (**a**,**b**,**e**), 63× (**c**,**d**,**f**,**g**).

A subpopulation of amacrine cells and some bipolar and horizontal cells was immunopositive to S100p. Moreover, the ganglion cells were S100p immunostained. Additionally, the axons of amacrine cells, bipolar cells, and ganglion cells in the inner plexiform layer (IPL) were immunoreactive to S100p (Figure 4).

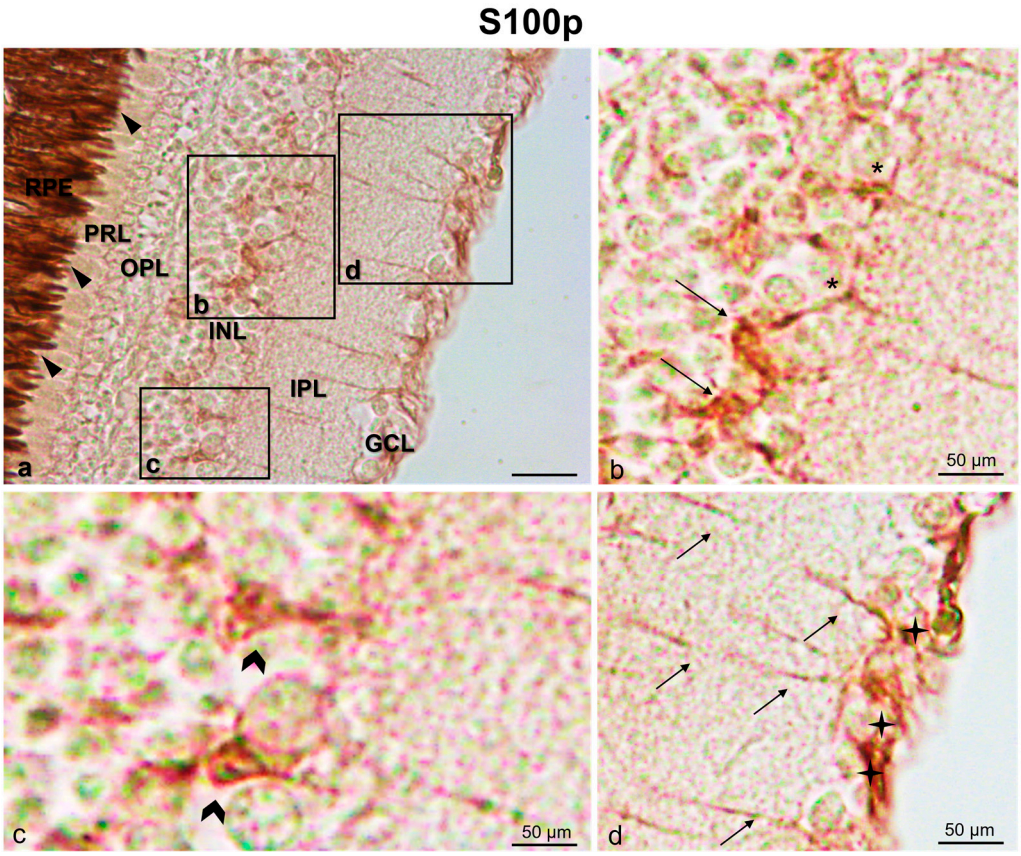

Figure 4. S100 protein immunostaining (indirect immunoperoxidase methos) in *N. guentheri* retina. (**a**) S100 immunoreactivity in the cytoplasmic prolongations of the cells in the retinal pigment epithelium (RPE) (arrowheads). (**b**) High magnification of inset in (**a**) showing a subpopulation of amacrine cells (arrows) and some horizontal cells (asterisks) immunoreative to S100p. (**c**) High magnification of inset in (**a**) showing S100-immunoreactive bipolar cells (gallon arrows). (**d**) High magnification of inset in (**a**) with S100-immunoreactive ganglion cells (stars) and axons in inner plexiform layer (arrows). Magnification: 20× (**a**), 40×, (**b**–**d**).

To ascertain the cellular identity of the immunopositive cells shown, the immunoreaction of anti-Opsin (specific for rods) and anti-Chat (specific for amacrine cells) antibodies was investigated (Figure 5).

