Perspective

Novel emphasis on somatostatinergic system in retinal ganglion cell neuroresilience

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The neuromodulatory peptide somatostatin (somatotropin release inhibiting factor, SRIF)-14 acts at multiple levels through five SRIF receptor subtypes (sst1 to sst5). SRIF-28 is also derived from a common propeptide translated from a single SRIF gene, although SRIF-14 is the predominant form in the mammalian nervous system. Due to its short half-life, synthetic SRIF analogs have been developed over the years and are available for therapeutic approaches. In particular, sandostatin (which contains octreotide) lanreotide and pasireotide are currently available in an injectable formulation. These analogs, alone or in combination with other agents (also as preoperative treatment), are used in clinical practice in endocrinological indications, i.e. acromegaly, Cushing's disease, thyrotropinomas and gastroenteropancreatic neuroendocrine tumors, and in gastrointestinal indications, i.e. complications after pancreatic surgery and gastroesophageal varices in patients with cirrhosis (Gomes-Porras et al., 2020). The variable success rate of the administration of SRIF analogs depends on the particular aspects related to the pathology and the expression of sst1-sst5 at the cellular and tissue level, since the type and the amount of receptors are crucial factors for the drug response. Of interest, SRIF analogs represent an off-label treatment option in several conditions in the field of endocrinology, oncology, digestive, general surgery and ophthalmology, including diabetic retinopathy (DR)/diabetic macular edema and Graves' orbitopathy. Indeed, SRIF analogs with potent neuroprotective properties are highly effective in protecting retinal cells from a variety of insults (Cammalleri et al., 2019). Since primary damage to retinal ganglion cells (RGCs) has been recognized as a major pathological feature in a number of vision-threatening diseases, this Perspective article will focus on recent preclinical evidence regarding the neuroprotective role of the SRIF system in RGCs. In particular, specific novel aspects related to the promising application of SRIF analogs in retinal neurodegeneration induced by metabolic insults will be discussed.

Novel emphasis on SRIF targeting RGCs: In the retina, SRIF is expressed during development and negatively regulates photoreceptor differentiation via sst2 (Weir et al., 2021). In developing human retinal organoids, sst2 has recently been shown to be the dominant receptor of the SRIF family (Chen et al., 2022). Specifically, sst2 signaling, i.e. the protein kinase C/protein tyrosine phosphatase cascade, promoted rod photoreceptor differentiation and inhibited cone growth, presumably through the negative regulation of protein kinase B (also called Akt). Among retinal neurons, RGC activity is detectable during tissue development long before photoreceptor differentiation. Therefore, RGCs may play a critical role in the maturation of the neuroretina. Notably, SRIF is abundantly expressed by immature mouse and human RGCs and acts as an endogenous ligand for sst2 released by RGCs to influence neurogenesis (Weir et al., 2021). Mature RGCs are responsible for generating fast action potentials in the brain, thereby sending visual information to higher visual centers. Because of their critical role, counteracting the loss of RGCs in retinal pathologies is crucial.

As recently reviewed, in the adult deep retina SRIF has been localized in wide-field GABAergic amacrine cells, displaced amacrine cells, and RGCs (Cammalleri et al., 2019). Furthermore, it is contained in the extensively distributed arborizations of the inner plexiform layer in all the retinal regions, suggesting a broad signaling role in visual transduction. Although expressed elsewhere in inner retina, SRIF receptors expression and signaling were specifically investigated in RGCs. In particular, RGCs expressing sst1 and sst5 were observed in rats, and those expressing sst4 were observed in rats (in dendrites and cell bodies) and mice (Gomes-Porras et al., 2020). Functionally, the activation of sst4 by SRIF or its agonist L-803087, has been shown to reduce the spike frequency of RGCs and to inhibit L-type Ca^{2+} channels via protein Gαq activation of the protein kinase C pathway and a voltage-independent protein Gβγ, thus providing potential targets to reduce intracellular Ca^{2+} levels in RGCs. Concerning sst5, they mediate SRIF-induced suppression of AMPA receptor currents via protein Gi/o-cyclic adenosine monophosphate-protein kinase A signaling (Cammalleri et al., 2019). In the last years it was also found that T-type Ca^{2+} currents were reduced by the administration of sst5 receptor-specific agonist L-817818, likely through the nitric oxide/cyclic guanosine 5′-monophosphate/protein kinase G pathway, thus preventing intracellular Ca^{2+} overload (Li et al., 2019). In a rat model of glaucoma, L-817818 was shown to increase RGCs survival, reducing apoptosis by acting on the pro-apoptotic protein Bax and the anti-apoptotic protein Bcl-2 (Zhang et al., 2021). Of interest, L-817818 treatment inhibited retinal oxidative stress, particularly the reactive oxygen species and malondialdehyde formation, which is a marker of cell injury. sst5 activation also reduced mitochondrial dysfunction, further suggesting sst5 actions in protecting RGCs.

