Pathophysiology of Diabetic Retinopathy and Alpha-V-Beta3 Integrin Receptor Antagonist [Tetra-Iodothyroacetic Acid (Tetrac)] Roles as Antiangiogenic and Anti-Inflammatory

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Conflict of interest: None declared

Funding: No funding sources

Abstract

Integrins are large, transmembrane glycoproteins, well-known as cell surface receptors that are essential in cell-to-cell interactions and thus to tissue structure. Integrins provide mechanical attachments between cells and the extracellular matrix (ECM) and other cells, and generate bidirectionally (inside-out and outside-in) cellular signals. so integrins have been proved to regulate cellular growth, proliferation, migration, signaling, and apoptosis, tissue repair, as well as in all processes critical to inflammation, infection, and angiogenesis. ,5,3′,5′ tetraiodothyroacetic acid (tetrac, TA4) is a naturally occurring, analogue of thyroid hormone (L-thyroxine, T4) that accounts for less than 1% of circulating thyroid hormones. For 30 or more years, tetrac has been known to be taken up by pituitary cells that secrete thyrotropin (TSH) and to inhibit endogenous human TSH release by the pituitary gland. This action has been considered potentially useful in the clinic in the setting of TSH-dependent thyroid cancer. As tetrac may undergo nuclear uptake and, in the nuclear compartment, tetrac has low-grade thyromimetic activity, a nano-formulation of tetrac called nanotetrac or nano-diamino-tetrac (NDAT) is formed by covalently bonding tetrac to a 150–200 nm poly lactic-co-glycolic acid (PLGA) nanoparticle. Tetrac has been described as an anti-angiogenic agent as it blocks the proangiogenic action of thyroid hormones on integrin αvβ3. But even in the absence of T4 and T3, tetrac and its nano-formulation also block the pro-angiogenic effect of different growth factors-mediated angiogenesis as vascular endothelial growth factor (VEGF), basic fibroblast growth factor-2 (bFGF-2) and platelet-derived growth factor via integrin αVβ3 antagonism. Tetrac has shown to have antioxidants effect. Tetrac reveals high free radical scavenging capacities greater than those of T3 and protects LDL from peroxidation. Tetrac has shown to have anti-inflammatory effects through regulation of the expression of some inflammation-related genes.

Keywords: Integrin, Tetrac, Antiangiogenic

Tob Regul Sci. ™ 2023;9(1): 4476 - 4487
DOI: doi.org/10.18001/TRS.9.1.315

Introduction

Pathophysiology of diabetic retinopathy

Diabetic retinopathy is a multifactorial condition occurring due to complex cellular interactions taking place in retina as a response to hyperglycemia through a number of biochemical changes with accumulation of advanced glycation end products (AGEs) **(Al-Kharashi, 2018, Tekin and Tekin, 2020).** Various previous studies had suggested that interaction of these biochemical changes may cause a cascade of events, such as oxidative stress, inflammation, hypoxia and angiogenesis which can lead to diabetic retinopathy **(Kusuhara et al., 2018; Tekin and Tekin, 2020).**

1- Oxidative stress:

Free radicals are produced continuously by normal cellular mechanisms, where the body utilizes approximately 95% of them for metabolism and 5% is converted to reactive oxygen species (ROS), which are eliminated by an efficient scavenging system. Imbalance due to increased ROS production and/or inefficient ROS removal can result in excessive levels of ROS, resulting in oxidative stress **(Tekin and Tekin, 2020).**

The retina is a high metabolically active tissue, so it is susceptible to damage from increased ROS production in diabetes, leading to oxidation of intracellular biomolecules as DNA, protein, carbohydrates and lipids **(Golden and Melov, 2001; Tekin and Tekin, 2020).**

Reactive oxygen species are formed by both enzymatic and non-enzymatic mechanisms. Enzymatic mechanism depends on nicotinamide adenine dinucleotide phosphate oxidase (NADPH Oxidases) (NOX), which catalyzes oxygen to superoxide and/or hydrogen peroxide **(Brown et al., 2021).** NOX 2 activity has shown to be increased in retinas of diabetic mice, associated with increased ROS production **(Rojas et al., 2013; Kang and Yang, 2020).**

