Journal of
Clinical Medicine

MDPI

Review

Neuroprotective Peptides in Retinal Disease

Davide Cervia [1,*], Elisabetta Catalani [1] and Giovanni Casini [2,3,*]

[1] Department for Innovation in Biological, Agro-food and Forest systems (DIBAF), Università degli Studi della Tuscia, largo dell Università snc, 01100 Viterbo, Italy
[2] Department of Biology, Università degli Studi di Pisa, via San Zeno 31, 56127 Pisa, Italy
[3] Interdepartmental Research Center Nutrafood "Nutraceuticals and Food for Health", Università degli Studi di Pisa, via del Borghetto 80, 56124 Pisa, Italy

* Correspondence: d.cervia@unitus.it (D.C.); giovanni.casini@unipi.it (G.C.); Tel.: +39-0761-357040 (D.C.); Tel.: +39-050-2211-423 (G.C.)

Received: 12 July 2019; Accepted: 31 July 2019; Published: 1 August 2019

Abstract: In the pathogenesis of many disorders, neuronal death plays a key role. It is now assumed that neurodegeneration is caused by multiple and somewhat converging/overlapping death mechanisms, and that neurons are sensitive to unique death styles. In this respect, major advances in the knowledge of different types, mechanisms, and roles of neurodegeneration are crucial to restore the neuronal functions involved in neuroprotection. Several novel concepts have emerged recently, suggesting that the modulation of the neuropeptide system may provide an entirely new set of pharmacological approaches. Neuropeptides and their receptors are expressed widely in mammalian retinas, where they exert neuromodulatory functions including the processing of visual information. In multiple models of retinal diseases, different peptidergic substances play neuroprotective actions. Herein, we describe the novel advances on the protective roles of neuropeptides in the retina. In particular, we focus on the mechanisms by which peptides affect neuronal death/survival and the vascular lesions commonly associated with retinal neurodegenerative pathologies. The goal is to highlight the therapeutic potential of neuropeptide systems as neuroprotectants in retinal diseases.

Keywords: neuropeptides; receptors; vertebrate retina; retinal neurons; cell death; neuroprotection; retina neurodegeneration; retinal vessels

1. Introduction

Programmed neuronal cell death plays a crucial role during development because of the limited ability of adult neurons to proliferate or be replaced, while neuronal cell death may also occur in the mature nervous system because of trauma or in the presence of a neurodegenerative disease. Neuronal cell damage triggers a chain of events that may lead to DNA fragmentation, engulfment of the cell, apoptosis, autophagy, necrosis, or other types of cell death mechanisms [1]. However, the distinction between the initiating factor that induces death and the executioner mechanism is not always clear. As excellently reviewed by Brown and colleagues [2], there are many ways for neurons, which cross-talk with each other, to die, and death is often triggered by interactions with neighboring cells, including glial cells. Of interest, neurons undergo most of the common forms of cell death experienced by non-neuronal cells, although their complexity makes them sensitive/susceptible to unique death styles, including ischemia-induced death, excitotoxicity (initiated by excitatory amino acid neurotransmitters), sodium overload and swelling, calcium overload, axon rupture, and death induced by cell cycle reentry (as adult neurons are essentially post-mitotic cells). Additional potential death factors are metabolic imbalance, energy/oxygen alterations (hypo/hyperglycemia or hypoxia), accumulation of peroxynitrite, and oxygen free radicals.

Aberrant neuronal cell death is a major cause of acute and chronic neurodegenerative diseases [3,4]. Given the critical importance of neuronal death in the pathogenesis of many disorders, and considering that neurodegeneration is mediated by multiple causal mechanisms that may temporarily overlap, a deeper understanding of the types, mechanisms, and roles of neuroprotection is of fundamental importance to develop strategies to combat neurodegeneration [2,4,5]. Neuroprotection is broadly considered as a process that contributes to the salvage, recovery, or regeneration of the nervous system, its cells, structure, and function [4]. There are many neurochemical modulators in the nervous system that also exert neuroprotective effects. Among them, secretory neuropeptides are distributed widely throughout the central and peripheral nervous systems; they commonly act as complementary signals to "classic" neurotransmitters to fine-tune the neurotransmission, thereby controlling the balance between excitation and inhibition [6–8]. By definition, neuropeptides are small protein-like molecules (in some cases "normal" proteins), which function primarily as transmitter molecules in neuronal cells [8]. Some of them have been found to be important for the regulation of cell death/survival in different neuronal systems [9–13]. In particular, neuropeptides and their receptors are expressed widely in mammalian retinas, where they exert multifaceted functions both during development and in the mature animal [14].

Here, we focus our attention on the novel advances achieved in the last decade or so, with the aim of better understanding the neuroprotective roles of neuropeptides in the retina. In particular, the present paper: (i) provides information on the major neuropeptides/receptors involved in retinal disease, (ii) reviews recent results obtained in both in vitro and in vivo models on the mechanisms by which peptides may modulate retinal neuronal death/survival, (iii) gives indications on possible positive effects of neuroprotective peptides on retinal vascular lesions that occur in many pathologies, and (iv) emphasizes neuropeptide systems as potential targets for the treatment of retinal neurodegenerative diseases.

2. Angiotensin

The renin–angiotensin system (RAS) plays a major role in the regulation of blood pressure. Renin, a proteolytic enzyme derived from the precursor prorenin and primarily released by the kidneys, cleaves angiotensinogen to angiotensin I (AngI). AngI is further processed by angiotensin-converting enzyme (ACE) and ACE2 to different peptide cleavage products. Among them, angiotensin II (AngII) is the main effector of the RAS acting at the angiotensin type I and type 2 receptors (AT1R and AT2R) [15]. AngII also acts on the adrenal cortex, triggering the release of aldosterone, which binds to its receptor (mineralocorticoid receptor—MR) and contributes to electrolyte and water balance in the body [16].

A tissue-specific RAS has been identified in several organs [17]. In particular, a local RAS is present in the retina, where RAS components have been localized mainly to ganglion cells, but also to Müller cells, amacrine cells, bipolar cells, and photoreceptors. A local aldosterone system is likely to be expressed in the retina [18]. AngII, acting directly through AT1R or indirectly through induction of aldosterone release and activation of MR expressed in the retina, has been observed to induce reactive oxygen species (ROS) generation, production of advanced glycation end-products, inflammation, microglia activation, vascular leakage, neovascularization, Müller cell activation, and ganglion cell damage [18–20]. In addition, the retinas of transgenic (mRen2) 27 rats, which have high plasma prorenin levels, were characterized by increased apoptosis of inner neurons and photoreceptors, loss of capillaries, and increase of inflammatory cytokines [21]. Interestingly, in a rat model of preeclampsia (a disorder occurring during pregnancy and characterized by high blood pressure and retinal damage), systemic delivery of agonistic AT1R autoantibodies provoked histopathologic retinal changes, apoptosis of retinal cells, increased ROS formation, and reduction of electroretinogram (ERG) a- and b-waves [22]. Consistent with these data, an increase in the expression of prorenin, renin, AngII and AT1R has been reported in diabetic retinas [23] and increased levels of RAS components have been observed in the vitreous of patients with proliferative diabetic retinopathy (PDR) and macular edema [24,25]. On the other hand, AngI cleavage by ACE2 may produce Ang (1–7), which exerts anti-inflammatory and anti-angiogenic actions through its

receptor, Mas. Similarly, AngII binding to AT2R may also antagonize the effects of AT1R activation [18]. Therefore, it appears that reduction of AngII expression (for instance, by blocking prorenin or renin actions) or blockade of AT1R, on the one hand, and stimulation of the ACE2/Ang (1–7)/Mas axis, on the other, may be exploited to counteract retinal damage occurring in retinal pathologies such as glaucoma, retinal ischemia, autoimmune uveitis, or diabetic retinopathy.

In in vitro experiments with purified rat retinal ganglion cells or cells of the 661W cell line, AT1R blockers such as telmisartan, valsartan, losartan, and candesartan were observed to prevent apoptosis and decrease ROS accumulation [26,27], while aliskiren (a renin inhibitor) prevented prorenin-induced expression of proinflammatory cytokines in cultured Müller cells [21]. In addition, irbesartan, another AT1R blocker, was reported to increase cell survival, improve ganglion cell dendritic arborizations, and reduce oxidative stress in cultured rat retinal explants [19]. These observations, indicating that inhibition of the prorenin/renin/AngI/AngII/AT1R pathway protects retinal cells from oxidative stress and apoptosis, were confirmed by observations in AT1R KO mice, in which retinal ganglion cell death induced by chronic alcohol consumption was significantly reduced with respect to wild-type animals [28].

Several investigations have provided evidence of a protective role exerted by AT1R inhibitors in in vivo models. For instance, systemic treatment with such inhibitors attenuated light-induced retinal damage in mice by reducing ROS accumulation, preventing photoreceptor apoptosis, and improving ERG responses [29]. Similarly, candesartan prevented retinal ganglion cell loss, thinning of the inner retina, and visual disturbances assessed with ERG in a retinal excitotoxicity mouse model [30]. Most of the studies have been conducted in rats or mice with increased intraocular pressure (IOP), used as models of glaucoma or ischemia–reperfusion, or in rats or mice with streptozotocin (STZ)-induced diabetes, used as models of diabetic retinopathy. Generally, in IOP models, AT1R blockade resulted in decreased ganglion cell loss, reduced ROS formation, and less extracellular glutamate [31–34]. Similar effects were induced by the renin inhibitor aliskiren, although the treatment did not seem to have any effect on retinal function as evaluated with ERG [35]. In diabetic models, blockers of AT1R, in addition to protecting the retina from oxidative stress, apoptotic cell death, and histopathologic damage [36–38], also prevented glial reaction, preserved mitochondrial integrity, increased the expression of neurotrophic factors, and improved functional ERG responses [36,37,39]. Finally, the renin inhibitor aliskiren was observed to prevent glial reaction, inflammation, and formation of acellular capillaries [21], while a prorenin receptor blocker inhibited inflammation and the diabetes-induced retinal expression of vascular endothelial growth factor (VEGF) [40].

A recent paper examined the expression of AngII and of Ang (1–7) in the retinas of normoglycemic and of diabetic rats. Both AngII and Ang (1–7) were localized to Müller cells. Interestingly, the diabetic condition resulted in increased AngII and decreased Ang (1–7) expression, while treatment of diabetic animals with the ACE inhibitor captopril reduced AngII and increased Ang (1–7) [41], indicating that, while the AngII-driven axis is associated to a pathologic condition, activation of the Ang(1–7)-driven axis is more compatible with a normal condition. In line with this view, studies have been conducted to investigate the possible therapeutic effects of ACE2 overexpression or of ACE2 activation in animal models of retinal disease. In experimental models of mouse autoimmune uveitis or of endotoxin-induced uveitis, the delivery of different formulations of ACE2 and/or Ang (1–7), as well as the administration of an ACE2 activator reduced retinal inflammation [42–44] and prevented histologic damage and functional deficits [43]. Similarly, both in rats with increased IOP and in rats with STZ-induced diabetic retinopathy, retinal ganglion cells were protected from apoptotic cell death by the administration of an ACE2 activator [45,46], while ACE2 gene delivery to diabetic mice or rats reduced oxidative stress, inflammation, vascular leakage, and the formation of acellular capillaries [47].

3. Glucagon-Like Peptide-1

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the L-cells of the gastrointestinal tract in response to food. It stimulates glucose-dependent insulin secretion and inhibits the secretion of glucagon [48]. GLP-1 and its receptor GLP-1R are expressed in the brain,

where GLP-1 may affect multiple neural circuits and modulate feeding behavior and reward [49]. Both GLP-1 and GLP-1R have been detected in human, rat, and mouse retinas at both the mRNA and the protein level [50–54]. Although it has been localized mainly to the ganglion cell layer, GLP-1R has also been reported in a rat Müller cell line [54], suggesting that this receptor may be expressed by Müller cells in mammalian retinas.

GLP-1R agonists such as exendin-4 (aka exenatide) or liraglutide were effective in protecting RGC-5 or R28 cells from damage caused by oxidative stress with a mechanism probably mediated by sirtuins [55,56]. Since oxidative stress is a causative event in many retinal pathologies, GLP-1R activation is likely to produce beneficial effects in a variety of conditions. For instance, intravitreal implants of beads with genetically modified cells producing GLP-1 decreased apoptosis and promoted survival of retinal ganglion cells in a rat model of optic nerve crush [57,58].

Perhaps the most extensive investigation of GLP-1 neuroprotective actions has been performed in models of diabetic retinopathy. That GLP-1 and GLP-1R are likely to play some role in human diabetic retinopathy is suggested by findings in human retinas reporting changes of GLP-1 or GLP-1R expression in the retinas of diabetic patients. In particular, one study conducted on diabetic patients with a diabetes duration of about six years reported a decrease of GLP-1 expression with respect to controls, but no changes were observed in GLP-1R expression [50]. In contrast, a study performed on the retinas of diabetic patients with a diabetes duration over 10 years, who had received laser photocoagulation and who were in an advanced stage of PDR, observed a decrease in GLP-1R expression with respect to the controls [51]. This discrepancy is likely due to the use of different techniques to detect GLP-1R or, more likely, to differences in the stage of diabetic retinopathy or in the treatment received by the patients. In the retinas of diabetic *db*/*db* mice, GLP-1 expression was decreased, while, similar to findings in diabetic patients without PDR, GLP-1R expression seemed to be unaffected by diabetes [50]. However, other studies in diabetic animal models reported downregulation of GLP-1R, which was prevented by administration of GLP-1 or of GLP-1R analogs [53,54,59,60]. Although somewhat contrasting, these observations indicate an involvement of GLP1/GLP-1R in the development of the disease.

The possible use of GLP-1, of GLP-1R analogs, or of inhibitors of dipeptidyl peptidase 4 (DPP4, the GLP-1 degrading enzyme) to treat diabetic retinopathy has been investigated in both in vitro and in vivo models. High glucose-induced apoptosis and mitochondrial changes in cells of the RGC-5 cell line were prevented by administrations of the GLP-1R agonist exendin-4 [61,62]. Similarly, exendin-4 also decreased the effects of high glucose in primary cultures of retinal Müller cells, where reduction of apoptosis and of glial fibrillary acidic protein (GFAP) expression was concomitant with inhibition of GLP-1R downregulation [59,60]. In diabetic animal models, treatments inducing increase of GLP-1R activation, including intravitreal, systemic, or topical administrations of GLP-1, of GLP-1R agonists, or of DPP4 inhibitors, commonly prevented cell loss and decrease of retinal thickness, reduced apoptosis, and activated prosurvival signaling pathways [50,52–55,60,63,64]. This increased resistance of retinal neurons to diabetic stress often resulted in significant functional improvement, as assessed by ERG [50,52,54,55,59,60,64], and in decreased glial activation, as indicated by reduced GFAP expression [50,60,64]. One possible mechanism by which GLP-1R activation protects the diabetic retina is likely to involve decreased accumulation of ROS and inhibition of oxidative stress [53,55,63], with the possible involvement of sirtuin1 and sirtuin3 [55]. Another mechanism may be related to an effect on glutamate excitotoxicity, as increased GLP-1R stimulation in the retinas of diabetic animals prevented both the downregulation of glutamate/aspartate transporter and the increase of retinal glutamate concentration [50,54,64]. Finally, neuronal protection may be induced by GLP-1 through an effect on inflammation. Indeed, linagliptin and exendin-4 have been reported to reduce the expression of pro-inflammatory factors in STZ rat retinas [63] and in a model of retinal ischemia–reperfusion [65], respectively.

Similar to other neuroprotective peptides, GLP-1 may also have an effect on VEGF expression. Indeed, exendin-4 has been observed to inhibit VEGF upregulation induced in vitro by high glucose or in the in vivo retina by a diabetic condition [59]. This anti-VEGF action is likely to result in decreased vascular lesions, as indicated by observations in diabetic or in ischemic retinas in which

increased GLP-1R activation prevented blood–retinal barrier (BRB) breakdown, acellular capillaries, and pericyte loss [59,63–65].