According to the results of quantitative analysis, Calretinin N-18, Parvalbumin, and S100 antibodies were immunolocalized in RPE, PRL, INL, and GCL. In particular, S100 p was found in different subpopulations of INL (amacrine cells, bipolar cells, horizontal cells), in GCL, and in IPL. The OPL did not show immunoreativity to Calretinin N-18, Parvalbumin, and S100p. A comparison of Calretinin N-18, Parvalbumin, and S100p in different cellular layers of *N. guentheri* retina is shown in Figure 6 and Table 2.

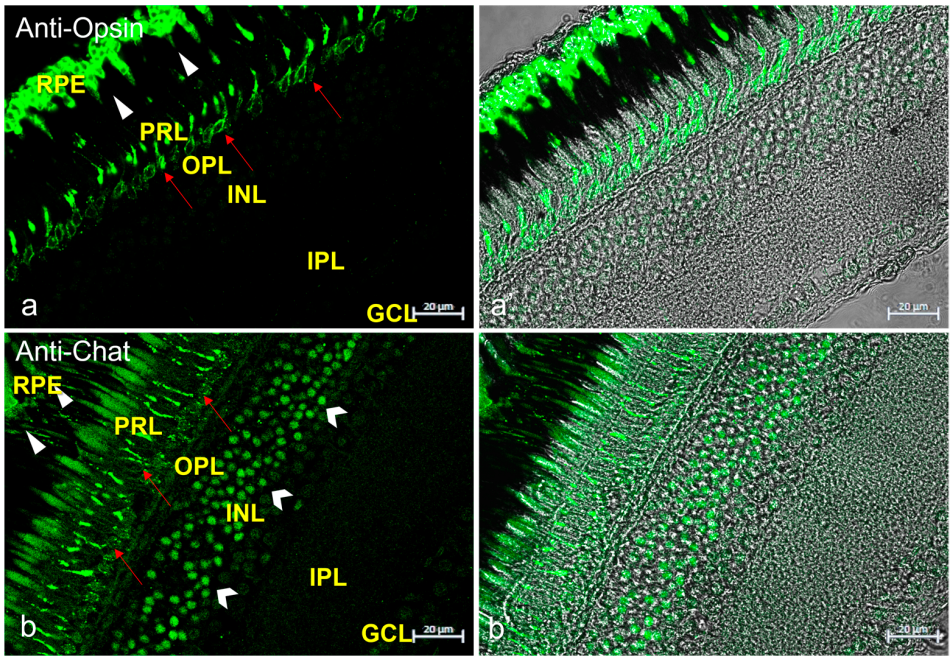

Figure 5. Anti-Opsin and anti-Chat immunostaining in *N. guentheri* retina. (**a**) Anti-Opsin immunoreactivity in the soma of rods (red arrows) and in the cytoplasmatic prolongation of retinal pigment epithelium (RPE) (arrowheads). (**a'**) transmitted light of anti-Opsin immunostaining. (**b**) Anti-Chat immunoreactivity in a subpopulation of amacrine cells (gallon arrows), in the prolongation of rods (red arrows), in the cytoplasmatic prolongation of the retinal pigment epithelium) (arrowheads). (**b'**) transmitted light of anti-Chat immunostaining. Magnification 40×.

Table 2. Mean data ± standard deviation (Δσ) of immunopositivity of: GC (ganglion cell); IPL (inner plexiform layer); INL (inner nuclear layer); OPL (outer plexiform layer); ONL (outer nuclear layer); RPE (retinal pigment epithelium) detected by Calretinin N-18, Parvalbumin, S100 protein, anti-Opsin, and anti-Chat in comparison to the total cells of a layer. The statistical analysis shows a different distribution pattern of the antibodies used in this study in cellular layer of *N. guentheri* retina. All features were evaluated per 174.286 ± 3.082 µm (mean). Statistical significance: *** $p < 0.001$, ** $p < 0.01$.