Also, increased arginase activity in the diabetic retina has been shown to be associated with endothelial cell dysfunction, with generation of superoxide that reacts with nitric oxide (NO) to form peroxynitrite; which enhances NADPH oxidase activity, and increases ROS production **(Narayanan et al., 2013; Tekin and Tekin, 2020).**

On the other hand, non-enzymatic production of ROS occurs when hyperglycemia induces production of superoxide by the mitochondrial electron transport chain (mETC) **(Brownlee, 2005).** Hyperglycemia-induced overproduction of superoxide by the mitochondrial electron transport chain inhibits glyceraldehyde 3-phosphate dehydrogenase (GAPDH) activity and

induces mutations in mitochondrial DNA resulting in defective subunits of the electron transport complexes and eventually causing increased superoxide production **(Brownlee, 2005; Tekin and Tekin, 2020).**

Accumulation of ROS in diabetes causes functional and structural alterations in retinal microvasculature. Oxidative stress causes thickening of basement membranes **(Tekin and Tekin, 2020)**, activation of nuclear factor kappa B (NF-κB), and increased expression of VEGF. ROS also stimulate endothelin-1, a potent vasoconstrictor **(Tekin and Tekin, 2020)**.

Moreover, exposure of pericytes and endothelial cells to high glucose with increased ROS production, and increased activity of caspase-3, nuclear factor kappa B (NF-κB), and other transcription factors leads to capillary cell death, leading to DNA damage and apoptosis (**Kowluru et al., 2003**). Also, ROS increase permeability of mitochondrial pores that induces the release of cytochrome C and other pro-apoptotic factors from retinal mitochondria to initiate apoptosis by the activation of caspases **(Dutta et al., 2006; Tekin and Tekin, 2020).**

2- **Inflammation:**

Inflammation is a significant contributor in the development and progression of diabetic retinopathy **(Brucklacher et al., 2008).** Inflammatory response of the retinal vasculature in diabetes can be triggered by various factors like hyperglycemia, advanced glycation end products, elevated of circulating or vitreous cytokines levels **(Abcouwer, 2013)**.

Leukocyte adhesion to the retina is one of the earlier events occurs in diabetic retina, with increase in the expression of endothelial adhesion molecules such as ICAM-1 and P-selectin **(Forrester et al., 2020)**. Inflammatory reaction between ROS and cell adhesion molecules causes breakdown of the blood retinal barrier and loss of endothelial cells **(Adamis and Berman, 2008; Al-Kharashi, 2018)**.

Activation of Müller glial cells, a significant source of inflammatory modulators, also occurs in diabetic retinopathy **(Rübsam et al., 2018).** Inflammatory cytokines (e.g., TNF-α, IL-6, IL-8, IL1β, etc.) and chemokines (e.g., Monocyte Chemoattractant Protein-1 (MCP-1) are upregulated in the serum as well as ocular samples of diabetic patients and are correlated with retinopathy severity **(Sinclair and Schwartz, 2019)**.

Also, NF-κB is found to be upregulated in rodent retinas (**Zheng et al., 2004**). NF-κB transcriptionally activates various cellular genes which are involved in inflammation with production of many proinflammatory cytokines **(Zheng et al., 2004; Mohammad et al., 2013)**. Activation of NF-kB results in increased expression of inducible NOS (iNOS) with increased nitric oxide (NO) production, which promote leukocyte adhesion to retinal vessels. This contributes to hyperpermeability and the breakdown of the blood retinal barrier, leading to angiogenesis and thrombosis **(Yamagishi et al., 2006)**.

Increased levels of TNFα have been found in the vitreous fluid of diabetic patients with a strong correlation between plasma levels of TNF-α and severity of DR **(El-Asrar, 2012)**. Several studies demonstrated that the expression of TNF-α is increased in the retina of diabetic rats and blockade of TNF-α reduces leukocyte adhesion, suppresses blood retinal barrier breakdown and reduces ICAM-1 expression **(Jang et al., 2020; Kovoor et al., 2022)**. High serum levels of TNF-α in a diabetic patient complicated with retinopathy and/or nephropathy have been shown to induce endothelial dysfunction **(Jonny et al., 2023)**. In addition, increased vascular TNF-α expression in animal models of diabetes induces NADPH oxidase and production of ROS leading to endothelial dysfunction **(Kovoor et al., 2022)**. In vivo studies demonstrated that TNF-α enhances angiogenesis **(Zhang et al., 2019)**.