4. Growth Hormone

Growth hormone (GH) is produced in the pituitary and has many documented effects throughout the body, particularly on cell differentiation, proliferation, and survival [66]. However, GH expression has also been found in tissues other than the pituitary. Indeed, the expression of genes or proteins related to GH has been reported in retinal ganglion cells of reptiles, birds, rodents, and primates, including humans [67–69], and low levels of GH in the human vitreous have been associated with retinal neurodegeneration [70]. In the retina, GH is expressed together with the GH receptor (GHR), suggesting a local autocrine/paracrine mode of action [71,72]. In addition, GH-releasing hormone (GHRH), which regulates the secretion of GH from the pituitary, is also expressed in the retina [68,73]. In primate retinas, expression of GHRH, GH, and GHR has been reported in all nuclear layers and in the retinal pigment epithelium (RPE) [68,69].

Although an excess of GH may alter visual function, as observed in ERG recordings from transgenic mice overexpressing bovine GH [74], the presence of a GH-related axis in the retina has been linked to pro-survival effects, mainly through the activation of anti-apoptotic pathways [75,76]. For instance, blockade of the GHRH receptor has been found to induce apoptotic cell death in a retinoblastoma cell line [77], and different studies in embryonic chick retinas or in immortalized avian retinal ganglion cells have provided evidence of the neuroprotective effects of GH against both the natural apoptotic death of retinal cells during development and the apoptosis of ganglion cells induced by retinal stress. In particular, knockdown of retinal GH in chick embryos resulted in increased apoptotic cell death [78], while other studies demonstrated the significant protective effects of GH against glutamate or kainate-induced retinal excitotoxicity [79,80]. In addition, GH may be effective at inducing some sort of neural regeneration, as GH administration was shown to protect retinal ganglion cell dendrites, promote synaptogenesis, and induce neurite outgrowth [80–82].

Similar to studies in chicks, GH protected retinal neurons from excitotoxic damage in the green iguana [72], while in the retinas of rats with STZ-induced diabetes GHRH agonists induced antioxidant and anti-inflammatory effects, thus promoting ganglion cell survival [73]. Finally, observations in postmortem human retinas reported that none of the ganglion cells expressing both GH and GRH immunoreactivity (about 35% of all the cells in the ganglion cell layer) was apoptotic, while other cells displaying TUNEL labeling did not express GH or GRH immunolabeling, suggesting that GH promotes survival in adult human retinal ganglion cells [76].

Regarding the mechanisms for the control of the retinal levels of GH, studies in immortalized quail retinal ganglion cells indicated that endogenous GHRH prevents cell death by increasing endogenous GH secretion [83], while other studies demonstrated that GH in the bloodstream translocates to the retina and internalizes into ganglion cells [84], suggesting that both exogenous (endocrine) and local (paracrine/autocrine) mechanisms may be involved in the regulation of retinal GH. Regarding the possible mechanisms mediating the protective effects of GH on retinal neurons, studies in embryonic neuroretinal cells reported that GH overexpression or GH administration may induce expression of brain-derived neurotrophic factor and of neurotrophin 3 [80], indicating that GH protective actions may be mediated by these neurotrophins. However, most data indicate that neuroprotective actions of GH are mediated in large part by another neurotrophic factor, namely insulin-like growth factor-1 (IGF-1) both in the developing retina [78,79,85] and in retinas under stress conditions [72]. Indeed, IGF-1 is the major mediator of growth hormone activity in humans and the IGF-I/IGF-IR system has been found to be expressed in the retina [86].

5. Neuropeptide Y

Neuropeptide Y (NPY) is involved in various physiological and homeostatic processes in both the central and peripheral nervous systems. NPY has been identified as the most abundant peptide present in the mammalian central nervous system. As excellently reviewed by Santos-Carvalho and colleagues [87,88], NPY is expressed and functionally active in different retinal cells of non-

mammalian and mammalian species, where it can have paracrine or autocrine effects by acting on NPY receptors. The NPY receptors are expressed in different retinal cell types, such as RPE, photoreceptors, horizontal, amacrine and ganglion cells, Müller cells, and microglia.

NPY exerted a neuroprotective effect against toxicity (necrosis and apoptosis) induced by MDMA (methylenedioxymethamphetamine, often known as "ecstasy") in rat retinal mixed cell cultures containing neurons, astrocytes, Muller cells, and microglial cells [89]. In rat retinal neurons, NPY inhibited the increase in intracellular Ca^{2+} evoked by KCl through the activation of NPY Y_1, Y_4, and Y_5 receptor subtypes, likely contributing to its neuroprotective effect [90]. Accordingly, in recent years, studies have suggested that the NPY system could be exploited for potential protective strategies in retinal degenerative diseases [87,88].

The induction of diabetes in rats (as in STZ-treated animals) decreased the retinal NPY mRNA levels, as well as the protein levels of NPY and of NPY Y_5 receptor [91]. Of interest, NPY was demonstrated a neuroprotective agent against necrotic and apoptotic cell death induced by cytotoxic glutamate in rat retinal cells both in vitro and in vivo. In particular, NPY protected retinal cells against glutamate-induced necrosis by activating NPY Y_2, Y_4, and Y_5 receptors and from apoptosis by activating NPY Y_5 receptors [92]. More recently, NPY attenuated the increase of intracellular Ca^{2+} triggered by glutamate in purified retinal ganglion cells and in ex vivo rat retinal preparations, mainly via NPY Y_1 receptor activation [93]. The NPY Y_1 receptor activation was also able to modulate directly ganglion cell responses by attenuating the NMDA-induced increase in ganglion cell spiking activity. NPY pretreatment also prevented NMDA-induced cell death, although in a rat model of retinal ischemia–reperfusion injury pretreatment with NPY could not prevent apoptosis or rescue retinal ganglion cells and retinal function [93], thus introducing some doubts about NPY's translational potential. In this line, a worsening effect induced in vivo by NPY following an ischemic insult has been reported. In particular, intravitreal injection of NPY after ischemia induction in pigs caused a significant reduction of retinal function, as evaluated by standard and global-flash multifocal ERG. This reduction was accompanied by histological damage, as for instance the reduction of ganglion cells, likely via NPY Y_1 and Y_2, but not Y_5 receptors [94].

6. Opioid Peptides

Opioid peptides are known as powerful analgesics, but they are involved in a variety of functions in the organism. Their effects are mediated by δ, κ, and μ opioid receptor subtypes [95]. Opioid receptors have been detected in virtually all major organ systems. In particular, the presence of functional opioid receptors has been reported in the retina, optic nerve, and optic nerve head astrocytes [96,97].

Evidence has been provided that the administration of morphine, a broad-range opioid agonist, is effective in reducing ischemic retinal injury [96]. Regarding specific opioid receptor subtypes, the δ opioid receptors have been implicated in neuroprotective effects in the retina [98]. The neuroprotective effects of opioids have been studied mainly in models of retinal ischemia, and they have been reviewed previously [99]. Here, we provide an update of the most recent findings.

In a rat model of ischemia–reperfusion injury caused by elevated IOP, morphine inhibited the production of the proinflammatory cytokine tumor necrosis factor α (TNFα), an effect antagonized by naloxone, a nonselective antagonist of opioid receptors [97]. In addition, a naloxone-sensitive effect of morphine was also reported in glaucomatous rats, where opioid agonism was observed to decrease ganglion cell death, to inhibit TNFα, caspase-8, and caspase-3 expression, and to improve functional retinal responses, as evaluated with pattern ERG [100]. Similar findings were reported in glaucomatous rats treated with a δ opioid receptor agonist [101]. The neuroprotective effect of δ agonism may be mediated, at least in part, by inhibition of inducible nitric oxide (NO) synthase (iNOS). Indeed, NO, mainly produced by iNOS, may play a detrimental role in glaucoma, and its inhibition by a δ opioid agonist results in neuroprotection [102]. The neuroprotective effects consequent to δ opioid activation are likely to be mediated through the PI3K/Akt pathway [103]. Activation of δ opioid receptors may induce ameliorative changes other than direct neuroprotection in models of retinal injury. Indeed, it has been shown that ARPE-19 cells challenged with high glucose

decrease TNFα production and preserve tight junction proteins when treated with epicatechin, which acts as a δ opioid activator, thus indicating a protective effect of opioid peptides on the integrity of the outer BRB [104]. Although most studies on the retinoprotective effects of opioid peptides are concerned with ischemic models and with the δ receptor subtype, a recent study using a model of retinal excitotoxicity and administrations of the opioid peptide ß-endorphin (a ligand of the μ opioid receptor) suggests that not only the δ but also the μ subtype of the opioid receptors may play important neuroprotective functions in retinal disease [105].

The data reported above indicate protective effects of opioid receptors that may be antagonized by the opioid antagonist naloxone, thus indicating naloxone as a detrimental compound when the objective is retinal neuroprotection. However, the neuroprotective effects of naloxone have been demonstrated in the central nervous system [106], although these effects are unlikely to depend on inhibition of the opioid system [107,108]. In the retina, naloxone was reported to protect from light-induced photoreceptor degeneration through the inhibition of activated microglia [109]. In a mouse model of age-related macular degeneration, naloxone has been shown to reduce the progress of retinal lesions, the production of pro-inflammatory cytokines, and microglia aggregation [110]. Since naloxone's greatest affinity is for the μ opioid receptor and the μ3 receptor is linked to NO production [111], naloxone may protect the retina from NO-induced neuronal damage playing an inhibitory action at this opioid receptor.

7. Somatostatin

Somatostatin (somatotropin release inhibiting factor—SRIF) is considered to be one of the key physiologically active neuropeptides expressed in the retina [112,113]. Five SRIF receptor subtypes coupled to different G-proteins have been cloned, namely sst1–5 [114], and they modulate the actions of multiple second messengers/transduction pathways [114–118]. SRIF receptors have been detected in different areas of the central nervous system [114,119,120], including the retina, where sst_1 and sst_2 are the most widely expressed in multiple retinal layers and cell types [112,113,121].

Clinically, the fact that lower vitreous levels and lower intraocular production of SRIF were found in patients with diabetic macular edema, chronic uveitis macular edema, and quiescent intraocular inflammation [122,123] suggests that SRIF alterations may be directly involved in the pathogenesis of these conditions. On the other hand, different pre-clinical observations supported a role for SRIF as a neuroprotective factor in a variety of retinal diseases [13,112,124,125]. The importance of the SRIF system in protecting the retina from noxious stimuli has been confirmed in recent years.

In the retinas of diabetic rats, treatment with SRIF eye drops inhibited glutamate accumulation and glutamate/aspartate transporter downregulation [126]. SRIF administration also prevented ERG abnormalities, glial activation, apoptosis, and the misbalance between proapoptotic and survival signaling [126]. Using in vitro systems mimicking diabetic-like conditions, SRIF was demonstrated to decrease endothelial cell apoptosis without affecting the response of human retinal pericytes expressing sst1 [127]. On the other hand, SRIF reduced the expression of pro-inflammatory markers and counteracted the imbalance between apoptotic and survival intermediates in human retinal pericytes exposed to conditioned media from activated microglia [128], thus suggesting a possible anti-inflammatory role in the early phases of PDR, a disease in which neurodegeneration is thought to occur prior to microvascular alterations. In this respect, SRIF and octreotide, a sst_2-preferring agonist, reduced apoptosis as well as VEGF expression and release in retinal explants exposed to stressors similar to those characterizing diabetic retinopathy, that is, high glucose, oxidative stress, or advanced glycation end-products [129,130]. SRIF was also shown to reduce high glucose-induced apoptosis in photoreceptor cells [130].

Retinal VEGF patterns are affected profoundly by the onset of an ischemic state and may represent a fast response of the VEGF system to severe shortage of nutrients and oxygen in retinal neurons [131]. It should be noted that an ischemic condition not only causes cell death, but also induces a vascular response and is a common clinical entity since it causes visual impairment and blindness [132,133]. There are indications that endogenous SRIF mediates the retinal protective effects

exerted by anti-inflammatory and neuroprotective factors during ischemic injury [124]. Notably, the activation of SRIF receptors, likely sst_2, protected neurons from apoptosis by ischemic damage and reduced VEGF overexpression as well as glutamate release [131,134–138]. These effects are likely to be due, at least in part, to a reduction of VEGF release by damaged neurons and its accumulation in the retinal capillaries [131]. Different approaches also demonstrated that octreotide treatment counteracts ischemia-induced oxidative stress and modulates various metabolic responses during ischemic damage [136,137]. Of interest, recent data indicated a cross-talk between apoptosis and autophagy in the ischemic or hypoxic retina [139,140]. This cross-talk may be altered by stressing conditions favoring apoptosis, but it may be re-equilibrated by autophagy-stimulating substances. In particular, the reported antiapoptotic actions of octreotide seem to be, at least in part, the result of a stimulation of the autophagic flux [139].

8. Substance P

The peptides of the tachykinin family are characterized by a common C-terminal amino acid sequence (Phe–X–Gly–Leu–Met–NH2). Substance P (SP) is the best characterized neuropeptide of this family, but other tachykinins have also been described so far, the two main ones being neurokinin A (NKA) and neurokinin B (NKB) [141]. The tachykinins act thorough specific NK receptors, namely NK1R, NK2R and NK3R. SP, NKA, and NKB have the highest affinity for NK1R, NK2R, and NK3R, respectively, but they do not bind them in a selective manner [141].

In the retina, SP is highly expressed in ganglion cells and in the inner plexiform layer where it has been localized in sparse amacrine cells, and a similar localization pattern has been described for the other two tachykinins, NKA and NKB [14,142,143]. There is evidence highlighting the potential for endogenous SP as a treatment for retinal damage. For instance, a greater content of SP has been reported in the retina in response to acute stress or in retinal pathologies [144,145]. In addition, results from studies in diabetic rats showed that the levels of SP in the retina and serum were reduced, with an associated increase in apoptosis and caspase-3 activity, while the restoration of endogenous SP levels paralleled the inhibition of apoptosis [146]. Similarly, the levels of SP and NKA/NKB decreased in an NMDA–excitotoxicity model of the rat retina [147], while both the severe retinal destruction and the dense neovascularization in laser-induced retinal degeneration models recovered after SP administrations [148]. Noteworthy, SP treatment suppressed early inflammatory responses in proliferative vitreoretinopathy-like retinal damage, with inhibition of cell death, limitation of the appearance of fibroblastic cells, and delay of the progression of retinal degeneration [149].

In ischemic retinas, SP reduced apoptotic cell death, VEGF overexpression, and glutamate release, also counteracting the oxidative stress and perturbations in the metabolome induced by the ischemic insult [136]. The NK1R were identified as the receptor subtype possibly involved in SP protective mechanisms [105,150]. Recently, the protective effect of SP against NMDA excitotoxic apoptosis of ganglion cells was established in ex vivo retinal explants and in vivo murine models [151]. Of interest, SP was also found to maintain endothelial tight junctions and to decrease VEGF-induced vascular permeability, thus inhibiting VEGF-induced BRB breakdown [151]. Finally, SP was effective at protecting RPE cells from oxidative stress-induced cell death via the NK1R [152] and in ameliorating RPE epithelial–mesenchymal transition and fibrotic change after inflammatory stimuli [149].

9. Vasoactive Intestinal Peptide and Pituitary Adenylate Cyclase Activating Polypeptide

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) belong to a peptide superfamily that also includes secretin and glucagon. Their receptors are G protein-coupled receptors that can be classified into two groups: PAC1R, which binds PACAP with higher affinity than VIP, and VPAC receptors (VPAC1R and VPAC2R), which bind PACAP and VIP with similar affinities [153]. VIP has been observed to support neuronal survival in both physiological and pathological conditions in the central as well as in the peripheral nervous system [154]. Similarly, widespread neuroprotective properties of PACAP, mediated mainly by the PAC1R

receptor, have been reported in a variety of in vitro and in vivo models and have been extensively reviewed [11,12,155–165].

Both VIP and PACAP occur in the retina. In particular, VIP has been reported in a population of amacrine cells, which, in the mouse retina, is likely to include different cell types [166]. PACAP, instead, localized to horizontal, amacrine, and ganglion cells [167,168]. The PACAP-containing ganglion cells have been identified as the melanopsin-expressing ganglion cells originating the retinohypothalamic tract, which connects the retina with the suprachiasmatic nucleus of the hypothalamus and is involved in the regulation of biological rhythms [169]. PAC1R were observed in amacrine and ganglion cells [170,171] as well as in in rat primary cultures of Müller cells [172]. Functionally, both VIP and PACAP have been found to be implicated in retinal development [14] (see also [173] for references) and to be involved in information processing of visual stimuli [174–176]. In addition, PACAP interacts with glutamate in the transmission of light stimuli to the suprachiasmatic nucleus [177].