	Total Cells of a Layer	Calretinin N-18	Parvalbumin	S100	Anti-Opsin	Anti-Chat
Mean ± Δσ in RPE	28.7 ± 4.9 ***	25.2 ± 4.5 ***	27.3 ± 3.57 ***	27.7 ± 5.36 ***	27.3 ± 3.57 ***	25.2 ± 4.5 ***
Mean ± Δσ in PRL	28.5 ± 4.7 **	26.3 ± 3.1 ***	27.4 ± 4.8 **	27.8 ± 5.97 ***	27.4 ± 4.8 **	28.5 ± 4.7 **
Mean ± Δσ in OPL	27.9 ± 5.6 ***	n/a	n/a	n/a	n/a	n/a
Mean ± Δσ in ACs	28.8 ± 5.11 ***	27.1 ± 4.08 **	26.5 ± 5.48 ***	26.7 ± 4.64 ***	n/a	27.7 ± 5.36 ***
Mean ± Δσ in BCs	27.7 ± 5.36 ***	n/a	n/a	25.8 ± 4.6 ***	n/a	n/a
Mean ± Δσ in HCs	28.5 ± 4.7 **	n/a	n/a	26.3 ± 4 **	n/a	n/a
Mean ± Δσ in IPL	27.7 ± 5.36 ***	n/a	n/a	27.4 ± 4.84 ***	n/a	n/a
Mean ± Δσ in GCs	28.8 ± 5.11 ***	26.4 ± 5.40 ***	26.7 ± 4.42 ***	26.5 ± 5.12 ***	n/a	n/a