SRIF system rebalances homeostasis of RGCs in hyperglycemic retinas: It has been recently reported that somatostatinergic system activation prevents neurodegeneration of RGCs and neurodysfunction in early DR conditions (Amato et al., 2018). Indeed, the preferred sst2/5 analog octreotide rescued the damage induced by high glucose in *ex vivo* mouse retinas, reducing apoptosis and determining an increase of autophagic flux due to the inhibition of the protein kinase mTOR (mammalian target of rapamycin). In particular, octreotide induced autophagy in bipolar and amacrine neurons as well as in RGCs. Interestingly, the autophagic blocker chloroquine abolished the protective effects of octreotide and provoked a marked increase in apoptotic cell death. These observations revealed the antithetic role of apoptosis and autophagy, highlighting their equilibrium from which neuronal survival is likely to depend. RGCs appeared primarily involved in the protecting action of octreotide, together with OFF bipolar cells that are all glutamatergic. That confirms a link between SRIF action and glutamate excitotoxicity, suggesting that SRIF receptors may contribute to re-equilibrate glutamate release in diabetic conditions.

In this line, we also showed that the retinal administration of octreotide plays a protective role in selected RGC populations during the onset of diabetes, when cell loss has not yet started (Amato et al., 2020). This evidence is of considerable interest since neuronal protection strategies in the early responses of RGCs to hyperglycaemic insult could help to counteract retinal cell loss that leads to DR. The ambition to protect RGCs is to preserve their dendritic arborizations and functional activity. Likewise, a timely intervention could prevent neurovascular disequilibrium that induces vasculopathy, classically associated with overt DR. Our extensive morpho-functional analysis of *in vivo* mouse retinas up to 2 weeks from diabetogenic insult evidenced the impairment of some RGC subtypes but not others, both ON-type and OFF-type, despite those with smaller dendritic arbors being less susceptible to diabetic insult (Amato et al., 2022). Presumably, large-size RGCs are more vulnerable than small-size RGCs because of their higher energy and oxygen supply demand, which become crucial during metabolic stress conditions. In addition, large RGCs could be more sensitive to glutamate excitotoxicity due to the higher number of glutamate receptors expressed on their dendrites. RGCs appeared as the first retinal neurons that exhibit functional deficits in the early stage of hyperglycaemia when apoptosis has not yet occurred. Noteworthy, intravitreal injections with octreotide recovered the functionality of RGCs, demonstrating that pharmacologic treatment in the initial phases of DR rescue damaged but still living neurons. Octreotide may exert its protective action by binding directly on sst5 receptors of RGCs and/or activating sst2 receptors expressed in amacrine cells, which may deliver surviving signals to RGCs. SRIF receptor activation induced adaptive morphological changes that are different for specific RGCs since larger cells appeared to respond better to treatment. In addition, depending on the complexity of the dendritic tree and/or the degree of heterologous coupling of RGCs, octreotide completely rescued

RGC morphometric parameters or induced further reductions of dendrite branching or soma size. These adaptive responses likely include eliminating cellular components to reduce energy utilization orchestrated, at least in part, by the modulation of autophagic pathway. Moreover, reducing the dendritic tree in some RGC subtypes may be a metabolic advantage sustaining RGC homeostasis.