9.1. Neuroprotective Effects of VIP in the Retina

VIP has been reported to protect retinal ganglion cells against glutamate excitotoxicity in vitro [178] and to reduce the retinal neurodegenerative effect of ischemia–reperfusion injury through an antioxidant action [179]. VIP may also mediate the reduction of t e inflammatory response and the improvement of retinal function induced by vagal stimulation in rats with acute ocular hypertension [180]. Recently, both PACAP and VIP have been shown to efficiently attenuate ischemic retinal degeneration induced by bilateral common carotid artery occlusion (BCCAO) when are bound to the cell penetrating peptide TAT and administered through eye drops [181]. However, VIP has been shown to be 10 times less active than PACAP in ischemic retinopathy [182]. In a retinal disease such as diabetic retinopathy, VIP may contribute to the protection of retinal neurons by reducing outer BRB dysfunction [183,184], probably through an inhibition of VEGF and of hypoxia-inducible factor 1α (HIF1-α), the main transcriptional regulator of VEGF expression [185].

The neuroprotective effects of VIP may be either direct through activation of the PAC1R [181], or indirect through regulation of activity-dependent neurotrophic protein (ADNP) [186–188]. Indeed, both ADNP and an 8-amino acid peptide derived from ADNP (referred to as NAP) display important neuroprotective activities [189]. In particular, NAP has been reported to enhance both survival and neurite outgrowth in retinal ganglion cells in vitro [190], while intraocular or intraperitoneal NAP administrations resulted in significant protection of retinal ganglion cells after retinal ischemia or optic nerve crush [191]. Similarly, intraocular or intravenous injections of NAP protected against laser-induced retinal damage [192]. In addition, stable transfection of NAP into retinal Müller cells with constant NAP production protected both Müller cells and retinal neurons from damage induced by hypoxia [193].

Interestingly, NAP, similar to VIP, seems to play different protective effects against pathologic changes induced by diabetic retinopathy, as it reduced both inflammation [194] and apoptosis [195] as well as the levels of HIF1-α and of VEGF [196] in retinas of rats with STZ-induced diabetes, and protected the integrity of the outer BRB exposed to hyperglycemic/hypoxic or inflammatory insult [194,197].

9.2. Neuroprotective Effects of PACAP in the Retina

The retinoprotective effects of PACAP have been widely investigated and the results of these studies have been reviewed previously [198–200]. Here we provide a summary of the findings of the last few years.

Recent evidence indicates that physiological expression levels of PACAP in the retina are necessary to maintain retinal integrity. Indeed, retinas of PACAP KO mice were characterized by abnormal sprouting of horizontal and rod bipolar cell dendrites, decreased ganglion cell number, altered MAPK signaling pathway, and GFAP upregulation in Müller cells [201], which is known to appear in response to retinal injury [202]. In addition, PACAP KO retinas displayed significantly worse structural and functional damage with respect to wild types following lipopolysaccharide-

induced eye inflammation [203], confirming that PACAP expression in the retina may represent a natural defense against injury. Consistent with this hypothesis, upregulation of both PACAP and PAC1R has been reported in retinas of rats after optic nerve crush [204].

Intravitreal administrations of PACAP have been shown to inhibit apoptosis and promote survival of retinal ganglion cells in different models of retinal injury [205,206]. Since PACAP is subjected to rapid enzymatic hydrolysis in the extracellular environment [207], the efficacy of a more stable, cyclized form of PACAP has been tested both in vitro and in vivo. In these studies, RGC-5 cells exposed to ultraviolet irradiation showed decreased apoptosis and less ROS generation when treated with cyclic PACAP, while intravitreal injection of the compound enhanced ERG and ganglion cell survival in rat retinas exposed to excitotoxic injury [208].

PACAP has been found to be very effective in protecting the retina from ischemia. In an ex vivo model, PACAP decreased apoptosis and glutamate accumulation, reduced peroxidized lipids and inflammatory mediators, and induced normalization of glutathione homeostasis. In addition, PACAP decreased VEGF expression, which was observed to increase in the ischemic retina [136]. In the BCCAO model, intravitreal PACAP was observed to ameliorate ERG responses [209], while intravitreal administrations of maxadilan (a PAC1R agonist) dose-dependently reduced the thinning of retinal layers and the loss of cells in the ganglion cell layer [210]. The ischemic damage was also combated by topical administrations of different formulations of PACAP through eye drops. Similar to intravitreal delivery, PACAP eye drops protected the retina from thinning and from cell loss [181,211,212], while they also reduced GFAP upregulation in Müller cells [211,212].

Some studies have investigated possible effects of PACAP against retinal damage caused by diabetic retinopathy. Both PACAP administration to ex vivo retinal explants treated with diabetic stressors and PACAP intraocular delivery in rats with STZ-induced diabetes protected the retina from apoptosis [129,213], maintained retinal synaptic integrity [214], and prevented the expression of inflammatory cytokines [215]. Interestingly, PACAP protective and antiapoptotic effects were paralleled by inhibition of upregulation of HIF1-α, of VEGF, and of VEGF receptors (VEGFRs) in retinal explants [129], in STZ rats [215,216], and in pigment epithelial cells of the ARPE-19 cell line [184].

10. Other Peptides

In addition to the neuropeptides discussed above, a variety of other peptidergic molecules with documented retinoprotective properties have been found, although available data in the literature are far from abundant. Here, we provide a (probably incomplete) summary of them.

10.1. α-Melanocyte-Stimulating Hormone

α-Melanocyte-stimulating hormone (α-MSH) is a widely-distributed 13-amino acid peptide derived from proteolytic cleavage of proopiomelanocortin [217]. It acts at 5 subtypes of G protein-coupled receptors (melanocortin receptors, MC1R to MC5R) [218] and regulates a variety of physiological functions, ranging from thermoregulation [219] to metabolism [220]. α-MSH is known to protect against ischemic damage of the brain [221]. In the retina, α-MSH acting at MC4R protected developing chicken retinas from glutamate induced excitotoxicity [222]. In addition, α-MSH protected the rat retina from both functional and structural damage induced by ischemia–reperfusion [223], suppressed inflammation and maintained the retinal structure in a mouse model of experimental autoimmune uveitis [224], and protected photoreceptors from degeneration in a rat model of retinal dystrophy [225]. In addition, intravitreal injections of α-MSH protected both the neuroretina and retinal vessels from oxidative stress and cell death in a rat model of STZ-induced diabetes [226]. Finally, α-MSH inhibited BRB breakdown and vascular leakage, improving both functional and morphological characteristics in early diabetic retinas, likely acting via MC4R [227].

10.2. Apelin

Apelin is an endogenous oligopeptide ligand for the G protein-coupled receptor APJ [228] and it has been reported to exert neuroprotective actions in the central nervous system (see [229] for references). In the retina, apelin has been reported in Müller cells [230,231], while APJ receptors have been localized to ganglion cells and to cholinergic amacrine cells [229]. Exogenous apelin prevented Müller cell apoptosis and stimulated Müller cell viability and migration under normal, hypoxic, or glucose-free conditions [230,231], while in an in vivo mouse model of retinal excitotoxicity, apelin was found to protect retinal ganglion cells from apoptosis and to ameliorate functional retinal responses, [229,232]. The protective effect of apelin against retinal excitotoxic damage was reported to be mediated by [229] or to be independent from [232] activation of APJ receptors.

10.3. Bradykinin

Bradykinin is a component of the kallikrein–kinin system, which may have a role in the development of diabetic retinopathy [233,234]. Kinins are important inflammatory mediators and exert their effects by binding two G-protein coupled bradykinin receptors named B1R and B2R [235]. Most components of the kallikrein-kinin system have been identified in the retina (see [236] for references). In particular, the B1R is overexpressed in the retina of rats with STZ-induced diabetes, where it is involved in BRB breakdown [237,238] suggesting a detrimental role of B1R in the development and the progression of diabetic retinopathy. Indeed, administrations of B1R blockers to STZ rats reduced retinal plasma extravasation, leukostasis, ROS formation, and mRNA levels of inflammatory mediators and of VEGFR2, and restored retinal Na^+/K^+-ATPase activity [236,239]. In addition, intravitreal injections of bradykinin in rats increased BRB permeability, an effect prevented by a B2R antagonist [240]. In apparent contrast with these findings, a recent investigation using two different models of diabetic mice reported that pancreatic kallikrein may activate B1R and B2R and ameliorate retinal oxidative stress, inflammation, apoptosis, acellular capillary formation, and vascular leakage [241].

10.4. Calcitonin Gene-Related Peptide

Calcitonin gene-related peptide (CGRP) and its receptors have been detected in the rat retina [242]. A protective role of endogenous retinal CGRP was suggested by studies in rats, in which a CGRP receptor antagonist was demonstrated to worsen the apoptotic rate of retinal ganglion cells following ischemia caused by acute myocardial infarction [243]. In addition, capsaicin-induced CGRP upregulation effectively protected retinal ganglion cells from apoptosis in retinas of rats with STZ-induced diabetes [244] or in rat retinas challenged with an excitotoxic insult [105,150].

10.5. Ghrelin

Ghrelin is a peptide hormone secreted by the stomach that is involved in regulation of food intake and energy balance. It acts at its receptor GH secretagogue receptor type 1a (GHSR-1a) [245]. In patients with glaucoma, ghrelin levels in the anterior chamber were reported to be significantly lower than in controls [246]. In rats with experimental glaucoma, ghrelin was effective in reducing autophagy and glial reaction and in protecting the retinal cells from oxidative stress and apoptosis [247,248], while ghrelin activation of GHSR-1a significantly protected RGC-5 cells from rotenone-induced toxicity [249]. Finally, obestatin, a peptide encoded by the ghrelin gene, has been reported recently to protect RGC-5 cells from oxidative stress by activating the TrkB pathway with a mechanism that is likely to involve GLP-1R [250].

10.6. Insulin

The insulin receptor is widely expressed in the neural retina and in the RPE [251]. Although there is some evidence indicating a neuroprotective role of insulin in the retina, it has not been investigated in detail. In rats with STZ induced diabetes, insulin has been reported to protect significantly retinal function, as assessed with ERG, and reduce retinal cell apoptosis, glial activation, VEGF upregulation, and BRB damage [252]. In addition, insulin receptors expressed by the RPE were

reported to support photoreceptors in the diabetic retina [253]. A recent review suggests that, more than insulin, the prohormone proinsulin is likely to exert significant neuroprotective actions in the retina [254].

10.7. Prolactin

Prolactin is another peptide hormone whose receptors have been identified in the retina [255]. Similar to insulin, there are also reports suggesting a neuroprotective action of this hormone in the retina, although the evidence is quite limited. Prolactin is likely to exert antioxidant actions in the retina [256]. In a model of light-induced retinal degeneration, experimentally induced hyperprolactinemia limited photoreceptor apoptosis, gliosis, and changes in neurotrophin expression, and it preserved the ERG responses [257]. In addition, vasoinhibins, a family of peptides originating from the proteolysis of prolactin [258], prevented the excessive vasopermeability associated with diabetes [259], decreased bradykinin-induced BRB permeability, and reduced the levels oxidative stress in retinas of STZ rats [240].

10.8. Urocortin

Urocortin 2 (Ucn 2) is a corticotropin-releasing factor (CRF) paralog preferentially activating CRF2 receptors [260], which have been identified in the retina [261]. Intraocular administrations of Ucn 2 have been reported to preserve retinal thickness and promote ganglion cell survival in the rat BCCAO model [262], while in a model of excitotoxicity-induced retinal degeneration, Ucn 2 has been observed to rescue neurochemically-identified bipolar and amacrine cells [263].

11. Concluding Remarks

Neuropeptide expression in vertebrate retinas has been known for many years and neuropeptide functions have been found to involve neuromodulation and participation to visual information processing within the retina. More recently, an increasing number of peptidergic substances expressed in the retina together with their receptors have been recognized to play neuroprotective actions in a variety of models of retinal disease. Generally, neuropeptides are likely to exert antioxidant or anti-inflammatory actions, or they may limit extracellular glutamate, thereby promoting retinal neuronal survival. It is interesting to note that in many circumstances neuroprotective effects of neuropeptides have been described together with a positive effect against the vascular lesions characterizing some retinal diseases, such as, for instance, diabetic retinopathy. These observations indicate a link between neural and vascular damage in these diseases and indicate that peptide neuroprotection may also prevent pathologic vascular changes. Additionally, there is a general agreement that neuropeptides are coupled to multiple components of transduction pathways [13,264], which may converge in restoring neuronal functions. The diversity of signaling reflects the pleiotropic actions of peptides; at the cellular level, many mechanisms are involved in the amplification effects. Given that different neuropeptides are associated with beneficial effects against retinal neurodegeneration, it would also be of interest to explore potential common mechanisms at the second messenger level in relation to the actions of marketed drugs, as previously suggested for antidepressants [265].

However, the fact that the investigation of possible peptide-based therapeutic approaches is still at the preclinical level, with only a few exceptions, indicates that there are problems in the development of such strategies. One of these problems is represented by the low bioavailability of peptidergic substances, due to their rapid degradation in the extracellular environment. Thus, the challenge is to find new peptide analogs or peptide receptor agonists with higher resistance to degrading enzymes and peptide formulations affording better pharmacokinetics and bioavailability. New peptide formulations should also allow easier delivery to the retina, avoiding the need of invasive intraocular injections in favor of methods for oral or topical delivery. A significant advancement in this field could come from the conjugation of neuropeptides or peptide analogs with different types of nanoparticles [266]. In conclusion, the use of peptidergic neuroprotectants may lend

unforeseen value and these substances may be regarded as a powerful tool for the development of therapies to cure neurodegenerative as well as vascular retinal diseases.

Author Contributions: D.C., E.C., and G.C. collected the references and organized the layout of the paper. D.C. and G.C. wrote the manuscript.

Funding: The research has been supported by grants from the Italian Ministry of Education, University and Research: "PRIN2015" to DC and "Departments of Excellence-2018" Program (Dipartimenti di Eccellenza) to DIBAF (University of Tuscia, Viterbo, Italy) (Project "Landscape 4.0-food, wellbeing and environment").