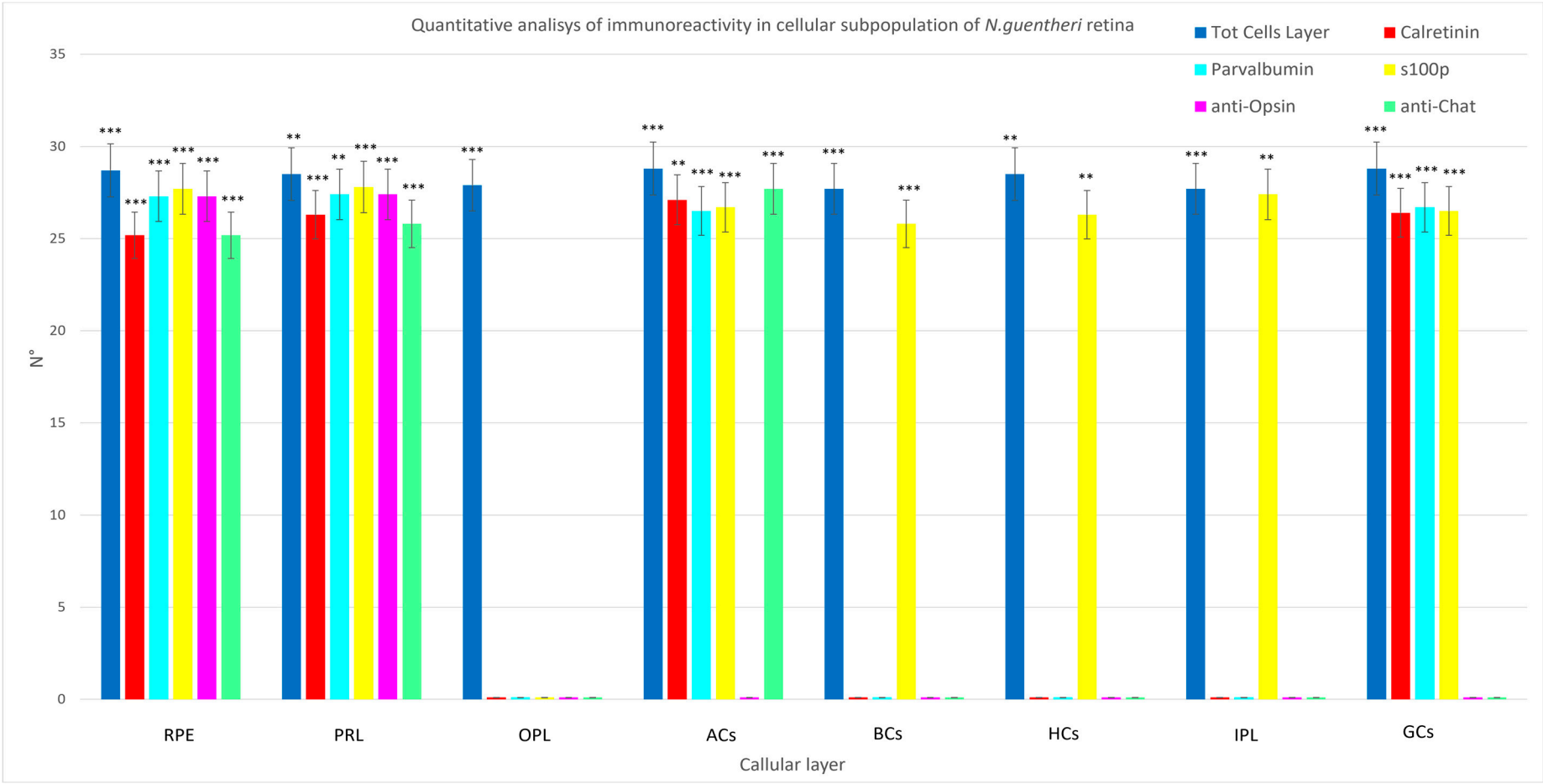

Figure 6. Graphical representation of immunoreactivity quantitative analysis in retinal pigment epithelium (RPE), photoreceptor layer (PRL), outer plexiform layer (OPL), amacrine cells (ACs), inner plexiform layer (IPL), bipolar cells (BCs), ganglion cells (GCs) detected by Calretinin N-18, Parvalbumin, S100 protein, anti-Opsin, and anti-Chat in comparison to the total cells of a layer. The statistical analysis shows a different distribution pattern of the antibodies used in this study in the cellular layer of *N. guentheri* retina. N°: mean of retinal layer cells immunoreactive to Calretinin-N18, Parvalbumin, and S100 protein. Statistical significance: *** $p < 0.001$, ** $p < 0.01$.

4. Discussion

In the 21st century, life expectancy has increased due to improved living conditions and medical advances. Contextually, the incidence of age-related disorders has risen too.

Aging is a significant risk factor both for non-neurodegenerative and neurodegenerative eye diseases. For instance, about 50 million people worldwide suffer from neurodegenerative diseases [38,39] affecting the visual system and the rest of the central nervous system, while on the other hand aging affects not only how well the visual system works but also how well it can safeguard and restore damaged or degenerating neurons [40,41].

The most recent WHO estimates place the number of people with visual impairments at 285 million. Unfortunately, there is no cure for the neurodegenerative eye condition due to aging or not. Moreover, in general, the study of aging is challenging because of the lack of an experimental model with a long life cycle.

However, killifish (*Nothobranchius* spp.) is a great aging model to fill this lack because it has a relatively short life cycle in comparison to other vertebrate models and numerous aging characteristics that have already been identified in humans [40,42]. In particular, it has been noted that Nothobranchius' central nervous system exhibits peculiar signs of aging of all the vertebrates [43–51].

Further, *Nothobranchius* spp. appear to be suitable models to research age-dependent cellular and molecular processes and/or neurodegenerative events.

The visual system of *N. guentheri* and of other fish species is similar, as demonstrated by Dmitry et al. [52], and the anatomy of the retina is comparable to that of other vertebrates, such as humans. The retina of *N. guentheri* has stratigraphy that is comparable to that of vertebrates, such as humans and *Danio rerio* [53], and few differences from other teleosts mainly related to habitat, feeding, and reproduction. Shortly before the end of the life cycle of *N. guentheri*, the retinal layers weaken, and the epithelial layer of the pigment shrinks, as observed in *Oryzias latipes* and *D. rerio* [54,55] and other vertebrates including only humans [56,57]. Finally, investigations on the *N. guentheri* retina's development have shown characteristics of neurogenesis and regeneration [52]. For these reasons, the retina of the annual killifish appears to be an ideal model in biomedical studies [52]. In both fish and mammals, the visual system is regarded as a crucial tool for understanding the brain as a whole. The central nervous system includes the retina as a necessary component [58]. Since the retina is seen as a window on the brain, recent research [59–62] has found that abnormal processes in the retina may reflect parallel processes in the central nervous system and vice versa. For instance, during Alzheimer's disease (AD), specific pathological findings in the brain occur in the retina also [63]. As a matter of fact, it has been demonstrated that Aβ plaques appear earlier in the retina of AD animals than in the brain [64].

