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Adrenomedullin: A potential therapeutic target for retinochoroidal disease

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ABSTRACT

Adrenomedullin (AM) is a 52-amino acid peptide with anti-inflammatory, anti-apoptotic, and anti-oxidative properties discovered in a human pheochromocytoma. It is a member of the calcitonin peptide superfamily, and its signal is mediated by calcitonin receptor-like receptor (CLR). CLR interacts with receptor activity-modifying proteins (RAMPs), among which RAMP-2 and RAMP-3 carry CLR from the endoplasmic reticulum to the cellular membrane to confer high affinity for AM.

In addition to being implicated in a variety of systemic diseases, AM is a critical contributor to the pathogenesis of retinochoroidal disease. It is robustly upregulated in retinochoroidal disease models of oxygen-induced retinopathy (OIR) and laser-induced choroidal neovascularisation (CNV) as well as in human patients with retinochoroidal diseases.

In this review, we discuss the most salient recent findings that strongly illustrate the role of AM in retinochoroidal disease. In the OIR model, AM was identified as a key angiogenic mediator of retinal vascularisation, and AM inhibition suppressed only pathological angiogenesis, not physiological angiogenesis. On the contrary, lesion size was larger in $AM^{+/-}$ CNV model mice, presumably due to the anti-inflammatory function of AM.

Despite the success of anti-vascular endothelial growth factor agents for the treatment of retinochoroidal disease, therapeutic shortcomings remain. Finding ways to modulate AM activity will

Abbreviations: AM, adrenomedullin; AMD, age-related macular degeneration; ApoE, apolipoprotein E; cAMP, cyclic adenosine monophosphate; CCL, chemokine C–C Motif Ligand; CFH, complement factor H; CGRP, calcitonin gene-related peptide; CLR, calcitonin receptor-like receptor; CNV, choroidal neovascularisation; CT, calcitonin; DM, diabetes mellitus; DR, diabetic retinopathy; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; GPCR, G-protein-coupled receptor; HIF-1, hypoxia inducible factor-1; HUVEC, human umbilical vein endothelial cells; IL, interleukin; mRNA, messenger RNA; NO, nitric oxide; OIR, oxygen-induced retinopathy; PDR, proliferative DR; RAMP, receptor activity-modifying protein; RPE, retinal pigment epithelium; RT-PCR, reverse transcriptase-polymerase chain reaction; SCR, short consensus repeats; TNF-α, tumor necrosis factor-α; VE-cadherin, vascular endothelial-cadherin; VEGF, vascular endothelial growth factor; WT, wild type.

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provide new treatment avenues. Potential treatment strategies modulating the action of AM and its signaling pathway have been studied extensively. AM and its signaling molecules are intriguing future treatment targets for retinochoroidal disease.

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1. Introduction

Retinochoroidal diseases can be attributed to pathological processes such as neovascularization, inflammation, and neoplasms in the eye, and can lead to severe visual loss. Biological mediators such as neuropeptides and vasoactive peptides are increasingly being recognized as key contributors to the pathogenesis of these diseases. Thus, understanding their functions is crucial to the development of future therapies for blinding conditions.

Adrenomedullin (AM) is a peptide with 52 amino acid residues and was first discovered in 1993 in a panel of peptides extracted from a human pheochromocytoma (Kitamura et al., 1993). AM is a multifunctional regulatory peptide with biochemical composition and function similar to those of calcitonin (CT) gene-related peptide (CGRP). Together with CT and amylin, AM forms the CGRP family of peptides. AM and CGRP share the same receptors in some tissues and primarily activate the CT receptor-like receptor (CLR) which is a type III G-protein-coupled receptor (GPCR). AM-specific receptors exist as a complex of modified CLR and receptor activity-modifying protein (RAMP)-2 or RAMP-3 (McLatchie et al., 1998) (detailed in section 2).

Many studies have been performed with animal and *in vitro* experiments that outline the therapeutic applications of AM. Shindo et al. (2001) created mice lacking AM and its receptors to demonstrate its critical roles in inflammation and angiogenesis (see Section 2).

In the eye, AM was originally localized to the retinal pigment epithelium (RPE) cells (Udono et al., 2002; Weng et al., 2006). However, subsequent studies showed that the AM gene is expressed in neural retinal cells as well and is upregulated in response to hypoxia (Thiersch et al., 2008). Other studies also reported the expression of AM in ocular cell types other than the RPE cells, including endothelial cells, ganglia, macrophages, and glial cells (Blom et al., 2012; Udono-Fujimori et al., 2003). CLRs and RAMP-2 AM receptors located in the inner retina trigger downstream signaling pathways, which can contribute to pathological