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Somatostatin analogues as therapeutics in retinal disease

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ABSTRACT

Despite the rapid development of new pharmacological and surgical modalities, the treatment of retinal disease all too often results in poor final visual acuity. The primary pathologic mechanism underlying suboptimal visual acuity following retinal disease is cell death. It is induced by a variety of stimuli including ischemia, inflammation, and oxidative stress. New neuroprotective strategies have recently being examined for the prevention of retinal cell death, yet there is still a need for pharmacological agents that are efficacious and lack adverse effects. These could possibly be employed alone or in combination with disease-specific treatments. The neuropeptide somatostatin and its sst_2 receptor selective analogues have been shown to inhibit the ischemia-induced neovascularization in models of retinal ischemia, and to protect from ischemia-induced cell death. The aim of this review is threefold: a) to address the functional role of somatostatin and its receptors in retinal circuitry, b) to present recent evidence supporting the neuroprotective role of somatostatin in experimental models of retinal disease and c) to present the clinical studies that have been performed to date and support the use of somatostatin and its analogues as therapeutics in ophthalmology.

Contents

1. Introduction

The neuropeptide somatostatin (somatotropin release inhibitory factor, SRIF) is a cyclic tetradecapeptide, which is widely distributed in the peripheral and central nervous system (Brazeau et al., 1973; Schulz et al., 2000; Tannenbaum & Epelbaum, 2000) [also read the editorial by Guillemin to a special issue on SRIF (Guillemin 2008)]. It mediates a diverse number of physiological actions by interacting with specific receptors (Thermos & Reisine, 1988; Thermos et al., 1989; Olias et al., 2004). Five SRIF receptor subtypes have been cloned, namely sst_{1-5}, with the sst_2 to exist as two-splice variants sst_{2A} and sst_{2B} (for nomenclature see, Hoyer et al., 1995; Møller et al., 2003; Olias et al., 2004). SRIF and its sst_2 analogues have been shown to have antiangiogenic properties (Smith et al., 1997; Higgins et al., 2002; Dal Monte et al., 2007), to be protective against retinal ischemia (Mastrodimou et al., 2005; Catalani et al., 2007; Kiagiadaki & Thermos, 2008; Mastrodimou et al., 2008) and to inhibit the proliferation of endothelial and retinal pigment epithelium (RPE) cells (Grant et al., 1993; Spraul et al., 1999; Spoerri et al., 2003; Baldysiak-Figiel et al., 2004; Sall et al., 2004). Ischemia influences vessel growth and the

Abbreviations: ARMD, Age-related macular degeneration; bFGF, basic fibroblast growth factor; CME, cystoid macular edema; CNV, choroidal neovascularization; DR, diabetic retinopathy; GH, growth hormone; IGF, insulin growth factor; RPE, retinal pigment epithelium; SRIF, somatotropin release inhibitory factor; sst(s), somatostatin receptor(s); VEGF, vascular endothelial growth factor.

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physiology and viability of the retina and the RPE. To date, there are not many efficacious drugs for the therapy of retinal diseases. Therefore, agents that prevent ischemic insults may be putative therapeutics in retinal disease.

A number of reviews have been published in recent years focusing primarily on the expression of SRIF, its receptors and the signalling mechanisms that are involved in the various neurochemical functions of SRIF in the retina, and secondly on SRIF's involvement in retinal diseases (Johnson et al., 2000; Akopian et al., 2000; Thermos, 2003; Bagnoli et al., 2003; Casini et al., 2005; Thermos et al., 2006; Cervia et al., 2008; Thermos, 2008). However, very few reviews have focused on the clinical use of SRIF analogues in retinopathies (Grant & Caballerom, 2002; Casini et al., 2005; Palii et al., 2007).

The aim of the present review is i) to set the stage for what are the current treatments employed in various retinal diseases and to depict their advantages and limitations, ii) to present the current understanding of the antineovascular and anti-ischemic actions of SRIF and iii) to provide the evidence supporting the use of SRIF analogues, either alone or in combination with ongoing therapies, in the treatment of specific retinopathies. Initially, the necessary information will be provided to aid the understanding of the mechanisms involved in retinal ischemia and its induction of ocular disease. Subsequently, emphasis will be given to the role of SRIF and its receptors in retinal circuitry and the animal and clinical studies performed to date that recommend the use of SRIFergic agents as therapeutics in retinal disease.

2. Retinal ischemia

Ischemia is characterized by the lack of oxygen and glucose supply and the insufficient removal of waste products. These result in cellular energy and metabolic failure, alteration of normal neuronal membrane processes and ionic homeostasis which lead to membrane depolarization, increase of extracellular glutamate levels and activation of ionotropic glutamate receptors (Lipton & Rosenberg, 1994; Lipton, 1999; Lipton et al., 2001). A subsequent cascade of events involving the rise in intracellular calcium levels and the activation of nitric oxide ($NO^{\cdot}$) formation are believed to be important in cell death (Osborne et al., 2004).