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ACE: angiotensin-converting enzyme
ADNP: activity-dependent neurotrophic protein
AngI: angiotensin I
APJ: apelin receptor
AT1R and AT2R: angiotensin type I and type 2 receptors
B1R and B2R: bradykinin receptors 1 and 2
BCCAO: bilateral common carotid artery occlusion
BRB: blood–retinal barrier
CGRP: calcitonin gene-related peptide receptor
CRF: corticotropin-releasing factor
DPP4: dipeptidyl peptidase 4
ERG: electroretinogram
GFAP: glial fibrillary acidic protein
GH: growth hormone
GHR: GH receptor
GHRH: GH-releasing hormone
GHSR-1a: GH secretagogue receptor type 1a
GLP-1: glucagon-like peptide-1
GLP-1R: GLP-1 receptor
HIF1-α: hypoxia-inducible factor 1α
IGF-1: insulin-like growth factor-1
iNOS: inducible NO synthase
IOP: intraocular pressure
MDMA: methylenedioxymethamphetamine
MC1-5R: melanocortin receptors 1-5
MR: mineralocorticoid receptor
NAP: 8-amino acid peptide derived from ADNP
NK1-3R: NK receptors 1-3
NKA and NKB: neurokinin A and B
NO: nitric oxide
NPY: neuropeptide Y
PAC1R: PACAP receptor 1
PACAP: pituitary adenylate cyclase-activating polypeptide
PDR: proliferative diabetic retinopathy
RAS: renin–angiotensin system
ROS: reactive oxygen species
RPE: retinal pigment epithelium
SP: substance P
SRIF: somatotropin release inhibiting factor—somatostatin
sst1–5: SRIF receptors 1-5
STZ: streptozotocin
TNFα: tumor necrosis factor α

Ucn 2: urocortin 2
VEGF: vascular endothelial growth factor
VEGFRs: VEGF receptors
VIP: vasoactive intestinal peptide
VPAC1R and VPAC2R: VIP and PACAP receptors 1 and 2
α-MSH: α-melanocyte-stimulating hormone

References

1. D'Arcy, M.S. Cell death: A review of the major forms of apoptosis, necrosis and autophagy. *Cell Biol. Int.* **2019**, *43*, 582–592.
2. Fricker, M.; Tolkovsky, A.M.; Borutaite, V.; Coleman, M.; Brown, G.C. Neuronal Cell Death. *Physiol. Rev.* **2018**, *98*, 813–880.
3. Fan, J.; Dawson, T.M.; Dawson, V.L. Cell Death Mechanisms of Neurodegeneration. *Adv. Neurobiol.* **2017**, *15*, 403–425.
4. Vajda, F.J. Neuroprotection and neurodegenerative disease. *J. Clin. Neurosci.* **2002**, *9*, 4–8.
5. Monteiro, M.C.; Coleman, M.D.; Hill, E.J.; Prediger, R.D.; Maia, C.S. Neuroprotection in Neurodegenerative Disease: From Basic Science to Clinical Applications. *Oxid. Med. Cell. Longev.* **2017**, *2017*, 2949102, doi:10.1155/2017/2949102.
6. Hokfelt, T.; Bartfai, T.; Bloom, F. Neuropeptides: Opportunities for drug discovery. *Lancet Neurol.* **2003**, *2*, 463–472.
7. Hoyer, D.; Bartfai, T. Neuropeptides and neuropeptide receptors: Drug targets, and peptide and non-peptide ligands: A tribute to Prof. Dieter Seebach. *Chem. Biodivers.* **2012**, *9*, 2367–2387.
8. Burbach, J.P. Neuropeptides from concept to online database www.neuropeptides.nl. *Eur. J. Pharmacol.* **2010**, *626*, 27–48.
9. Catalani, E.; De Palma, C.; Perrotta, C.; Cervia, D. Current Evidence for a Role of Neuropeptides in the Regulation of Autophagy. *Biomed Res. Int.* **2017**, *2017*, 5856071, doi:10.1155/2017/5856071.
10. Linden, R.; Martins, R.A.; Silveira, M.S. Control of programmed cell death by neurotransmitters and neuropeptides in the developing mammalian retina. *Prog. Retin. Eye Res.* **2005**, *24*, 457–491.
11. Reglodi, D.; Renaud, J.; Tamas, A.; Tizabi, Y.; Socias, S.B.; Del-Bel, E.; Raisman-Vozari, R. Novel tactics for neuroprotection in Parkinson's disease: Role of antibiotics, polyphenols and neuropeptides. *Prog. Neurobiol.* **2017**, *155*, 120–148.
12. Chen, X.Y.; Du, Y.F.; Chen, L. Neuropeptides Exert Neuroprotective Effects in Alzheimer's Disease. *Front. Mol. Neurosci.* **2018**, *11*, 493, doi:10.3389/fnmol.2018.00493.
13. Cervia, D.; Casini, G. The Neuropeptide Systems and their Potential Role in the Treatment of Mammalian Retinal Ischemia: A Developing Story. *Curr. Neuropharmacol.* **2013**, *11*, 95–101.
14. Bagnoli, P.; Dal Monte, M.; Casini, G. Expression of neuropeptides and their receptors in the developing retina of mammals. *Histol. Histopathol.* **2003**, *18*, 1219–1242.
15. Fletcher, E.L.; Phipps, J.A.; Ward, M.M.; Vessey, K.A.; Wilkinson-Berka, J.L. The renin-angiotensin system in retinal health and disease: Its influence on neurons, glia and the vasculature. *Prog. Retin. Eye Res.* **2010**, *29*, 284–311.
16. Waanders, F.; de Vries, L.V.; van Goor, H.; Hillebrands, J.L.; Laverman, G.D.; Bakker, S.J.; Navis, G. Aldosterone, from (patho)physiology to treatment in cardiovascular and renal damage. *Curr. Vasc. Pharmacol.* **2011**, *9*, 594–605.
17. Paul, M.; Mehr, A.P.; Kreutz, R. Physiology of Local Renin-Angiotensin Systems. *Physiol. Rev.* **2006**, *86*, 747–803.
18. Wilkinson-Berka, J.L.; Agrotis, A.; Deliyanti, D. The retinal renin-angiotensin system: Roles of angiotensin II and aldosterone. *Peptides* **2012**, *36*, 142–150.
19. White, A.J.; Heller, J.P.; Leung, J.; Tassoni, A.; Martin, K.R. Retinal ganglion cell neuroprotection by an angiotensin II blocker in an ex vivo retinal explant model. *J. Renin Angiotensin Aldosterone Syst.* **2015**, *16*, 1193–1201.
20. Phipps, J.A.; Vessey, K.A.; Brandli, A.; Nag, N.; Tran, M.X.; Jobling, A.I.; Fletcher, E.L. The Role of Angiotensin II/AT1 Receptor Signaling in Regulating Retinal Microglial Activation. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 487–498.

21. Batenburg, W.W.; Verma, A.; Wang, Y.; Zhu, P.; van den Heuvel, M.; van Veghel, R.; Danser, A.H.; Li, Q. Combined renin inhibition/(pro)renin receptor blockade in diabetic retinopathy—A study in transgenic (mREN2)27 rats. *PLoS ONE* **2014**, *9*, e100954, doi:10.1371/journal.pone.0100954.
22. Liu, F.; Yang, L.; Zheng, Y.; Zhang, W.; Zhi, J. Effects and molecular mechanisms of AT1-AA in retinopathy of preeclampsia. *Acta Biochim. Biophys. Sin. (Shanghai)* **2019**, *51*, 51–58.
23. Nagai, N.; Izumi-Nagai, K.; Oike, Y.; Koto, T.; Satofuka, S.; Ozawa, Y.; Yamashiro, K.; Inoue, M.; Tsubota, K.; Umezawa, K.; et al. Suppression of diabetes-induced retinal inflammation by blocking the angiotensin II type 1 receptor or its downstream nuclear factor-kappaB pathway. *Investig. Ophthalmol. Vis. Sci.* **2007**, *48*, 4342–4350.
24. Danser, A.H.; van den Dorpel, M.A.; Deinum, J.; Derkx, F.H.; Franken, A.A.; Peperkamp, E.; de Jong, P.T.; Schalekamp, M.A. Renin, prorenin, and immunoreactive renin in vitreous fluid from eyes with and without diabetic retinopathy. *J. Clin. Endocrinol. Metab.* **1989**, *68*, 160–167.
25. Funatsu, H.; Yamashita, H.; Nakanishi, Y.; Hori, S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with proliferative diabetic retinopathy. *Br. J. Ophthalmol.* **2002**, *86*, 311–315.
26. Ozawa, Y.; Yuki, K.; Yamagishi, R.; Tsubota, K.; Aihara, M. Renin-angiotensin system involvement in the oxidative stress-induced neurodegeneration of cultured retinal ganglion cells. *Jpn. J. Ophthalmol.* **2013**, *57*, 126–132.
27. Yin, Y.; Huang, S.W.; Zheng, Y.J.; Dong, Y.R. Angiotensin II type 1 receptor blockade suppresses H2O2-induced retinal degeneration in photoreceptor cells. *Cutan. Ocul. Toxicol.* **2015**, *34*, 307–312.
28. Miao, X.; Lv, H.; Wang, B.; Chen, Q.; Miao, L.; Su, G.; Tan, Y. Deletion of angiotensin II type 1 receptor gene attenuates chronic alcohol-induced retinal ganglion cell death with preservation of VEGF expression. *Curr. Eye Res.* **2013**, *38*, 185–193.
29. Narimatsu, T.; Ozawa, Y.; Miyake, S.; Nagai, N.; Tsubota, K. Angiotensin II type 1 receptor blockade suppresses light-induced neural damage in the mouse retina. *Free Radic. Biol. Med.* **2014**, *71*, 176–185.
30. Semba, K.; Namekata, K.; Guo, X.; Harada, C.; Harada, T.; Mitamura, Y. Renin-angiotensin system regulates neurodegeneration in a mouse model of normal tension glaucoma. *Cell Death Dis.* **2014**, *17*, e1333, doi:10.1038/cddis.2014.296.
31. Yang, H.; Hirooka, K.; Fukuda, K.; Shiraga, F. Neuroprotective effects of angiotensin II type 1 receptor blocker in a rat model of chronic glaucoma. *Investig. Ophthalmol. Vis. Sci.* **2009**, *50*, 5800–5804.
32. Quigley, H.A.; Pitha, I.F.; Welsbie, D.S.; Nguyen, C.; Steinhart, M.R.; Nguyen, T.D.; Pease, M.E.; Oglesby, E.N.; Berlinicke, C.A.; Mitchell, K.L.; et al. Losartan Treatment Protects Retinal Ganglion Cells and Alters Scleral Remodeling in Experimental Glaucoma. *PLoS ONE* **2015**, *10*, e0141137, doi:10.1371/journal.pone.0141137.
33. Liu, Y.; Hirooka, K.; Nishiyama, A.; Lei, B.; Nakamura, T.; Itano, T.; Fujita, T.; Zhang, J.; Shiraga, F. Activation of the aldosterone/mineralocorticoid receptor system and protective effects of mineralocorticoid receptor antagonism in retinal ischemia-reperfusion injury. *Exp. Eye Res.* **2012**, *96*, 116–123.
34. Fujita, T.; Hirooka, K.; Nakamura, T.; Itano, T.; Nishiyama, A.; Nagai, Y.; Shiraga, F. Neuroprotective effects of angiotensin II type 1 receptor (AT1-R) blocker via modulating AT1-R signaling and decreased extracellular glutamate levels. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 4099–4110.
35. Tenkumo, K.; Hirooka, K.; Sherajee, S.J.; Nakamura, T.; Itano, T.; Nitta, E.; Fujita, T.; Nishiyama, A.; Shiraga, F. Effect of the renin inhibitor aliskiren against retinal ischemia-reperfusion injury. *Exp. Eye Res.* **2014**, *122*, 110–118.
36. Silva, K.C.; Rosales, M.A.; Biswas, S.K.; Lopes de Faria, J.B.; Lopes de Faria, J.M. Diabetic retinal neurodegeneration is associated with mitochondrial oxidative stress and is improved by an angiotensin receptor blocker in a model combining hypertension and diabetes. *Diabetes* **2009**, *58*, 1382–1390.
37. Ola, M.S.; Ahmed, M.M.; Abuohashish, H.M.; Al-Rejaie, S.S.; Alhomida, A.S. Telmisartan ameliorates neurotrophic support and oxidative stress in the retina of streptozotocin-induced diabetic rats. *Neurochem. Res.* **2013**, *38*, 1572–1579.
38. Thangaraju, P.; Chakrabarti, A.; Banerjee, D.; Hota, D.; Tamilselvan; Bhatia, A.; Gupta, A. Dual blockade of Renin Angiotensin system in reducing the early changes of diabetic retinopathy and nephropathy in a diabetic rat model. *N. Am. J. Med. Sci.* **2014**, *6*, 625–632.
39. Ozawa, Y.; Kurihara, T.; Tsubota, K.; Okano, H. Regulation of posttranscriptional modification as a possible therapeutic approach for retinal neuroprotection. *J. Ophthalmol.* **2011**, *2011*, 506137.

40. Satofuka, S.; Ichihara, A.; Nagai, N.; Noda, K.; Ozawa, Y.; Fukamizu, A.; Tsubota, K.; Itoh, H.; Oike, Y.; Ishida, S. (Pro)renin receptor-mediated signal transduction and tissue renin-angiotensin system contribute to diabetes-induced retinal inflammation. *Diabetes* **2009**, *58*, 1625–1633.
41. Senanayake, P.D.; Bonilha, V.L.; Peterson, W.J.; Yamada, Y.; Karnik, S.S.; Daneshgari, F.; Brosnihan, K.B.; Hollyfield, J.G. Retinal angiotensin II and angiotensin-(1-7) response to hyperglycemia and an intervention with captopril. *J. Renin Angiotensin Aldosterone Syst.* **2018**, *19*, 1470320318789323, doi:10.1177/1470320318789323.
42. Qiu, Y.; Shil, P.K.; Zhu, P.; Yang, H.; Verma, A.; Lei, B.; Li, Q. Angiotensin-converting enzyme 2 (ACE2) activator diminazene aceturate ameliorates endotoxin-induced uveitis in mice. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 3809–3818.
43. Qiu, Y.; Tao, L.; Zheng, S.; Lin, R.; Fu, X.; Chen, Z.; Lei, C.; Wang, J.; Li, H.; Li, Q.; et al. AAV8-Mediated Angiotensin-Converting Enzyme 2 Gene Delivery Prevents Experimental Autoimmune Uveitis by Regulating MAPK, NF-kappaB and STAT3 Pathways. *Sci. Rep.* **2016**, *6*, 31912, doi:10.1038/srep31912.
44. Shil, P.K.; Kwon, K.C.; Zhu, P.; Verma, A.; Daniell, H.; Li, Q. Oral delivery of ACE2/Ang-(1-7) bioencapsulated in plant cells protects against experimental uveitis and autoimmune uveoretinitis. *Mol. Ther.* **2014**, *22*, 2069–2082.
45. Foureaux, G.; Nogueira, B.S.; Coutinho, D.C.; Raizada, M.K.; Nogueira, J.C.; Ferreira, A.J. Activation of endogenous angiotensin converting enzyme 2 prevents early injuries induced by hyperglycemia in rat retina. *Braz. J. Med. Biol. Res.* **2015**, *48*, 1109–1114.
46. Foureaux, G.; Nogueira, J.C.; Nogueira, B.S.; Fulgencio, G.O.; Menezes, G.B.; Fernandes, S.O.; Cardoso, V.N.; Fernandes, R.S.; Oliveira, G.P.; Franca, J.R.; et al. Antiglaucomatous effects of the activation of intrinsic Angiotensin-converting enzyme 2. *Investig. Ophthalmol. Vis. Sci.* **2013**, *54*, 4296–4306.
47. Verma, A.; Shan, Z.; Lei, B.; Yuan, L.; Liu, X.; Nakagawa, T.; Grant, M.B.; Lewin, A.S.; Hauswirth, W.W.; Raizada, M.K.; et al. ACE2 and Ang-(1-7) confer protection against development of diabetic retinopathy. *Mol. Ther.* **2012**, *20*, 28–36.
48. Drucker, D.J.; Nauck, M.A. The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* **2006**, *368*, 1696–1705.
49. Smith, N.K.; Hackett, T.A.; Galli, A.; Flynn, C.R. GLP-1: Molecular mechanisms and outcomes of a complex signaling system. *Neurochem. Int.* **2019**, *128*, 94–105.
50. Hernandez, C.; Bogdanov, P.; Corraliza, L.; Garcia-Ramirez, M.; Sola-Adell, C.; Arranz, J.A.; Arroba, A.I.; Valverde, A.M.; Simo, R. Topical Administration of GLP-1 Receptor Agonists Prevents Retinal Neurodegeneration in Experimental Diabetes. *Diabetes* **2016**, *65*, 172–187.
51. Hebsgaard, J.B.; Pyke, C.; Yildirim, E.; Knudsen, L.B.; Heegaard, S.; Kvist, P.H. Glucagon-like peptide-1 receptor expression in the human eye. *Diabetes Obes. Metab.* **2018**, *20*, 2304–2308.
52. Zhang, Y.; Wang, Q.; Zhang, J.; Lei, X.; Xu, G.T.; Ye, W. Protection of exendin-4 analogue in early experimental diabetic retinopathy. *Graefes Arch. Clin. Exp. Ophthalmol.* **2009**, *247*, 699–706.
53. Cai, X.; Li, J.; Wang, M.; She, M.; Tang, Y.; Li, H.; Hui, H. GLP-1 Treatment Improves Diabetic Retinopathy by Alleviating Autophagy through GLP-1R-ERK1/2-HDAC6 Signaling Pathway. *Int. J. Med. Sci.* **2017**, *14*, 1203–1212.
54. Zhang, Y.; Zhang, J.; Wang, Q.; Lei, X.; Chu, Q.; Xu, G.T.; Ye, W. Intravitreal injection of exendin-4 analogue protects retinal cells in early diabetic rats. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 278–285.
55. Zeng, Y.; Yang, K.; Wang, F.; Zhou, L.; Hu, Y.; Tang, M.; Zhang, S.; Jin, S.; Zhang, J.; Wang, J.; et al. The glucagon like peptide 1 analogue, exendin-4, attenuates oxidative stress-induced retinal cell death in early diabetic rats through promoting Sirt1 and Sirt3 expression. *Exp. Eye Res.* **2016**, *151*, 203–211.
56. Ma, X.; Lin, W.; Lin, Z.; Hao, M.; Gao, X.; Zhang, Y.; Kuang, H. Liraglutide alleviates H2O2-induced retinal ganglion cells injury by inhibiting autophagy through mitochondrial pathways. *Peptides* **2017**, *92*, 1–8.
57. Zhang, R.; Zhang, H.; Xu, L.; Ma, K.; Wallrapp, C.; Jonas, J.B. Effect of intravitreal cell-based produced glucagon-like peptide-1 on Bcl and BAX expression in the optic nerve crush model. *Acta Ophthalmol.* **2012**, 90, e250-2. doi:10.1111/j.1755-3768.2011.02197.x.
58. Zhang, R.; Zhang, H.; Xu, L.; Ma, K.; Wallrapp, C.; Jonas, J.B. Neuroprotective effect of intravitreal cell-based glucagon-like peptide-1 production in the optic nerve crush model. *Acta Ophthalmol.* **2011**, *89*, 1755–3768.