A common denominator in brain aging, in the pathogenesis of different neurodegenerative diseases, retinal pathology, and age-related degeneration of the retina is a disturbance in calcium balance and signaling [65,66].

In this context, CaBPs' regulation may exert an influence on cellular survival. Calretinin N-18, Parvalbumin, S100p, and other members of the CaBPs' family are involved in calcium balance control on which crucial cellular functions rely (e.g., gene expression, cell cycle progression, synaptic transmission, and apoptosis) [67,68]. In the peripheral and central nervous systems, the retina included, CaBPs are extensively disseminated [19–22] and they are employed as markers of specific nerve cells [69–73]. Specifically, Car-N18 is involved in calcium signaling regulation and neuronal excitability modulation [74–76]. Parvalbumin is related to the occurrence of various clinical diseases and age-related cognitive deficits and nervous system disorders [77]. The S100 protein is recognized as a marker of sensory cells and expressed in the nervous system of fish and other vertebrates [21,32,70,71,78–80]. It has already been found in several areas of the central nervous system of *N. furzeri* [81–84]. Urvashi and Shamsher [85] have shown the role of protein s 100 in neurodegenerative disease. Furthermore, calcium-binding proteins are of fundamental significance for the proper functioning of the neurotrophin/receptor system [70,86–90].

To our knowledge, there are no reports of CaBPs in the retina of the aging-emerging model *N. guentheri* in the current scientific literature. In this study, we show for the first time the localization of the calcium-binding proteins Calretinin N-18, Parvalbumin, and S100p in *N. guentheri* retina.

The occurrence in the retina of calcium-binding proteins has been studied extensively, but their neural function in retinal layers still remains unclear.

According to our data, Calretinin N-18 was present in the pigmented epithelium and in the photoreceptors layer of *N. guentheri*, such as in zebrafish and rats. On the other hand, our result are not compliant with the literature regarding Calretinin localization in the inner and outer plexiform layer of rats. In *N. guentheri* and in humans, the outer plexiform layer is not Calretinin N-18-immuoreactive, unlike rats in which the outer plexiform layer was Calretinin-immunopositive [73,91–99]. These data could corroborate the suitability of *N. guentheri* as a model for translational medicine.

Moreover, Calretinin N-18 was found in *N. guentheri* ganglion cell layer as in other model organisms (rats and mice) and humans.

N. guentheri showed Parvalbumin-immunopositivity in pigmented epithelium, but it has never been investigated in other model organisms and humans according to our knowledge. The photoreceptor layer of *N. guentheri* was Parvalbumin-immunoreactive as in zebrafish. Finally, Parvalbumin was localized in ganglion cell layer of *N. guentheri* as in other model organisms and humans [76,95,99–105].

Immunoreactivity to S100 was observed in pigmented epithelium of *N. guentheri* and humans. The ganglion cell layer of *N. guentheri* was immunopositive to S100p, as in rats, mice, and humans [73,93,94,96,104]. The inner nuclear layer of *N. guentheri* retina showed immunoreactivity to Calretinin and S100p as in rats, mice, and humans [73,91–94,96,99,100].

Calretinin, Parvalbumin, and S100p are distributed separately in the subpopulations of neurons in the nuclear layers of the retina [106,107], although species-specific variations exist. Regarding the inner nuclear layer, the results of our investigation on *N. guentheri* showed Calretinin N-18 and Parvalbumin localization in the amacrine cells. The S100p was immunoreactive amacrine, bipolar, and horizontal cells of *N. guentheri*. In the retina of rabbit, anti-Calretinin antibodies mark amacrine cells (AII cells), bipolar cells, and numerous cellular bodies in the ganglion cell layer [107–109], while anti-Parvalbumin antibodies stain amacrine cells (AII cells), horizontal cells, and ganglion cells [107,110]. Amacrine cells are the main cell type expressing Calretinin in vertebrates. Wässle et al. [111,112] identified the amacrine AII type cells and some rods in the retina of *M. fascicularis* as Calretinin-reactive. Comparable data were submitted by Bordt et al. [113] and Chiquet et al. [114]. Also, another subpopulation of amacrine cells and ganglion cells in the human retina is Calretinin-immunopositive [96]. Horizontal cells in the outer part of the inner plexiform layer and their processes in the outer plexiform layer are the primary type of Parvalbumin-positive cell in the retina of *Macaca* sp. and *Cercopithecus aethiops* [115–117]. Parvalbumin-positive amacrine and ganglion cells were found [118]. To compare the localization of CaBPs (Calretinin N-18, Parvalbumin, S100p) in different retinal cell layers of the different models with humans, see Table 3.