3- Retinal hypoxia

Deficits in oxygen delivery to the retina are observed in diabetes, and retinal tissue hypoxia has also been suggested to occur in early stage of the disease due to chronic hyperglycemia which leads to the accumulation of many substances, such as advanced glycation end-products (AGEs) **(Katagiri et al., 2018)** and protein kinase C **(Geraldes and King. 2010)**, through which, chronic hyperglycemia causes thickening of the retinal basement membrane, loss of pericytes, formation of microvascular networks, and damage to the blood-retinal barrier (BRB) with consequent leakage of capillary endothelial cells. These pathological changes lead to retinal ischemia and hypoxia, which result in the increased expression of hypoxia-inducible factor-1alpha (HIF-1α) ;an oxygen-sensitive transcription factor. This induces the expression of a series of angiogenesis factors, primarily VEGF, leading to PDR development **(Arjamaa and Nikinmaa, 2006; Al-Kharashi, 2018; Li et al., 2020)**.

Also, retinal hypoxia may contribute to inflammation of the retinal vasculature which results in capillary dropout and development of a progressive, irreversible ischemic hypoxia leading to microvascular changes of diabetic retinopathy (Curtis et al., 2009; Arden and Sivaprasad, 2011).

4- Angiogenesis

Retinal neovascularization is a hallmark feature of proliferative diabetic retinopathy (PDR) which is characterized by abnormal new vessel formation from preexisting vessels by a process called angiogenesis leading to more hypoxia and vascular leakage (**Al-Kharashi, 2018**).

Fu et al. (2016) has reported that the major driving force for angiogenesis in retinopathy is early loss of blood vessels, leading to hypoxia and fuel deficiency. Under hypoxic conditions, hypoxia-inducible factor (HIF-1) protein is increased due to decreased activity of prolyl-hydroxylase, which normally degrades HIF-1rapidly under normal oxygen tension **(Fu et al. 2016)**. Accumulation of HIF-1 protein induces the expression of angiogenic factors like vascular endothelial growth factor A (VEGF-A) **(Hu et al., 2016)**. VEGF-A promotes blood vessel proliferation, in an attempt to re-establish the oxygen and nutritional supply to the retina.

However, these newly formed vessels are abnormal and leaky, leading to retinal damage and even blindness in severe cases **(Lee et al., 2015)**.

In diabetic retinopathy, damage of retinal endothelium is accompanied by breakdown of the inner blood-retinal barrier and the release of many growth factors and cytokines, which exert a proangiogenic activity **(Yamashiro et al., 2003; Feng et al., 2007)**. Enhancement of proangiogenic cytokines in diabetic retina, together with deficiency in the production of endogenous antiangiogenic mediators lead to angiogenesis and progression to diabetic retinopathy **(Hermans, 2007)**.

VEGF is a primary angiogenic factor which mediates ischemia-induced retinal neovascularization **(Simó et al., 2006)**. VEGF is a cytokine responsible for a series of events leading to vasculogenesis; the process of physiological de novo formation of vessels, as well as the pathological angiogenesis in the body **(Behl and Kotwani, 2015)**. Hyperglycemia-induced VEGF overexpression results in angiogenesis, increased permeability of endothelium, disruption of the vascular homeostasis and diabetic macular edema **(Penn et al., 2008; Boyer et al., 2013; Behl and Kotwani, 2015)**.

5- The renin-angiotensin system (RAS) activation:

The renin-angiotensin system (RAS) is one of the oldest studied hormone systems in the body and is well known for its roles in systemic vascular control and electrolyte homeostasis. Angiotensinogen is cleaved by renin to form angiotensin I (Ang I), which in turn is converted to the key effector molecule angiotensin II (Ang II) via angiotensin-converting enzyme (ACE) **(Phipps et al., 2019)**.