59. Fan, Y.; Liu, K.; Wang, Q.; Ruan, Y.; Ye, W.; Zhang, Y. Exendin-4 alleviates retinal vascular leakage by protecting the blood-retinal barrier and reducing retinal vascular permeability in diabetic Goto-Kakizaki rats. *Exp. Eye Res.* **2014**, *127*, 104–116.
60. Fan, Y.; Liu, K.; Wang, Q.; Ruan, Y.; Zhang, Y.; Ye, W. Exendin-4 protects retinal cells from early diabetes in Goto-Kakizaki rats by increasing the Bcl-2/Bax and Bcl-xL/Bax ratios and reducing reactive gliosis. *Mol. Vis.* **2014**, *20*, 1557–1568.
61. Fu, Z.; Kuang, H.Y.; Hao, M.; Gao, X.Y.; Liu, Y.; Shao, N. Protection of exenatide for retinal ganglion cells with different glucose concentrations. *Peptides* **2012**, *37*, 25–31.
62. Hao, M.; Kuang, H.Y.; Fu, Z.; Gao, X.Y.; Liu, Y.; Deng, W. Exenatide prevents high-glucose-induced damage of retinal ganglion cells through a mitochondrial mechanism. *Neurochem. Int.* **2012**, *61*, 1–6.
63. Dietrich, N.; Kolibabka, M.; Busch, S.; Bugert, P.; Kaiser, U.; Lin, J.; Fleming, T.; Morcos, M.; Klein, T.; Schlotterer, A.; et al. The DPP4 Inhibitor Linagliptin Protects from Experimental Diabetic Retinopathy. *PLoS ONE* **2016**, *11*, e0167853, doi:10.1371/journal.pone.0167853.
64. Hernandez, C.; Bogdanov, P.; Sola-Adell, C.; Sampedro, J.; Valeri, M.; Genis, X.; Simo-Servat, O.; Garcia-Ramirez, M.; Simo, R. Topical administration of DPP-IV inhibitors prevents retinal neurodegeneration in experimental diabetes. *Diabetologia* **2017**, *60*, 2285–2298.
65. Goncalves, A.; Lin, C.M.; Muthusamy, A.; Fontes-Ribeiro, C.; Ambrosio, A.F.; Abcouwer, S.F.; Fernandes, R.; Antonetti, D.A. Protective Effect of a GLP-1 Analog on Ischemia-Reperfusion Induced Blood-Retinal Barrier Breakdown and Inflammation. *Investig. Ophthalmol. Vis. Sci.* **2016**, *57*, 2584–2592.
66. Oberbauer, A.M. Developmental programming: The role of growth hormone. *J. Anim. Sci. Biotechnol.* **2015**, *6*, 8.
67. Harvey, S.; Martinez-Moreno, C.G.; Avila-Mendoza, J.; Luna, M.; Aramburo, C. Growth hormone in the eye: A comparative update. *Gen. Comp. Endocrinol.* **2016**, *234*, 81–87.
68. Perez-Ibave, D.C.; Garza-Rodriguez, M.L.; Perez-Maya, A.A.; Rodriguez-Sanchez, I.P.; Luna-Munoz, M.; Martinez-Moreno, C.G.; Aramburo-de la Hoz, C.; Mohamed-Noriega, J.; Mohamed-Noriega, K.; Mohamed-Hamsho, J.; et al. Expression of growth hormone and growth hormone receptor genes in human eye tissues. *Exp. Eye Res.* **2019**, *181*, 61–71.
69. Perez-Ibave, D.C.; Rodriguez-Sanchez, I.P.; Garza-Rodriguez, M.L.; Perez-Maya, A.A.; Luna, M.; Aramburo, C.; Tsin, A.; Perry, G.; Mohamed-Noriega, K.; Mohamed-Noriega, J.; et al. Expression of growth hormone gene in the baboon eye. *Exp. Eye Res.* **2018**, *169*, 157–169.
70. Ziaei, M.; Tennant, M.; Sanders, E.J.; Harvey, S. Vitreous growth hormone and visual dysfunction. *Neurosci. Lett.* **2009**, *460*, 87–91.
71. Harvey, S.; Martinez-Moreno, C.G.; Luna, M.; Aramburo, C. Autocrine/paracrine roles of extrapituitary growth hormone and prolactin in health and disease: An overview. *Gen. Comp. Endocrinol.* **2015**, *220*, 103–111.
72. Avila-Mendoza, J.; Mora, J.; Carranza, M.; Luna, M.; Aramburo, C. Growth hormone reverses excitotoxic damage induced by kainic acid in the green iguana neuroretina. *Gen. Comp. Endocrinol.* **2016**, *234*, 57–67.
73. Thounaojam, M.C.; Powell, F.L.; Patel, S.; Gutsaeva, D.R.; Tawfik, A.; Smith, S.B.; Nussbaum, J.; Block, N.L.; Martin, P.M.; Schally, A.V.; et al. Protective effects of agonists of growth hormone-releasing hormone (GHRH) in early experimental diabetic retinopathy. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 13248–13253.
74. Martin, B.T.; List, E.O.; Kopchick, J.J.; Sauve, Y.; Harvey, S. Selective inner retinal dysfunction in growth hormone transgenic mice. *Growth Horm. IGF Res.* **2011**, *21*, 219–227.
75. Sanders, E.J.; Parker, E.; Harvey, S. Growth hormone-mediated survival of embryonic retinal ganglion cells: Signaling mechanisms. *Gen. Comp. Endocrinol.* **2008**, *156*, 613–621.
76. Sanders, E.J.; Parker, E.; Harvey, S. Endogenous growth hormone in human retinal ganglion cells correlates with cell survival. *Mol. Vis.* **2009**, *15*, 920–926.
77. Chu, W.K.; Law, K.S.; Chan, S.O.; Yam, J.C.; Chen, L.J.; Zhang, H.; Cheung, H.S.; Block, N.L.; Schally, A.V.; Pang, C.P. Antagonists of growth hormone-releasing hormone receptor induce apoptosis specifically in retinoblastoma cells. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 14396–14401.
78. Sanders, E.J.; Lin, W.Y.; Parker, E.; Harvey, S. Growth hormone promotes the survival of retinal cells in vivo. *Gen. Comp. Endocrinol.* **2011**, *172*, 140–150.
79. Martinez-Moreno, C.G.; Avila-Mendoza, J.; Wu, Y.; Arellanes-Licea Edel, C.; Louie, M.; Luna, M.; Aramburo, C.; Harvey, S. Neuroprotection by GH against excitotoxic-induced cell death in retinal ganglion cells. *Gen. Comp. Endocrinol.* **2016**, *234*, 68–80.

80. Martinez-Moreno, C.G.; Fleming, T.; Carranza, M.; Avila-Mendoza, J.; Luna, M.; Harvey, S.; Aramburo, C. Growth hormone protects against kainate excitotoxicity and induces BDNF and NT3 expression in chicken neuroretinal cells. *Exp. Eye Res.* **2018**, *166*, 1–12.
81. Fleming, T.; Martinez-Moreno, C.G.; Carranza, M.; Luna, M.; Harvey, S.; Aramburo, C. Growth hormone promotes synaptogenesis and protects neuroretinal dendrites against kainic acid (KA) induced damage. *Gen. Comp. Endocrinol.* **2018**, *265*, 111–120.
82. Baudet, M.L.; Rattray, D.; Martin, B.T.; Harvey, S. Growth hormone promotes axon growth in the developing nervous system. *Endocrinology* **2009**, *150*, 2758–2766.
83. Martinez-Moreno, C.G.; Giterman, D.; Henderson, D.; Harvey, S. Secretagogue induction of GH release in QNR/D cells: Prevention of cell death. *Gen. Comp. Endocrinol.* **2014**, *203*, 274–280.
84. Fleming, T.; Martinez-Moreno, C.G.; Mora, J.; Aizouki, M.; Luna, M.; Aramburo, C.; Harvey, S. Internalization and synaptogenic effect of GH in retinal ganglion cells (RGCs). *Gen. Comp. Endocrinol.* **2016**, *234*, 151–160.
85. Sanders, E.J.; Baudet, M.L.; Parker, E.; Harvey, S. Signaling mechanisms mediating local GH action in the neural retina of the chick embryo. *Gen. Comp. Endocrinol.* **2009**, *163*, 63–69.
86. Burren, C.P.; Berka, J.L.; Edmondson, S.R.; Werther, G.A.; Batch, J.A. Localization of mRNAs for insulin-like growth factor-I (IGF-I), IGF-I receptor, and IGF binding proteins in rat eye. *Investig. Ophthalmol. Vis. Sci.* **1996**, *37*, 1459–1468.
87. Santos-Carvalho, A.; Ambrosio, A.F.; Cavadas, C. Neuropeptide Y system in the retina: From localization to function. *Prog. Retin. Eye Res.* **2015**, *47*, 19–37.
88. Santos-Carvalho, A.; Alvaro, A.R.; Martins, J.; Ambrosio, A.F.; Cavadas, C. Emerging novel roles of neuropeptide Y in the retina: From neuromodulation to neuroprotection. *Prog. Neurobiol.* **2014**, *112*, 70–79.
89. Alvaro, A.R.; Martins, J.; Costa, A.C.; Fernandes, E.; Carvalho, F.; Ambrosio, A.F.; Cavadas, C. Neuropeptide Y protects retinal neural cells against cell death induced by ecstasy. *Neuroscience* **2008**, *152*, 97–105.
90. Alvaro, A.R.; Rosmaninho-Salgado, J.; Ambrosio, A.F.; Cavadas, C. Neuropeptide Y inhibits $[Ca^{2+}]i$ changes in rat retinal neurons through NPY Y1, Y4, and Y5 receptors. *J. Neurochem.* **2009**, *109*, 1508–1515.
91. Campos, E.J.; Martins, J.; Brudzewsky, D.; Correia, S.; Santiago, A.R.; Woldbye, D.P.; Ambrosio, A.F. Impact of type 1 diabetes mellitus and sitagliptin treatment on the neuropeptide Y system of rat retina. *Clin. Exp. Ophthalmol.* **2018**, *46*, 783–795.
92. Santos-Carvalho, A.; Elvas, F.; Alvaro, A.R.; Ambrosio, A.F.; Cavadas, C. Neuropeptide Y receptors activation protects rat retinal neural cells against necrotic and apoptotic cell death induced by glutamate. *Cell Death Dis.* **2013**, *4*, e636, doi:10.1038/cddis.2013.160.
93. Martins, J.; Elvas, F.; Brudzewsky, D.; Martins, T.; Kolomiets, B.; Tralhao, P.; Gotzsche, C.R.; Cavadas, C.; Castelo-Branco, M.; Woldbye, D.P.; et al. Activation of Neuropeptide Y Receptors Modulates Retinal Ganglion Cell Physiology and Exerts Neuroprotective Actions In Vitro. *ASN Neuro* **2015**, *7*, 1759091415598292, doi:10.1177/1759091415598292.
94. Christiansen, A.T.; Sorensen, N.B.; Haanes, K.A.; Blixt, F.W.; la Cour, M.; Warfvinge, K.; Klemp, K.; Woldbye, D.P.D.; Kiilgaard, J.F. Neuropeptide Y treatment induces retinal vasoconstriction and causes functional and histological retinal damage in a porcine ischaemia model. *Acta Ophthalmol.* **2018**, *96*, 812–820.
95. Husain, S.; Potter, D.E. The opioidergic system: Potential roles and therapeutic indications in the eye. *J. Ocul. Pharmacol. Ther.* **2008**, *24*, 117–140.
96. Husain, S.; Potter, D.E.; Crosson, C.E. Opioid receptor-activation: Retina protected from ischemic injury. *Investig. Ophthalmol. Vis. Sci.* **2009**, *50*, 3853–3859.
97. Husain, S.; Liou, G.I.; Crosson, C.E. Opioid receptor activation: Suppression of ischemia/reperfusion-induced production of TNF-alpha in the retina. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 2577–2583.
98. Husain, S. Delta Opioids: Neuroprotective Roles in Preclinical Studies. *J. Ocul. Pharmacol. Ther.* **2018**, *34*, 119–128.
99. Husain, S.; Abdul, Y.; Potter, D.E. Non-analgesic effects of opioids: Neuroprotection in the retina. *Curr. Pharm. Des.* **2012**, *18*, 6101–6108.
100. Husain, S.; Abdul, Y.; Crosson, C.E. Preservation of retina ganglion cell function by morphine in a chronic ocular-hypertensive rat model. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 4289–4298.

