Effects of Retinoids on Vasculatures

Rehana Parvin, Akiko Saito-Hakoda, Susumu Suzuki, Erika Noro, Hiroki Shimada, Atsushi Yokoyama and Akira Sugawara*

Department of Molecular Endocrinology, Tohoku University Graduate School of Medicine, Japan

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*Corresponding author: Akira Sugawara, Professor, Department of Molecular Endocrinology, Tohoku University Graduate School of Medicine, 2-1, Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8575, Japan, Tel: 022-717-7483; Fax: 022-717-8083; Email: akiras2i@med.tohoku.ac.jp

Abstract

Retinoids are natural and synthetic derivatives of retinol, otherwise known as vitamin A. Retinoids bind to several classes of proteins including retinoid-binding proteins and retinoid nuclear receptors leading to the activation of specific regulatory elements of DNA that are involved in regulating cell growth, differentiation, and apoptosis. Several clinical studies have examined the role of retinoids in disease, and research is still ongoing. A natural retinoid, all-transretinoic acid, possesses various beneficial effects on the vasculature. ATRA regulates various types of important cellular functions via retinoic acid receptor. Thromboxane induced contraction and proliferation of vascular smooth muscle cells was completely abrogated by retinoid treatment, which has been recognized to have beneficial effects against atherosclerotic vascular disorders. Therefore retinoids can be a potential therapeutic candidate against vascular disorders. At present, retinoids are used in various fields of medicine. This paper aims to review the recently revealed actions of retinoids on the vasculature as well as some of their current use in vasculogenesis.

Keywords: Retinoids; Vasculatures

Abbreviations: RA: Retinoic Acid; RAR: Retinoic Acid Receptor; RXR: Retinoid X Receptor; ATRA: All-Trans Retinoic Acid; Ppars: Peroxisome Proliferator-Activated Receptors; VDR: Vitamin D Receptor; THR: Thyroid Hormone Receptors; FXR: Farnesoid X Receptor; LXR: Liver X Receptor; VSMC: Vascular Smooth Muscle Cell; EC: Endothelial Cell; AKAP: A-Kinase Anchoring Protein; TX: Thromboxane; TXR: Thromboxane receptor; Enos: Endothelial NO Synthase; NO: Nitric Oxide; KLF5: Kruppel-Like Zinc-Finger Transcription Factor 5; KLF4: Kruppel-Like Zinc-Finger Transcription Factor 4; CAD: Coronary Artery Disease; IR: Ischemia/Reperfusion; BBB: Blood Brain Barrier; MCAO: Middle Cerebral Artery Occlusion

Introduction

Retinoids are natural active metabolites and synthetic derivatives of vitamin A (retinol) [1]. Though vitamin A was discovered more than one hundred years ago, the research history of vitamin A began in 1925 when rats deprived of dietary vitamin A showed increased epithelial growth, including neoplastic responses [2]. Vitamin A is an essential vitamin a deficiency of which causes impaired cellular differentiation, reduced resistance to infection, anemia and even death. In contrast, many aquatic species like sharks may be protected from cancer as a result of their high vitamin A content [3]. At present, retinoids are used in dermatological diseases [4], as a primary treatment for acute promyelocytic leukemia [5] and also for Cushing’s disease [6].

Retinoids

Almost three decades ago, nuclear retinoic acid receptors were identified that belong to the superfamily of nuclear receptors, which led to significant progress in understanding the mechanism of action of retinoids. Retinoids show their biological effects through specific members of the steroid hormone nuclear receptor family, including retinoic acid receptor (RAR) and retinoic X receptor (RXR). RAR and RXR possess three subtypes, α, β, and γ with various isoforms. Activity of retinoids, retinoic acid (RA) have different forms, including all-trans RA (ATRA), 9 cis RA, all-trans 3-4 didehydro RA, and 4-oxo RA, whose synthesis is probably cell specifically modulated [7-10]. RARs α, β and γ bind both ATRA and 9-cis RA with high affinity, while RXR α, β and γ only bind rapaciously to 9-cis RA, and 13-cis RA activates neither RAR nor RXR. The physiological function of 13-cis RA is detected at very lower concentrations in both mice and humans [11,12]. The retinoid, 13-cis RA is not a ligand for retinoid receptors, but can be readily converted to one. Moreover, 13-cis-RA and ATRA occur in vivo, whereas the in vivo occurrence of 9-cis-RA remains controversial [12,13]. RARs, RXRs, and RXRβ are ubiquitously expressed, whereas RARγ, γ, and RXRγ are expressed in tissue-restricted patterns.
Retinoids and Vasculature