In agreement with the existing literature, our data show that each CaBPs is specifically expressed in subtypes of retinal neurons [118].

Table 3. Comparison of different species' CaBPs (Calretinin N-18, Parvalbumin, S100p) with regard to the localization and expression in the retina layers of *N. guentheri*.

Species	*Nothobranchius guentheri* *			Zebrafish			Ref	Rat			Ref	Mouse			Ref	Human			Ref
Antibodies	**Calretinin N-18**	**Parvalbumin**	**S100p**	**Calretini N-18**	**Parvalbumin**	**S100p**		**Calretinin N-18**	**Parvalbumin**	**S100p**		**Calretini N-18**	**Parvalbumin**	**S100p**		**Calretini N-18**	**Parvalbumin**	**S100p**	
RPE	+	+	+	+	n/a	n/a	[91]	+	n/a	n/a	[92]	n/a	n/a	n/a		n/a	n/a	+	[93,94]
PRL	+	+	–	+	+	n/a	[119]	+	n/a	n/a	[92,95]	n/a	n/a	n/a	[120]	–	n/a	n/a	[76,95,101, 121,122]
OPL	–	–	–	–	n/a	n/a	[119]	+	n/a	+	[95,123,124]	n/a	+	n/a	[100,125]	–	n/a	+	[93–95,126]
INL	+	+	+	n/a	+	n/a	[119]	+	n/a	+	[92,95,103, 110,123,127–129]	+	n/a		[98,99]	+	n/a	+	[73,96,130]
Bipolar Cells (INL)	–	–	+	–	n/a	n/a	[119]	–	n/a	n/a	[92,131]	–	n/a		[76]	+	+	+	[76,94–96]
Amacrine Cells (INL)	+	+	+	–	n/a	n/a		+	+	n/a	[95,101,103–105,132,133]	+	+		[76,100, 134]	+	+	n/a	[76,95,96, 101]
IPL	–	–	+	–	+	n/a	[119]	+	+	n/a	[92,95,99,103, 123,128]	+	+	n/a	[98–100, 134,135]	+	n/a	n/a	[93,96,136]
GLC	+	+	+	–	+	n/a	[119]	+	+	+	[92,95,101, 104,105,110, 123,127,128, 137]	+	+	n/a	[76,99,100, 134]	+	+	+	[76,94–96,101,122, 130]

(*) these data refer to the sample of the present study. Retinal pigment epithelium (RPE), photoreceptor layer (PRL), outer plexiform layer (OPL), inner plexiform layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL). (+) positive for the considered antibody; (–) negative for the considered antibody; (n/a) references data not known, to the best of our knowledge.

Finally, a consistent piece of evidence in the scientific literature reports the neuroprotective role of the CaBPs. CaBPs showed a protective role against toxicity caused by the increased release of neurotransmitters by regulating intracellular calcium levels [138,139] and that their expression can change during neurodegenerative conditions [140] and during pathological conditions affecting the retina [91,140–142]. Therefore, it could be speculated that the expression of CaBPs can be studied to understand the mechanisms of age-related damage of retina [104].

5. Conclusions

The present study showed the localization identification of calcium-binding proteins (CaBPs) Calretinin N-18, Parvalbumin, and S100p in *N. guentheri* retina for the first time. The localization of Calretinin N-18 and Parvalbumin in the retina of *N. guentheri* could demonstrate the neuroprotective role of these two CaBPs during aging and validate anti-Calretinin and anti-Parvalbumin antibodies as specific markers to identify subpopulations of retinal neurons to facilitate the study of retinal impairments induced by aging and/or neurodegenerative diseases. Future studies are needed to better understand the role of CaBPs and their expression patterns during the aging process and/or in transgenic specimens for neurodegenerative diseases.

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