101. Abdul, Y.; Akhter, N.; Husain, S. Delta-opioid agonist SNC-121 protects retinal ganglion cell function in a chronic ocular hypertensive rat model. *Investig. Ophthalmol. Vis. Sci.* **2013**, *54*, 1816–1828.
102. Husain, S.; Abdul, Y.; Singh, S.; Ahmad, A.; Husain, M. Regulation of nitric oxide production by delta-opioid receptors during glaucomatous injury. *PLoS ONE* **2014**, *9*, e110397, doi:10.1371/journal.pone.0110397.
103. Husain, S.; Ahmad, A.; Singh, S.; Peterseim, C.; Abdul, Y.; Nutaitis, M.J. PI3K/Akt Pathway: A Role in delta-Opioid Receptor-Mediated RGC Neuroprotection. *Investig. Ophthalmol. Vis. Sci.* **2017**, *58*, 6489–6499.
104. Rosales, M.A.; Silva, K.C.; Duarte, D.A.; Rossato, F.A.; Lopes de Faria, J.B.; Lopes de Faria, J.M. Endocytosis of tight junctions caveolin nitrosylation dependent is improved by cocoa via opioid receptor on RPE cells in diabetic conditions. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 6090–6100.
105. Sakamoto, K.; Kuroki, T.; Sagawa, T.; Ito, H.; Mori, A.; Nakahara, T.; Ishii, K. Opioid receptor activation is involved in neuroprotection induced by TRPV1 channel activation against excitotoxicity in the rat retina. *Eur. J. Pharmacol.* **2017**, *812*, 57–63.
106. Wang, X.; Sun, Z.J.; Wu, J.L.; Quan, W.Q.; Xiao, W.D.; Chew, H.; Jiang, C.M.; Li, D. Naloxone attenuates ischemic brain injury in rats through suppressing the NIK/IKKalpha/NF-kappaB and neuronal apoptotic pathways. *Acta Pharmacol. Sin.* **2019**, *40*, 170–179.
107. Liu, B.; Hong, J.S. Role of microglia in inflammation-mediated neurodegenerative diseases: Mechanisms and strategies for therapeutic intervention. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 1–7.
108. Kang, J.; Park, E.J.; Jou, I.; Kim, J.H.; Joe, E.H. Reactive oxygen species mediate A beta (25–35)-induced activation of BV-2 microglia. *Neuroreport* **2001**, *12*, 1449–1452.
109. Ni, Y.Q.; Xu, G.Z.; Hu, W.Z.; Shi, L.; Qin, Y.W.; Da, C.D. Neuroprotective effects of naloxone against light-induced photoreceptor degeneration through inhibiting retinal microglial activation. *Investig. Ophthalmol. Vis. Sci.* **2008**, *49*, 2589–2598.
110. Shen, D.; Cao, X.; Zhao, L.; Tuo, J.; Wong, W.T.; Chan, C.C. Naloxone ameliorates retinal lesions in Ccl2/Cx3cr1 double-deficient mice via modulation of microglia. *Investig. Ophthalmol. Vis. Sci.* **2011**, *52*, 2897–2904.
111. Stagni, E.; Bucolo, C.; Motterlini, R.; Drago, F. Morphine-induced ocular hypotension is modulated by nitric oxide and carbon monoxide: Role of mu3 receptors. *J. Ocul. Pharmacol. Ther.* **2010**, *26*, 31–35.
112. Cervia, D.; Casini, G.; Bagnoli, P. Physiology and pathology of somatostatin in the mammalian retina: A current view. *Mol. Cell. Endocrinol.* **2008**, *286*, 112–122.
113. Casini, G.; Catalani, E.; Dal Monte, M.; Bagnoli, P. Functional aspects of the somatostatinergic system in the retina and the potential therapeutic role of somatostatin in retinal disease. *Histol. Histopathol.* **2005**, *20*, 615–632.
114. Kumar, U.; Grant, M. Somatostatin and somatostatin receptors. *Results Probl. Cell Differ.* **2010**, *50*, 137–184.
115. Cervia, D.; Bagnoli, P. An update on somatostatin receptor signaling in native systems and new insights on their pathophysiology. *Pharmacol. Ther.* **2007**, *116*, 322–341.
116. Cervia, D.; Fehlmann, D.; Hoyer, D. Native somatostatin sst2 and sst5 receptors functionally coupled to Gi/o-protein, but not to the serum response element in AtT-20 mouse tumour corticotrophs. *Naunyn Schmiedebergs Arch. Pharmacol.* **2003**, *367*, 578–587.
117. Cervia, D.; Fiorini, S.; Pavan, B.; Biondi, C.; Bagnoli, P. Somatostatin (SRIF) modulates distinct signaling pathways in rat pituitary tumor cells; negative coupling of SRIF receptor subtypes 1 and 2 to arachidonic acid release. *Naunyn Schmiedebergs Arch. Pharmacol.* **2002**, *365*, 200–209.
118. Cervia, D.; Langenegger, D.; Schuepbach, E.; Cammalleri, M.; Schoeffter, P.; Schmid, H.A.; Bagnoli, P.; Hoyer, D. Binding and functional properties of the novel somatostatin analogue KE 108 at native mouse somatostatin receptors. *Neuropharmacology* **2005**, *48*, 881–893.
119. Cammalleri, M.; Cervia, D.; Dal Monte, M.; Martini, D.; Langenegger, D.; Fehlmann, D.; Feuerbach, D.; Pavan, B.; Hoyer, D.; Bagnoli, P. Compensatory changes in the hippocampus of somatostatin knockout mice: Upregulation of somatostatin receptor 2 and its function in the control of bursting activity and synaptic transmission. *Eur. J. Neurosci.* **2006**, *23*, 2404–2422.
120. Cammalleri, M.; Cervia, D.; Langenegger, D.; Liu, Y.; Dal Monte, M.; Hoyer, D.; Bagnoli, P. Somatostatin receptors differentially affect spontaneous epileptiform activity in mouse hippocampal slices. *Eur. J. Neurosci.* **2004**, *20*, 2711–2721.
121. Thermos, K. Functional mapping of somatostatin receptors in the retina: A review. *Vis. Res.* **2003**, *43*, 1805–1815.

122. Fonollosa, A.; Coronado, E.; Catalan, R.; Gutierrez, M.; Macia, C.; Zapata, M.A.; Martinez-Alday, N.; Simo, R.; Garcia-Arumi, J. Vitreous levels of somatostatin in patients with chronic uveitic macular oedema. *Eye (Lond)* **2012**, *26*, 1378–1383.
123. Simo, R.; Carrasco, E.; Fonollosa, A.; Garcia-Arumi, J.; Casamitjana, R.; Hernandez, C. Deficit of somatostatin in the vitreous fluid of patients with diabetic macular edema. *Diabetes Care* **2007**, *30*, 725–727.
124. Wang, J.; Tian, W.; Wang, S.; Wei, W.; Wu, D.; Wang, H.; Wang, L.; Yang, R.; Ji, A.; Li, Y. Anti-inflammatory and retinal protective effects of capsaicin on ischaemia-induced injuries through the release of endogenous somatostatin. *Clin. Exp. Pharmacol. Physiol.* **2017**, *44*, 803–814.
125. Hernandez, C.; Simo-Servat, O.; Simo, R. Somatostatin and diabetic retinopathy: Current concepts and new therapeutic perspectives. *Endocrine* **2014**, *46*, 209–214.
126. Hernandez, C.; Garcia-Ramirez, M.; Corraliza, L.; Fernandez-Carneado, J.; Farrera-Sinfreu, J.; Ponsati, B.; Gonzalez-Rodriguez, A.; Valverde, A.M.; Simo, R. Topical administration of somatostatin prevents retinal neurodegeneration in experimental diabetes. *Diabetes* **2013**, *62*, 2569–2578.
127. Beltramo, E.; Lopatina, T.; Mazzeo, A.; Arroba, A.I.; Valverde, A.M.; Hernandez, C.; Simo, R.; Porta, M. Effects of the neuroprotective drugs somatostatin and brimonidine on retinal cell models of diabetic retinopathy. *Acta Diabetol.* **2016**, *53*, 957–964.
128. Mazzeo, A.; Arroba, A.I.; Beltramo, E.; Valverde, A.M.; Porta, M. Somatostatin protects human retinal pericytes from inflammation mediated by microglia. *Exp. Eye Res.* **2017**, *164*, 46–54.
129. Amato, R.; Biagioni, M.; Cammalleri, M.; Dal Monte, M.; Casini, G. VEGF as a Survival Factor in Ex Vivo Models of Early Diabetic Retinopathy. *Invest. Ophthalmol. Vis. Sci.* **2016**, *57*, 3066–3076.
130. Arroba, A.I.; Mazzeo, A.; Cazzoni, D.; Beltramo, E.; Hernandez, C.; Porta, M.; Simo, R.; Valverde, A.M. Somatostatin protects photoreceptor cells against high glucose-induced apoptosis. *Mol. Vis.* **2016**, *22*, 1522–1531.
131. Cervia, D.; Catalani, E.; Dal Monte, M.; Casini, G. Vascular endothelial growth factor in the ischemic retina and its regulation by somatostatin. *J. Neurochem.* **2012**, *120*, 818–829.
132. Osborne, N.N.; Casson, R.J.; Wood, J.P.; Chidlow, G.; Graham, M.; Melena, J. Retinal ischemia: Mechanisms of damage and potential therapeutic strategies. *Prog. Retin. Eye Res.* **2004**, *23*, 91–147.
133. Stitt, A.W.; O'Neill, C.L.; O'Doherty, M.T.; Archer, D.B.; Gardiner, T.A.; Medina, R.J. Vascular stem cells and ischaemic retinopathies. *Prog. Retin. Eye Res.* **2011**, *30*, 149–166.
134. Catalani, E.; Cervia, D.; Martini, D.; Bagnoli, P.; Simonetti, E.; Timperio, A.M.; Casini, G. Changes in neuronal response to ischemia in retinas with genetic alterations of somatostatin receptor expression. *Eur. J. Neurosci.* **2007**, *25*, 1447–1459.
135. Cervia, D.; Martini, D.; Ristori, C.; Catalani, E.; Timperio, A.M.; Bagnoli, P.; Casini, G. Modulation of the neuronal response to ischaemia by somatostatin analogues in wild-type and knock-out mouse retinas. *J. Neurochem.* **2008**, *106*, 2224–2235.
136. D'Alessandro, A.; Cervia, D.; Catalani, E.; Gevi, F.; Zolla, L.; Casini, G. Protective effects of the neuropeptides PACAP, substance P and the somatostatin analogue octreotide in retinal ischemia: A metabolomic analysis. *Mol. Biosyst.* **2014**, *10*, 1290–1304.
137. Wang, J.; Sun, Z.; Shen, J.; Wu, D.; Liu, F.; Yang, R.; Ji, S.; Ji, A.; Li, Y. Octreotide Protects the Mouse Retina against Ischemic Reperfusion Injury through Regulation of Antioxidation and Activation of NF-kappaB. *Oxid. Med. Cell. Longev.* **2015**, *2015*, 970156, doi:10.1155/2015/970156.
138. Kokona, D.; Mastrodimou, N.; Pediaditakis, I.; Charalampopoulos, I.; Schmid, H.A.; Thermos, K. Pasireotide (SOM230) protects the retina in animal models of ischemia induced retinopathies. *Exp. Eye Res.* **2012**, *103*, 90–98.
139. Amato, R.; Catalani, E.; Dal Monte, M.; Cammalleri, M.; Di Renzo, I.; Perrotta, C.; Cervia, D.; Casini, G. Autophagy-mediated neuroprotection induced by octreotide in an ex vivo model of early diabetic retinopathy. *Pharmacol. Res.* **2018**, *128*, 167–178.
140. Cammalleri, M.; Locri, F.; Catalani, E.; Filippi, L.; Cervia, D.; Dal Monte, M.; Bagnoli, P. The Beta Adrenergic Receptor Blocker Propranolol Counteracts Retinal Dysfunction in a Mouse Model of Oxygen Induced Retinopathy: Restoring the Balance between Apoptosis and Autophagy. *Front. Cell. Neurosci.* **2017**, *11*, 395, doi:10.3389/fncel.2017.00395.
141. Onaga, T. Tachykinin: Recent developments and novel roles in health and disease. *Biomol. Concepts* **2014**, *5*, 225–243.

142. Catalani, E.; Dal Monte, M.; Gangitano, C.; Lucattelli, M.; Fineschi, S.; Bosco, L.; Bagnoli, P.; Casini, G. Expression of substance P, neurokinin 1 receptors (NK1) and neurokinin 3 receptors in the developing mouse retina and in the retina of NK1 knockout mice. *Neuroscience* **2006**, *138*, 487–499.
143. Schmid, E.; Leierer, J.; Kieselbach, G.; Teuchner, B.; Kralinger, M.; Fischer-Colbrie, R.; Krause, J.E.; Nguyen, Q.A.; Haas, G.; Stemberger, K.; et al. Neurokinin A and neurokinin B in the human retina. *Peptides* **2006**, *27*, 3370–3376.
144. Lorenz, K.; Troger, J.; Fischer-Colbrie, R.; Kremser, B.; Schmid, E.; Kralinger, M.; Teuchner, B.; Bechrakis, N.; Kieselbach, G. Substance P and secretoneurin in vitreous aspirates of patients with various vitreoretinal diseases. *Peptides* **2008**, *29*, 1561–1565.
145. Yang, J.H.; Meng, X.X.; Xie, L.S.; Guo, Z. Acute myocardial ischemia up-regulates substance P in the retina of rats. *Neurosci. Lett.* **2008**, *443*, 218–222.
146. Yang, J.H.; Guo, Z.; Zhang, T.; Meng, X.X.; Xie, L.S. Restoration of endogenous substance P is associated with inhibition of apoptosis of retinal cells in diabetic rats. *Regul. Pept.* **2013**, *187*, 12–16.
147. Teuchner, B.; Dimmer, A.; Troger, J.; Fischer-Colbrie, R.; Schmid, E.; Kieselbach, G.; Dietrich, H.; Bechrakis, N. Secretoneurin and the tachykinins substance P and neurokinin-A/B in NMDA-induced excitotoxicity in the rat retina. *Regul. Pept.* **2010**, *165*, 123–127.
148. Hong, H.S.; Kim, S.; Nam, S.; Um, J.; Kim, Y.H.; Son, Y. Effect of substance P on recovery from laser-induced retinal degeneration. *Wound Repair Regen. Off. Publ. Wound Heal. Soc. Eur. Tissue Repair Soc.* **2015**, *23*, 268–277.
149. Yoo, K.; Son, B.K.; Kim, S.; Son, Y.; Yu, S.Y.; Hong, H.S. Substance P prevents development of proliferative vitreoretinopathy in mice by modulating TNF-alpha. *Mol. Vis.* **2017**, *23*, 933–943.
150. Sakamoto, K.; Kuroki, T.; Okuno, Y.; Sekiya, H.; Watanabe, A.; Sagawa, T.; Ito, H.; Mizuta, A.; Mori, A.; Nakahara, T.; et al. Activation of the TRPV1 channel attenuates N-methyl-D-aspartic acid-induced neuronal injury in the rat retina. *Eur. J. Pharmacol.* **2014**, *733*, 13–22.
151. Ou, K.; Mertsch, S.; Theodoropoulou, S.; Wu, J.; Liu, J.; Copland, D.A.; Schrader, S.; Liu, L.; Dick, A.D. Restoring retinal neurovascular health via substance P. *Exp. Cell Res.* **2019**, *380*, 115–123.
152. Baek, S.M.; Yu, S.Y.; Son, Y.; Hong, H.S. Substance P promotes the recovery of oxidative stress-damaged retinal pigmented epithelial cells by modulating Akt/GSK-3beta signaling. *Mol. Vis.* **2016**, *22*, 1015–1023.
153. Vaudry, D.; Falluel-Morel, A.; Bourgault, S.; Basille, M.; Burel, D.; Wurtz, O.; Fournier, A.; Chow, B.K.; Hashimoto, H.; Galas, L.; et al. Pituitary adenylate cyclase-activating polypeptide and its receptors: 20 years after the discovery. *Pharmacol. Rev.* **2009**, *61*, 283–357.
154. Deng, G.; Jin, L. The effects of vasoactive intestinal peptide in neurodegenerative disorders. *Neurol. Res.* **2017**, *39*, 65–72.
155. Bourgault, S.; Vaudry, D.; Dejda, A.; Doan, N.D.; Vaudry, H.; Fournier, A. Pituitary adenylate cyclase-activating polypeptide: Focus on structure-activity relationships of a neuroprotective Peptide. *Curr. Med. Chem.* **2009**, *16*, 4462–4480.
156. Lee, E.H.; Seo, S.R. Neuroprotective roles of pituitary adenylate cyclase-activating polypeptide in neurodegenerative diseases. *BMB Rep.* **2014**, *47*, 369–375.
157. Ohtaki, H.; Nakamachi, T.; Dohi, K.; Shioda, S. Role of PACAP in ischemic neural death. *J. Mol. Neurosci.* **2008**, *36*, 16–25.
158. Reglodi, D.; Kiss, P.; Lubics, A.; Tamas, A. Review on the protective effects of PACAP in models of neurodegenerative diseases in vitro and in vivo. *Curr. Pharm. Des.* **2011**, *17*, 962–972.
159. Reglodi, D.; Tamas, A.; Jungling, A.; Vaczy, A.; Rivnyak, A.; Fulop, B.D.; Szabo, E.; Lubics, A.; Atlasz, T. Protective effects of pituitary adenylate cyclase activating polypeptide against neurotoxic agents. *Neurotoxicology* **2018**, *66*, 185–194.
160. Reglodi, D.; Vaczy, A.; Rubio-Beltran, E.; MaassenVanDenBrink, A. Protective effects of PACAP in ischemia. *J. Headache Pain* **2018**, *19*, 018–0845.
161. Rivnyak, A.; Kiss, P.; Tamas, A.; Balogh, D.; Reglodi, D. Review on PACAP-Induced Transcriptomic and Proteomic Changes in Neuronal Development and Repair. *Int. J. Mol. Sci.* **2018**, *19*, 1020, doi:10.3390/ijms19041020.
162. Shioda, S.; Nakamachi, T. PACAP as a neuroprotective factor in ischemic neuronal injuries. *Peptides* **2015**, *72*, 202–207.