Retinoids possess pleiotropic agents of therapy for vascular diseases, dermatological and neoplastic diseases. Since vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) express most retinoid receptors, the mechanisms underlying retinoid-mediated events in these cells and the vessel wall are related to altered genetic variations. Therefore, retinoid-response genes represent promising therapy targets for the treatment of vascular diseases [22]. In this review, we will consider the recent advances in the understanding of retinoids and their relationship with the vasculature. Retinoids are versatile biological response modifiers of the vascular smooth muscle phenotype [23]. Other research has demonstrated a novel function for retinoids in the induction of an A-kinase anchoring protein (AKAP) tumor suppressor that blocks VSMC growth providing novel molecular observations concerning how retinoids may utilize their anti-proliferative effects in the injured vessel wall [24]. ATRA has been reported to be beneficial for atherosclerotic vascular disorders by inducing differentiation and inhibiting the proliferation of VSMCs [23,25,26]. Moreover, retinal pigment epithelium rescues the vascular endothelium from retinoic acid-induced apoptosis [24]. RA and nuclear receptor, RAR-mediated signalling have protective effects on the vascular system. Whether the circulating levels of RA are associated with mortality in patients with coronary artery disease is still not known [27]. Our previous research showed that thromboxane (TX) A2 induces contraction and proliferation of VSMCs through its specific membrane TX receptor (TXR), probably leading to the progression of atherosclerosis. TXR gene expression and transcriptional activity were diminished by ATRA or 9-cis retinoic acid. TX induced contraction and proliferation of VSMCs were completely abrogated by ATRA treatment, which has been recognized to have a beneficial effect against atherosclerotic vascular disorders. Our study revealed a novel anti-atherosclerotic action of retinoids in VSMCs [28].

ATRA increases the antithrombotic effect in microvascular EC, a very relevant compartment for tumor and/or antitumor therapy-associated vascular complications [29].
by inducing differentiation and inhibiting the proliferation of VSMCs, which is recently receiving more attention in research on cardiovascular disorders [23,25,28,30,33,34,39,37].

ATRA attenuates hepatic ischemia/reperfusion (IR) injury in rats [46]. Moreover, RARα mediated ATRA pre-treatment alleviated liver IR injury by inducing autophagy [47]. RA and environmental enrichemnt alter the sub-ventricular zone and striatal neurogenesis after stroke [48]. RA participates in blood brain barrier (BBB) development, preventing the disruption of BBB in ischemic stroke. Therefore, RA could be a good treatment for alleviating the ischemic stroke-induced increase of vascular permeability, as suggested in rat models of middle cerebral artery occlusion (MCAO) [49]. Moreover, RA-loaded polymeric nanoparticles improve the vascular regulation of neural stem cell survival and differentiation after ischemia [50]. From the above discussion, it can be concluded that retinoids could be a promising candidate for the treatment of vasculature-related diseases of the heart, liver, and brain.

**Conclusion**

Almost one century has passed since retinoid research was first reported. Reports describing novel pleotropic effects are still being published. In our previous research, we showed that ATRA increases NO production by eNOS phosphorylation through RARα mediated activation in vascular ECs and probably has beneficial effects in the vascular endothelium. Therefore, retinoids may be novel therapeutic agents against vascular-related disorders with endothelial damage. In this review, we considered recent advances in research on retinoids and their relationship with atherosclerosis and vascular disorders. Very recently we demonstrated the inhibitory effect of HX630 on Pomc gene regulation via RXR [6]. In the future, it could be useful to examine the RXR-mediated effect of HX630 on vasculature-related genes in VSMC and EC, which may lead to the discovery of new treatments for various types of vascular disease. Additional studies are needed to elucidate how metabolite-specific retinoid effects affect the vasculature in various organs including the heart, brain, and liver.

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**Conflict of Interest**

The authors have declared that no competing interests exist.

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