Retinal ischemia leads to vision impairment and blindness. Ischemia is implicated in many ocular diseases such as diabetic retinopathy (DR), retinopathy of prematurity and glaucoma. Ischemia is also believed to play an important role in the pathogenesis of neovascular age-related macular degeneration (ARMD; Osborne et al., 2004). As early as 1948, Michaelson (1948) suggested that ischemia led to the chemically controlled formation of new vessels. Neovascularization involves angiogenesis and vasculogenesis (McLeod et al., 1987, 1996). In reaction to ischemia, the retinal vasculature responds by increasing endothelial cell proliferation, and endothelial precursor cells enter the circulation (for a recent review see, Afzal et al., 2007). In 1956, Wise suggested the existence of an intraretinal substance — "factor x"— that leads to neovascularization. About three decades later, it was shown that retinal hypoxia stimulates the release of growth factors and "factor x" was first identified to be the vascular endothelial growth factor (VEGF) (Chen & Chen, 1987; Miller et al., 1994). The fact that increased levels of VEGF was found in the retina and vitreous of patients with ischemic retinopathies established the importance of VEGF in the pathophysiology of these diseases (Campochiaro, 2000). Other growth factors such as insulin growth factor (IGF) and growth hormone (GH), as well as cytokines, also act as modulators of endothelial precursor cell and resident endothelial cell function and drive the retinal angiogenic processes (Adamis et al., 1994; Grant, 1996; Ziche et al., 1997).

The use of animal models of ischemia, such as high intraocular pressure (Smith & Baird 1952; Buchi et al., 1991; Gehlbach & Purple, 1994; Osborne et al., 2002), excitotoxicity (Schwarcz & Coyle, 1977), laser induced ablation (Mosinger et al., 1991), ligature of the optic nerve bundle and artery occlusion (Stephanson et al., 1988; Osborne et al., 1991), has enabled the elucidation of the effects of ischemia on neovascularization and retinal cell viability, as well as the pathways leading to retinal cell death. The availability of such animal models is essential to the study of the neuroprotective properties of different agents that may lead to new therapeutics for the treatment of the ischemia-induced retinopathies mentioned above.

3. Retinal disease therapeutics

Over the years, therapies for ischemic neovascular diseases have been focused on the regulation of the aberrant proliferation of blood vessels. These therapies were non-specific and involved laser treatment, namely photocoagulation. Two types of photocoagulation have been employed, focal and scatter photocoagulation. Focal photocoagulation can be used to destroy leaking blood vessels, whereas scatter photocoagulation (areas of peripheral retina are destroyed by the laser) is used to control the growth of abnormal blood vessels. Laser photocoagulation therapy is applied alone or in combination with verteporfin, a photosensitizing porphyrin (i.e. for the treatment of the wet form of ARMD; see below for more extensive discussion on these disease). This combination has been recommended by the UK National Institute of Health and Clinical Excellence (National Institute for Clinical Excellence, 2003).

The technique of laser photocoagulation has limitations. To mention a few, it does not restore lost vision, it leads to an immediate reduction in central vision and there is an approximate 50% chance that leakage will recur during the following two years (Fine et al., 2000). Photodynamic therapy, on the other hand, is effective in treating established pathological vessels but it does not prevent new vessel formation (van Wijngaarden et al., 2005). The photosensitive drug remains in the body for up to 48 h, and patients have to avoid direct sunlight. In addition, there are no data regarding the long-term effects of the drug. Both overdose of the drug or laser can result in permanent irreversible vision loss (Meads et al., 2001).

While laser photocoagulation and photodynamic therapies are still in clinical use, new therapeutic targets with improved efficacy and fewer side effects are under investigation. In the last few years, the US Food and Drug Administration (FDA) approved new drugs targeting the VEGF system for the treatment of retinopathies. These agents prevent angiogenesis when administered intravitreally. Ranibizumab (Lucentis) was approved by the FDA in 2006 for the treatment of wet ARMD. It is a humanized antibody fragment raised against VEGF-A (Ferrara et al., 2006). It therefore binds to VEGF-A, and blocks new blood vessel growth. It is administered by intravitreal injection. Bevacizumab (Avastin, FDA approval for metastatic cancer, but no FDA approval for ARMD as of yet) is also an antiangiogenic agent. It is a monoclonal antibody against VEGF-A with pharmacological actions similar to those of ranibizumab. These two agents are presently examined in a comparative clinical trial study for their relative safety and effectiveness in treating ARMD. Pegaptanib (Macugen) is a pegylated-modified oligonucleotide that binds with high specificity and affinity to $VEGF_{165}$, an isoform of VEGF that is involved in ocular neovascularization. It blocks the neovascular actions of $VEGF_{165}$ and the growth of blood vessels. Approval for its circulation was obtained by the FDA in 2004. Like ranibizumab, it is administered by intravitreal injection. A systematic review of ranibizumab and pegaptanib has recently been published (Colquitt et al., 2008).

The advent of anti-VEGF therapy has given new hope to patients with wet ARMD and choroidal neovascularization (CNV) (see below for more extensive discussion on these diseases). However, the visual acuity of patients who benefited from the Leucentis administration did not enable them to read or drive normally (Ferrara et al., 2006). In addition, serious ocular adverse events were observed after the