163. Shioda, S.; Ohtaki, H.; Nakamachi, T.; Dohi, K.; Watanabe, J.; Nakajo, S.; Arata, S.; Kitamura, S.; Okuda, H.; Takenoya, F.; et al. Pleiotropic functions of PACAP in the CNS: Neuroprotection and neurodevelopment. *Ann. N. Y. Acad. Sci.* **2006**, *1070*, 550–560.
164. Tamas, A.; Reglodi, D.; Farkas, O.; Kovesdi, E.; Pal, J.; Povlishock, J.T.; Schwarcz, A.; Czeiter, E.; Szanto, Z.; Doczi, T.; et al. Effect of PACAP in central and peripheral nerve injuries. *Int. J. Mol. Sci.* **2012**, *13*, 8430–8448.
165. Yang, R.; Jiang, X.; Ji, R.; Meng, L.; Liu, F.; Chen, X.; Xin, Y. Therapeutic potential of PACAP for neurodegenerative diseases. *Cell. Mol. Biol. Lett.* **2015**, *20*, 265–278.
166. Perez de Sevilla Muller, L.; Solomon, A.; Sheets, K.; Hapukino, H.; Rodriguez, A.R.; Brecha, N.C. Multiple cell types form the VIP amacrine cell population. *J. Comp. Neurol.* **2019**, *527*, 133–158.
167. Izumi, S.; Seki, T.; Shioda, S.; Zhou, C.J.; Arimura, A.; Koide, R. Ultrastructural localization of PACAP immunoreactivity in the rat retina. *Ann. N. Y. Acad. Sci.* **2000**, *921*, 317–320.
168. Seki, T.; Shioda, S.; Izumi, S.; Arimura, A.; Koide, R. Electron microscopic observation of pituitary adenylate cyclase-activating polypeptide (PACAP)-containing neurons in the rat retina. *Peptides* **2000**, *21*, 109–113.
169. Hannibal, J.; Fahrenkrug, J. Target areas innervated by PACAP-immunoreactive retinal ganglion cells. *Cell Tissue Res.* **2004**, *316*, 99–113.
170. Seki, T.; Izumi, S.; Shioda, S.; Zhou, C.J.; Arimura, A.; Koide, R. Gene expression for PACAP receptor mRNA in the rat retina by in situ hybridization and in situ RT-PCR. *Ann. N. Y. Acad. Sci.* **2000**, *921*, 366–369.
171. Seki, T.; Shioda, S.; Ogino, D.; Nakai, Y.; Arimura, A.; Koide, R. Distribution and ultrastructural localization of a receptor for pituitary adenylate cyclase activating polypeptide and its mRNA in the rat retina. *Neurosci. Lett.* **1997**, *238*, 127–130.
172. Seki, T.; Hinohara, Y.; Taki, C.; Nakatani, M.; Ozawa, M.; Nishimura, S.; Takaki, A.; Itho, H.; Takenoya, F.; Shioda, S. PACAP stimulates the release of interleukin-6 in cultured rat Muller cells. *Ann. N. Y. Acad. Sci.* **2006**, *1070*, 535–539.
173. Denes, V.; Hideg, O.; Nyisztor, Z.; Lakk, M.; Godri, Z.; Berta, G.; Geck, P.; Gabriel, R. The Neuroprotective Peptide PACAP1-38 Contributes to Horizontal Cell Development in Postnatal Rat Retina. *Investig. Ophthalmol. Vis. Sci.* **2019**, *60*, 770–778.
174. Akrouh, A.; Kerschensteiner, D. Morphology and function of three VIP-expressing amacrine cell types in the mouse retina. *J. Neurophysiol.* **2015**, *114*, 2431–2438.
175. Dragich, J.M.; Loh, D.H.; Wang, L.M.; Vosko, A.M.; Kudo, T.; Nakamura, T.J.; Odom, I.H.; Tateyama, S.; Hagopian, A.; Waschek, J.A.; et al. The role of the neuropeptides PACAP and VIP in the photic regulation of gene expression in the suprachiasmatic nucleus. *Eur. J. Neurosci.* **2010**, *31*, 864–875.
176. Webb, I.C.; Coolen, L.M.; Lehman, M.N. NMDA and PACAP receptor signaling interact to mediate retinal-induced scn cellular rhythmicity in the absence of light. *PLoS ONE* **2013**, *8*, e76365, doi:10.1371/journal.pone.0076365.
177. Gompf, H.S.; Fuller, P.M.; Hattar, S.; Saper, C.B.; Lu, J. Impaired circadian photosensitivity in mice lacking glutamate transmission from retinal melanopsin cells. *J. Biol. Rhythm.* **2015**, *30*, 35–41.
178. Shoge, K.; Mishima, H.K.; Saitoh, T.; Ishihara, K.; Tamura, Y.; Shiomi, H.; Sasa, M. Protective effects of vasoactive intestinal peptide against delayed glutamate neurotoxicity in cultured retina. *Brain Res.* **1998**, *809*, 127–136.
179. Tuncel, N.; Basmak, H.; Uzuner, K.; Tuncel, M.; Altiokka, G.; Zaimoglu, V.; Ozer, A.; Gurer, F. Protection of rat retina from ischemia-reperfusion injury by vasoactive intestinal peptide (VIP): The effect of VIP on lipid peroxidation and antioxidant enzyme activity of retina and choroid. *Ann. N. Y. Acad. Sci.* **1996**, *805*, 489–498.
180. Jiang, M.N.; Zhou, Y.Y.; Hua, D.H.; Yang, J.Y.; Hu, M.L.; Xing, Y.Q. Vagal Nerve Stimulation Attenuates Ischemia-Reperfusion Induced Retina Dysfunction in Acute Ocular Hypertension. *Front. Neurosci.* **2019**, *13*, 87, doi:10.3389/fnins.2019.00087.
181. Atlasz, T.; Werling, D.; Song, S.; Szabo, E.; Vaczy, A.; Kovari, P.; Tamas, A.; Reglodi, D.; Yu, R. Retinoprotective Effects of TAT-Bound Vasoactive Intestinal Peptide and Pituitary Adenylate Cyclase Activating Polypeptide. *J. Mol. Neurosci.* **2018**, *12*, 018–1229.
182. Szabadfi, K.; Danyadi, B.; Kiss, P.; Tamas, A.; Fabian, E.; Gabriel, R.; Reglodi, D. Protective effects of vasoactive intestinal peptide (VIP) in ischemic retinal degeneration. *J. Mol. Neurosci.* **2012**, *48*, 501–507.

183. Maugeri, G.; D'Amico, A.G.; Gagliano, C.; Saccone, S.; Federico, C.; Cavallaro, S.; D'Agata, V. VIP Family Members Prevent Outer Blood Retinal Barrier Damage in a Model of Diabetic Macular Edema. *J. Cell. Physiol.* **2017**, *232*, 1079–1085.
184. Scuderi, S.; D'Amico, A.G.; Castorina, A.; Imbesi, R.; Carnazza, M.L.; D'Agata, V. Ameliorative effect of PACAP and VIP against increased permeability in a model of outer blood retinal barrier dysfunction. *Peptides* **2013**, *39*, 119–124.
185. Maugeri, G.; D'Amico, A.G.; Saccone, S.; Federico, C.; Cavallaro, S.; D'Agata, V. PACAP and VIP Inhibit HIF-1alpha-Mediated VEGF Expression in a Model of Diabetic Macular Edema. *J. Cell. Physiol.* **2017**, *232*, 1209–1215.
186. Zusev, M.; Gozes, I. Differential regulation of activity-dependent neuroprotective protein in rat astrocytes by VIP and PACAP. *Regul. Pept.* **2004**, *123*, 33–41.
187. Giladi, E.; Hill, J.M.; Dresner, E.; Stack, C.M.; Gozes, I. Vasoactive intestinal peptide (VIP) regulates activity-dependent neuroprotective protein (ADNP) expression in vivo. *J. Mol. Neurosci.* **2007**, *33*, 278–283.
188. Bassan, M.; Zamostiano, R.; Davidson, A.; Pinhasov, A.; Giladi, E.; Perl, O.; Bassan, H.; Blat, C.; Gibney, G.; Glazner, G.; et al. Complete sequence of a novel protein containing a femtomolar-activity-dependent neuroprotective peptide. *J. Neurochem.* **1999**, *72*, 1283–1293.
189. Magen, I.; Gozes, I. Davunetide: Peptide therapeutic in neurological disorders. *Curr. Med. Chem.* **2014**, *21*, 2591–2598.
190. Lagreze, W.A.; Pielen, A.; Steingart, R.; Schlunck, G.; Hofmann, H.D.; Gozes, I.; Kirsch, M. The peptides ADNF-9 and NAP increase survival and neurite outgrowth of rat retinal ganglion cells in vitro. *Investig. Ophthalmol. Vis. Sci.* **2005**, *46*, 933–938.
191. Jehle, T.; Dimitriu, C.; Auer, S.; Knoth, R.; Vidal-Sanz, M.; Gozes, I.; Lagreze, W.A. The neuropeptide NAP provides neuroprotection against retinal ganglion cell damage after retinal ischemia and optic nerve crush. *Graefes Arch. Clin. Exp. Ophthalmol.* **2008**, *246*, 1255–1263.
192. Belokopytov, M.; Shulman, S.; Dubinsky, G.; Gozes, I.; Belkin, M.; Rosner, M. Ameliorative effect of NAP on laser-induced retinal damage. *Acta Ophthalmol.* **2011**, *89*, 1755–3768.
193. Zheng, Y.; Zeng, H.; She, H.; Liu, H.; Sun, N. Expression of peptide NAP in rat retinal Muller cells prevents hypoxia-induced retinal injuries and promotes retinal neurons growth. *Biomed. Pharmacother.* **2010**, *64*, 417–423.
194. D'Amico, A.G.; Maugeri, G.; Rasa, D.; Federico, C.; Saccone, S.; Lazzara, F.; Fidilio, A.; Drago, F.; Bucolo, C.; D'Agata, V. NAP modulates hyperglycemic-inflammatory event of diabetic retina by counteracting outer blood retinal barrier damage. *J. Cell. Physiol.* **2019**, *234*, 5230–5240.
195. Scuderi, S.; D'Amico, A.G.; Castorina, A.; Federico, C.; Marrazzo, G.; Drago, F.; Bucolo, C.; D'Agata, V. Davunetide (NAP) protects the retina against early diabetic injury by reducing apoptotic death. *J. Mol. Neurosci.* **2014**, *54*, 395–404.
196. D'Amico, A.G.; Maugeri, G.; Bucolo, C.; Saccone, S.; Federico, C.; Cavallaro, S.; D'Agata, V. Nap Interferes with Hypoxia-Inducible Factors and VEGF Expression in Retina of Diabetic Rats. *J. Mol. Neurosci.* **2017**, *61*, 256–266.
197. D'Amico, A.G.; Maugeri, G.; Rasa, D.M.; La Cognata, V.; Saccone, S.; Federico, C.; Cavallaro, S.; D'Agata, V. NAP counteracts hyperglycemia/hypoxia induced retinal pigment epithelial barrier breakdown through modulation of HIFs and VEGF expression. *J. Cell. Physiol.* **2018**, *233*, 1120–1128.
198. Atlasz, T.; Szabadfi, K.; Kiss, P.; Racz, B.; Gallyas, F.; Tamas, A.; Gaal, V.; Marton, Z.; Gabriel, R.; Reglodi, D. Pituitary adenylate cyclase activating polypeptide in the retina: Focus on the retinoprotective effects. *Ann. N. Y. Acad. Sci.* **2010**, *1200*, 128–139.
199. Nakamachi, T.; Matkovits, A.; Seki, T.; Shioda, S. Distribution and protective function of pituitary adenylate cyclase-activating polypeptide in the retina. *Front. Endocrinol.* **2012**, *3*, 145, doi:10.3389/fendo.2012.00145.
200. Shioda, S.; Takenoya, F.; Wada, N.; Hirabayashi, T.; Seki, T.; Nakamachi, T. Pleiotropic and retinoprotective functions of PACAP. *Anat. Sci. Int.* **2016**, *91*, 313–324.
201. Kovacs-Valasek, A.; Szabadfi, K.; Denes, V.; Szalontai, B.; Tamas, A.; Kiss, P.; Szabo, A.; Setalo, G., Jr.; Reglodi, D.; Gabriel, R. Accelerated retinal aging in PACAP knock-out mice. *Neuroscience* **2017**, *348*, 1–10.
202. Lewis, G.P.; Fisher, S.K. Up-regulation of glial fibrillary acidic protein in response to retinal injury: Its potential role in glial remodeling and a comparison to vimentin expression. *Int. Rev. Cytol.* **2003**, *230*, 263–290.

203. Vaczy, A.; Kovari, P.; Kovacs, K.; Farkas, K.; Szabo, E.; Kvarik, T.; Kocsis, B.; Fulop, B.; Atlasz, T.; Reglodi, D. Protective Role of Endogenous PACAP in Inflammation-induced Retinal Degeneration. *Curr. Pharm. Des.* **2018**, *24*, 3534–3542.
204. Ye, D.; Yang, Y.; Lu, X.; Xu, Y.; Shi, Y.; Chen, H.; Huang, J. Spatiotemporal Expression Changes of PACAP and Its Receptors in Retinal Ganglion Cells After Optic Nerve Crush. *J. Mol. Neurosci.* **2018**, *10*, 018–1203.
205. Lakk, M.; Denes, V.; Gabriel, R. Pituitary Adenylate Cyclase-Activating Polypeptide Receptors Signal via Phospholipase C Pathway to Block Apoptosis in Newborn Rat Retina. *Neurochem. Res.* **2015**, *40*, 1402–1409.
206. Ye, D.; Shi, Y.; Xu, Y.; Huang, J. PACAP Attenuates Optic Nerve Crush-Induced Retinal Ganglion Cell Apoptosis Via Activation of the CREB-Bcl-2 Pathway. *J. Mol. Neurosci.* **2019**, *68*, 475–484.
207. Green, B.D.; Irwin, N.; Flatt, P.R. Pituitary adenylate cyclase-activating peptide (PACAP): Assessment of dipeptidyl peptidase IV degradation, insulin-releasing activity and antidiabetic potential. *Peptides* **2006**, *27*, 1349–1358.
208. Cheng, H.; Ding, Y.; Yu, R.; Chen, J.; Wu, C. Neuroprotection of a novel cyclopeptide C*HSDGIC* from the cyclization of PACAP (1-5) in cellular and rodent models of retinal ganglion cell apoptosis. *PLoS ONE* **2014**, *9*, e108090.
209. Danyadi, B.; Szabadfi, K.; Reglodi, D.; Mihalik, A.; Danyadi, T.; Kovacs, Z.; Batai, I.; Tamas, A.; Kiss, P.; Toth, G.; et al. PACAP application improves functional outcome of chronic retinal ischemic injury in rats-evidence from electroretinographic measurements. *J. Mol. Neurosci.* **2014**, *54*, 293–299.
210. Vaczy, A.; Reglodi, D.; Somoskeoy, T.; Kovacs, K.; Lokos, E.; Szabo, E.; Tamas, A.; Atlasz, T. The Protective Role of PAC1-Receptor Agonist Maxadilan in BCCAO-Induced Retinal Degeneration. *J. Mol. Neurosci.* **2016**, *60*, 186–194.
211. Werling, D.; Banks, W.A.; Salameh, T.S.; Kvarik, T.; Kovacs, L.A.; Vaczy, A.; Szabo, E.; Mayer, F.; Varga, R.; Tamas, A.; et al. Passage through the Ocular Barriers and Beneficial Effects in Retinal Ischemia of Topical Application of PACAP1-38 in Rodents. *Int. J. Mol. Sci.* **2017**, *18*, 675, doi:10.3390/ijms18030675.
212. Werling, D.; Reglodi, D.; Banks, W.A.; Salameh, T.S.; Kovacs, K.; Kvarik, T.; Vaczy, A.; Kovacs, L.; Mayer, F.; Danyadi, B.; et al. Ocular Delivery of PACAP1-27 Protects the Retina From Ischemic Damage in Rodents. *Investig. Ophthalmol. Vis. Sci.* **2016**, *57*, 6683–6691.
213. Szabadfi, K.; Szabo, A.; Kiss, P.; Reglodi, D.; Setalo, G., Jr.; Kovacs, K.; Tamas, A.; Toth, G.; Gabriel, R. PACAP promotes neuron survival in early experimental diabetic retinopathy. *Neurochem. Int.* **2014**, *64*, 84–91.
214. Szabadfi, K.; Reglodi, D.; Szabo, A.; Szalontai, B.; Valasek, A.; Setalo, G., Jr.; Kiss, P.; Tamas, A.; Wilhelm, M.; Gabriel, R. Pituitary Adenylate Cyclase Activating Polypeptide, A Potential Therapeutic Agent for Diabetic Retinopathy in Rats: Focus on the Vertical Information Processing Pathway. *Neurotox. Res.* **2016**, *29*, 432–446.
215. D'Amico, A.G.; Maugeri, G.; Rasa, D.M.; Bucolo, C.; Saccone, S.; Federico, C.; Cavallaro, S.; D'Agata, V. Modulation of IL-1beta and VEGF expression in rat diabetic retinopathy after PACAP administration. *Peptides* **2017**, *97*, 64–69.
216. D'Amico, A.G.; Maugeri, G.; Reitano, R.; Bucolo, C.; Saccone, S.; Drago, F.; D'Agata, V. PACAP Modulates Expression of Hypoxia-Inducible Factors in Streptozotocin-Induced Diabetic Rat Retina. *J. Mol. Neurosci.* **2015**, *57*, 501–509.
217. Wardlaw, S.L. Hypothalamic proopiomelanocortin processing and the regulation of energy balance. *Eur. J. Pharmacol.* **2011**, *660*, 213–219.
218. Yang, Y. Structure, function and regulation of the melanocortin receptors. *Eur. J. Pharmacol.* **2011**, *660*, 125–130.
219. Zhang, Y.; Kerman, I.A.; Laque, A.; Nguyen, P.; Faouzi, M.; Louis, G.W.; Jones, J.C.; Rhodes, C.; Munzberg, H. Leptin-receptor-expressing neurons in the dorsomedial hypothalamus and median preoptic area regulate sympathetic brown adipose tissue circuits. *J. Neurosci.* **2011**, *31*, 1873–1884.
220. Nohara, K.; Zhang, Y.; Waraich, R.S.; Laque, A.; Tiano, J.P.; Tong, J.; Munzberg, H.; Mauvais-Jarvis, F. Early-life exposure to testosterone programs the hypothalamic melanocortin system. *Endocrinology* **2011**, *152*, 1661–1669.
221. Forslin Aronsson, S.; Spulber, S.; Popescu, L.M.; Winblad, B.; Post, C.; Oprica, M.; Schultzberg, M. alpha-Melanocyte-stimulating hormone is neuroprotective in rat global cerebral ischemia. *Neuropeptides* **2006**, *40*, 65–75.