Other *in vivo* experiments in db/db mouse retina, a spontaneous model of type 2 diabetes, confirmed that topical administration of SRIF protects all retinal cell layers from neuronal apoptosis (Hernández et al., 2020). SRIF reduced the extracellular concentration of glutamate, inhibited Müller glial cell and microglial activation, and restored functional anomalies, especially oscillatory potentials that reflect the activity of inner retina neurons, mostly RGCs. These results further support the hypothesis that the somatostatinergic system controls glutamate excitotoxicity and preserves inner retinal cell health also acting as an anti-inflammatory substance.

Drug administration to the eye is characterized by several critical issues, such as side effects in neurons and challenging delivery due to the presence of various anatomic and physiologic barriers. The optimization of the intraocular delivery of SRIF-based compounds could thus represent an innovation toward a next-generation treatment of retinal neurodegeneration. Interestingly, a preparation of octreotide bound to magnetic nanoparticles was recently tested (Amato et al., 2020). Results obtained in mouse retinal explants suggested that magnetic nanoparticles might be used as an octreotide intraocular delivery system that may ensure octreotide localization to the retina and enhanced bioactivity.

Conclusion: Recent observations concerning the ligand selectivity and activation mechanisms of sst1-sst5 open new perspectives for drug design in SRIF-related pathologies (Robertson et al., 2022; Zhao et al., 2022). During retinal neurodegeneration, RGCs appear crucial and their homeostasis represents a target for neuroprotective interventions to rebalance morphological and functional dysfunctions of the eye. Functional deficits and abnormalities in morphometric parameters frequently characterize the suffering but still living RGCs. Pharmacologic treatments with neuroprotective SRIF analogs could induce adaptive responses in RGCs. They include the homeostatic balance of apoptosis/autophagy (cell death/survival), the restoration, at least in part, of RGC physiology, and the modulation of inflammatory status, all involved in the reduction of neurodegenerative events (**Figure 1**). To counteract the hyperglycaemic-induced neuronal damage, the challenge is to intervene in the very first phase of the pathology. Since in many cases, there are no disease-modifying interventions for common neurodegenerative disorders, protective strategies may also focus on boosting homeostatic mechanisms - building neuroresilience - to prevent or slow degeneration. In this context, the neuroprotection/neuroresilience role exerted by SRIF receptor activation on RGCs is still an object of intense investigations and the clinical translation potential of novel SRIF analogs deserves to be exploited.

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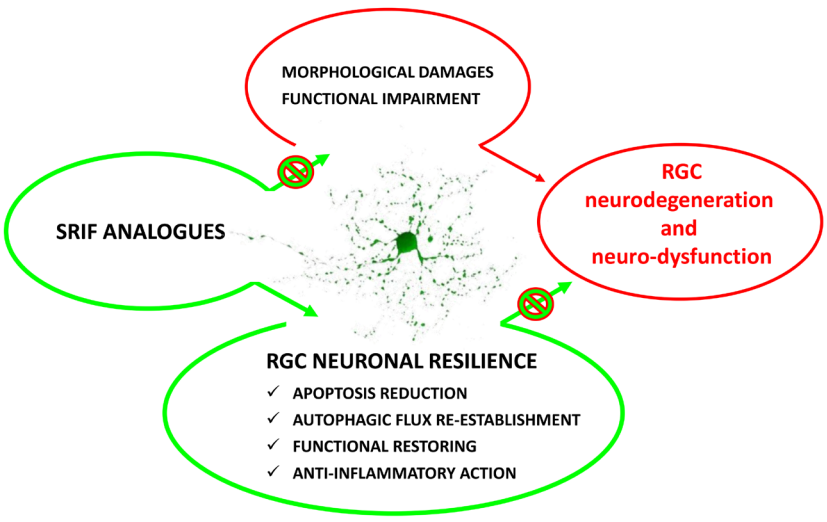

Figure 1 | **Schematic representation of RGCs as SRIF targets for neuroprotective interventions to rebalance morphological and functional impairments.**
RGC: Retinal ganglion cell; SRIF: somatotropin release inhibiting factor.

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