222. Zhang, Y.; Bo, Q.; Wu, W.; Xu, C.; Yu, G.; Ma, S.; Yang, Q.; Cao, Y.; Han, Q.; Ru, Y.; et al. Alpha-Melanocyte-stimulating hormone prevents glutamate excitotoxicity in developing chicken retina via MC4R-mediated down-regulation of microRNA-194. *Sci. Rep.* **2015**, *5*, 15812, doi:10.1038/srep15812.
223. Varga, B.; Gesztelyi, R.; Bombicz, M.; Haines, D.; Szabo, A.M.; Kemeny-Beke, A.; Antal, M.; Vecsernyes, M.; Juhasz, B.; Tosaki, A. Protective effect of alpha-melanocyte-stimulating hormone (alpha-MSH) on the recovery of ischemia/reperfusion (I/R)-induced retinal damage in a rat model. *J. Mol. Neurosci.* **2013**, *50*, 558–570.
224. Edling, A.E.; Gomes, D.; Weeden, T.; Dzuris, J.; Stefano, J.; Pan, C.; Williams, J.; Kaplan, J.; Perricone, M.A. Immunosuppressive activity of a novel peptide analog of alpha-melanocyte stimulating hormone (alpha-MSH) in experimental autoimmune uveitis. *J. Neuroimmunol.* **2011**, *236*, 1–9.
225. Naveh, N. Melanocortins applied intravitreally delay retinal dystrophy in Royal College of Surgeons rats. *Graefes Arch. Clin. Exp. Ophthalmol.* **2003**, *241*, 1044–1050.
226. Zhang, L.; Dong, L.; Liu, X.; Jiang, Y.; Zhang, X.; Li, X.; Zhang, Y. Alpha-Melanocyte-stimulating hormone protects retinal vascular endothelial cells from oxidative stress and apoptosis in a rat model of diabetes. *PLoS ONE* **2014**, *9*, e93433, doi:10.1371/journal.pone.0093433.
227. Cai, S.; Yang, Q.; Hou, M.; Han, Q.; Zhang, H.; Wang, J.; Qi, C.; Bo, Q.; Ru, Y.; Yang, W.; et al. Alpha-Melanocyte-Stimulating Hormone Protects Early Diabetic Retina from Blood-Retinal Barrier Breakdown and Vascular Leakage via MC4R. *Cell. Physiol. Biochem.* **2018**, *45*, 505–522.
228. Tatemoto, K.; Hosoya, M.; Habata, Y.; Fujii, R.; Kakegawa, T.; Zou, M.X.; Kawamata, Y.; Fukusumi, S.; Hinuma, S.; Kitada, C.; et al. Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor. *Biochem. Biophys. Res. Commun.* **1998**, *251*, 471–476.
229. Ishimaru, Y.; Sumino, A.; Kajioka, D.; Shibagaki, F.; Yamamuro, A.; Yoshioka, Y.; Maeda, S. Apelin protects against NMDA-induced retinal neuronal death via an APJ receptor by activating Akt and ERK1/2, and suppressing TNF-alpha expression in mice. *J. Pharmacol. Sci.* **2017**, *133*, 34–41.
230. Lu, Q.; Jiang, Y.R.; Qian, J.; Tao, Y. Apelin-13 regulates proliferation, migration and survival of retinal Muller cells under hypoxia. *Diabetes Res. Clin. Pract.* **2013**, *99*, 158–167.
231. Wang, X.L.; Tao, Y.; Lu, Q.; Jiang, Y.R. Apelin supports primary rat retinal Muller cells under chemical hypoxia and glucose deprivation. *Peptides* **2012**, *33*, 298–306.
232. Sakamoto, K.; Murakami, Y.; Sawada, S.; Ushikubo, H.; Mori, A.; Nakahara, T.; Ishii, K. Apelin-36 is protective against N-methyl-D-aspartic-acid-induced retinal ganglion cell death in the mice. *Eur. J. Pharmacol.* **2016**, *791*, 213–220.
233. Phipps, J.A.; Feener, E.P. The kallikrein-kinin system in diabetic retinopathy: Lessons for the kidney. *Kidney Int.* **2008**, *73*, 1114–1119.
234. Feener, E.P. Plasma kallikrein and diabetic macular edema. *Curr. Diabetes Rep.* **2010**, *10*, 270–275.
235. Regoli, D.; Nsa Allogho, S.; Rizzi, A.; Gobeil, F.J. Bradykinin receptors and their antagonists. *Eur. J. Pharmacol.* **1998**, *348*, 1–10.
236. Pouliot, M.; Talbot, S.; Senecal, J.; Dotigny, F.; Vaucher, E.; Couture, R. Ocular application of the kinin B1 receptor antagonist LF22-0542 inhibits retinal inflammation and oxidative stress in streptozotocin-diabetic rats. *PLoS ONE* **2012**, *7*, e33864, doi:10.1371/journal.pone.0033864.
237. Abdouh, M.; Khanjari, A.; Abdelazziz, N.; Ongali, B.; Couture, R.; Hassessian, H.M. Early upregulation of kinin B1 receptors in retinal microvessels of the streptozotocin-diabetic rat. *Br. J. Pharmacol.* **2003**, *140*, 33–40.
238. Abdouh, M.; Talbot, S.; Couture, R.; Hassessian, H.M. Retinal plasma extravasation in streptozotocin-diabetic rats mediated by kinin B(1) and B(2) receptors. *Br. J. Pharmacol.* **2008**, *154*, 136–143.
239. Catanzaro, O.; Labal, E.; Andornino, A.; Capponi, J.A.; Di Martino, I.; Sirois, P. Blockade of early and late retinal biochemical alterations associated with diabetes development by the selective bradykinin B1 receptor antagonist R-954. *Peptides* **2012**, *34*, 349–352.
240. Arredondo Zamarripa, D.; Diaz-Lezama, N.; Melendez Garcia, R.; Chavez Balderas, J.; Adan, N.; Ledesma-Colunga, M.G.; Arnold, E.; Clapp, C.; Thebault, S. Vasoinhibins regulate the inner and outer blood-retinal barrier and limit retinal oxidative stress. *Front. Cell. Neurosci.* **2014**, *8*, 333, doi:10.3389/fncel.2014.00333.
241. Cheng, Y.; Yu, X.; Zhang, J.; Chang, Y.; Xue, M.; Li, X.; Lu, Y.; Li, T.; Meng, Z.; Su, L.; et al. Pancreatic kallikrein protects against diabetic retinopathy in KK Cg-A(y)/J and high-fat diet/streptozotocin-induced mouse models of type 2 diabetes. *Diabetologia* **2019**, *62*, 1074–1086.

242. Blixt, F.W.; Radziwon-Balicka, A.; Edvinsson, L.; Warfvinge, K. Distribution of CGRP and its receptor components CLR and RAMP1 in the rat retina. *Exp. Eye Res.* **2017**, *161*, 124–131.
243. Yang, J.H.; Zhang, Y.Q.; Guo, Z. Endogenous CGRP protects retinal cells against stress induced apoptosis in rats. *Neurosci. Lett.* **2011**, *501*, 83–85.
244. Yang, J.H.; Guo, Z.; Zhang, T.; Meng, X.X.; Sun, T.; Wu, J. STZ treatment induced apoptosis of retinal cells and effect of up-regulation of calcitonin gene related peptide in rats. *J. Diabetes Complicat.* **2013**, *27*, 531–537.
245. Lv, Y.; Liang, T.; Wang, G.; Li, Z. Ghrelin, a gastrointestinal hormone, regulates energy balance and lipid metabolism. *Biosci. Rep.* **2018**, *38*, BSR20181061, doi:10.1042/BSR20181061.
246. Katsanos, A.; Dastiridou, A.; Georgoulias, P.; Cholevas, P.; Kotoula, M.; Tsironi, E.E. Plasma and aqueous humour levels of ghrelin in open-angle glaucoma patients. *Clin. Exp. Ophthalmol.* **2011**, *39*, 324–329.
247. Can, N.; Catak, O.; Turgut, B.; Demir, T.; Ilhan, N.; Kuloglu, T.; Ozercan, I.H. Neuroprotective and antioxidant effects of ghrelin in an experimental glaucoma model. *Drug Des. Dev. Ther.* **2015**, *9*, 2819–2829.
248. Zhu, K.; Zhang, M.L.; Liu, S.T.; Li, X.Y.; Zhong, S.M.; Li, F.; Xu, G.Z.; Wang, Z.; Miao, Y. Ghrelin Attenuates Retinal Neuronal Autophagy and Apoptosis in an Experimental Rat Glaucoma Model. *Investig. Ophthalmol. Vis. Sci.* **2017**, *58*, 6113–6122.
249. Liu, S.; Chen, S.; Ren, J.; Li, B.; Qin, B. Ghrelin protects retinal ganglion cells against rotenone via inhibiting apoptosis, restoring mitochondrial function, and activating AKT-mTOR signaling. *Neuropeptides* **2018**, *67*, 63–70.
250. Liu, Y.; Xing, Y.X.; Gao, X.Y.; Kuang, H.Y.; Zhang, J.; Liu, R. Obestatin prevents H2O2-induced damage through activation of TrkB in RGC-5 cells. *Biomed. Pharmacother.* **2018**, *97*, 1061–1065.
251. Naeser, P. Insulin receptors in human ocular tissues. Immunohistochemical demonstration in normal and diabetic eyes. *Upsala J. Med. Sci.* **1997**, *102*, 35–40.
252. Rong, X.; Ji, Y.; Zhu, X.; Yang, J.; Qian, D.; Mo, X.; Lu, Y. Neuroprotective effect of insulin-loaded chitosan nanoparticles/PLGA-PEG-PLGA hydrogel on diabetic retinopathy in rats. *Int. J. Nanomed.* **2019**, *14*, 45–55.
253. Tarchick, M.J.; Cutler, A.H.; Trobenter, T.D.; Kozlowski, M.R.; Makowski, E.R.; Holoman, N.; Shao, J.; Shen, B.; Anand-Apte, B.; Samuels, I.S. Endogenous insulin signaling in the RPE contributes to the maintenance of rod photoreceptor function in diabetes. *Exp. Eye Res.* **2019**, *180*, 63–74.
254. de Pablo, F.; Hernandez-Sanchez, C.; de la Rosa, E.J. The Prohormone Proinsulin as a Neuroprotective Factor: Past History and Future Prospects. *Front. Mol. Neurosci.* **2018**, *11*, 426, doi:10.3389/fnmol.2018.00426.
255. Rivera, J.C.; Aranda, J.; Riesgo, J.; Nava, G.; Thebault, S.; Lopez-Barrera, F.; Ramirez, M.; Martinez de la Escalera, G.; Clapp, C. Expression and cellular localization of prolactin and the prolactin receptor in mammalian retina. *Exp. Eye Res.* **2008**, *86*, 314–321.
256. Thebault, S. Potential mechanisms behind the antioxidant actions of prolactin in the retina. *Exp. Eye Res.* **2017**, *160*, 56–61.
257. Arnold, E.; Thebault, S.; Baeza-Cruz, G.; Arredondo Zamarripa, D.; Adan, N.; Quintanar-Stephano, A.; Condes-Lara, M.; Rojas-Piloni, G.; Binart, N.; Martinez de la Escalera, G.; et al. The hormone prolactin is a novel, endogenous trophic factor able to regulate reactive glia and to limit retinal degeneration. *J. Neurosci.* **2014**, *34*, 1868–1878.
258. Clapp, C.; Aranda, J.; Gonzalez, C.; Jeziorski, M.C.; Martinez de la Escalera, G. Vasoinhibins: Endogenous regulators of angiogenesis and vascular function. *Trends Endocrinol. Metab. TEM* **2006**, *17*, 301–307.
259. Garcia, C.; Aranda, J.; Arnold, E.; Thebault, S.; Macotela, Y.; Lopez-Casillas, F.; Mendoza, V.; Quiroz-Mercado, H.; Hernandez-Montiel, H.L.; Lin, S.H.; et al. Vasoinhibins prevent retinal vasopermeability associated with diabetic retinopathy in rats via protein phosphatase 2A-dependent eNOS inactivation. *J. Clin. Investig.* **2008**, *118*, 2291–2300.
260. Fekete, E.M.; Zorrilla, E.P. Physiology, pharmacology, and therapeutic relevance of urocortins in mammals: Ancient CRF paralogs. *Front. Neuroendocrinol.* **2007**, *28*, 1–27.
261. Dautzenberg, F.M.; Hauger, R.L. The CRF peptide family and their receptors: Yet more partners discovered. *Trends Pharmacol. Sci.* **2002**, *23*, 71–77.
262. Szabadfi, K.; Atlasz, T.; Reglodi, D.; Kiss, P.; Danyadi, B.; Fekete, E.M.; Zorrilla, E.P.; Tamas, A.; Szabo, K.; Gabriel, R. Urocortin 2 protects against retinal degeneration following bilateral common carotid artery occlusion in the rat. *Neurosci. Lett.* **2009**, *455*, 42–45.
263. Szabadfi, K.; Kiss, P.; Reglodi, D.; Fekete, E.M.; Tamas, A.; Danyadi, B.; Atlasz, T.; Gabriel, R. Urocortin 2 treatment is protective in excitotoxic retinal degeneration. *Acta Physiol. Hung.* **2014**, *101*, 67–76.

264. Bunnett, N.W.; Cottrell, G.S. Trafficking and signaling of G protein-coupled receptors in the nervous system: Implications for disease and therapy. *CNS Neurol. Disord. Drug Targets* **2010**, *9*, 539–556.
265. Vetulani, J.; Nalepa, I. Antidepressants: Past, present and future. *Eur. J. Pharmacol.* **2000**, *405*, 351–363.
266. Amato, R.; Dal Monte, M.; Lulli, M.; Raffa, V.; Casini, G. Nanoparticle-Mediated Delivery of Neuroprotective Substances for the Treatment of Diabetic Retinopathy. *Curr. Neuropharmacol.* **2018**, *16*, 993–1003.