Angiotensin II elicits biological effects via two receptor classes, including angiotensin receptor 1 (AT1-R) and angiotensin receptor 2 (AT2-R). AT1-Rs are located on neurons, glia and blood vessels of the retina, so it is possible that Ang II has a role in regulating communication and function between these three cell types, and therefore potentially regulates neurovascular coupling **(Phipps et al., 2019)**.

The origin of Ang II within this local RAS is most likely to be within retinal glia. Indeed, the enzymatic cleavage of angiotensinogen to Ang II has been shown to occur within glia in the CNS **(Wosik et al., 2007)**, and angiotensinogen mRNA has been identified within rat retinal glial cells **(Gerhardingeret al., 2005)**. Localization of AT1-R in the retina is primarily on macroglia and blood vessels **(Downie et al., 2010)**, with more recent studies also demonstrating localization of this receptor to the principal immune cells of the retina, the microglia **(Phipps et al., 2018)**. In contrast, AT2-Rs are expressed by inner retinal neurons, including amacrine cells **(Downie et al., 2010)**.

The role of Ang II in the normal retina is most likely retinal homeostasis, including blood vessel constriction, regulation of glial cell function, and modulation of neuronal function **(Fletcher et al., 2010)**. In eye diseases such as diabetic and hypertensive retinopathy, both Ang II and angiotensinogen **(Gao et al., 2008)** levels have been shown to increase.

6- Dyslipidemia

Dyslipidemia is defined as the presence of one or more abnormal serum lipid concentrations **(Zabeen et al., 2018).** Diabetic retinopathy is positively associated with high serum concentration of triglycerides, low-density lipoprotein (LDL) and apolipoprotein B (ApoB); the principal lipoprotein component of LDL **(Lyons et al., 2004)**. Previous studies have shown that modified lipoproteins, particularly ox-LDL, promote vascular damage through complex inflammatory and immunologic mechanisms (**Sherer and Shoenfeld, 2006; Wu et al., 2008).**

Wu et al. (2008) has proved the presence of extravasated apolipoprotein B and ox-LDL in retinas from diabetic patients, correlating with the severity of DR. Further, in PDR, the presence of macrophages and their co-localization with apolipoprotein B was observed. Ox-LDL induced apoptosis in human retinal capillary pericytes (HRCPs) through the activation of caspases pathways and mitochondrial dysfunction. These findings support the notion that oxidized, glycated LDL is implicated in the initiation and development of DR **(Wu et al., 2008).**

Alpha-V-Beta3 Integrin Receptor Antagonist [Tetra-Iodothyroacetic Acid (Tetrac)]

Integrins are large, transmembrane glycoproteins, well-known as cell surface receptors that are essential in cell-to-cell interactions and thus to tissue structure **(Ahmad et al., 2021)**. Integrins provide mechanical attachments between cells and the extracellular matrix (ECM) and other cells, and generate bidirectionally (inside-out and outside-in) cellular signals. **(Humphries, 2000; Hynes, 2002; Ahmad et al., 2021)**, so integrins have been proved to regulate cellular growth, proliferation, migration, signaling, and apoptosis, tissue repair, as well as in all processes critical to inflammation, infection, and angiogenesis **(Hamidi et al., 2016; Hedhli et al., 2018; Davis et al., 2021; Mezu-Ndubuisi and Maheshwari, 2021).** Integrins also play vital roles in the immune system for leukocyte trafficking and migrating, immunological synapse formation, and phagocytosis **(Rocha-Perugini et al., 2016; Davis et al., 2021).**

Integrins are heterodimeric in structure consisting of 2 subunits; alpha (α) and beta (β) that are non-covalently linked **(Mors et al., 2014; Mezu-Ndubuisi and Maheshwari, 2021).** Mammalian integrins are the result of 18 α-subunits and 8 β-subunits that form 24 different heterodimers, each of which has specific functions and is expressed in different tissues **(Takada et al., 2007; Ahmad et al., 2021).**

Each integrin unit features a large extracellular domain resembling a head and a short cytoplasmic domain **(Mezu-Ndubuisi and Maheshwari, 2021).** The head includes sites for ligand binding, while the cytosolic domains of integrin mediate interactions with intracellular

cytoskeletal and signaling proteins **(Campbell and Humphries, 2011; Mezu-Ndubuisi and Maheshwari, 2021).** So integrins function bidirectionally across the plasma membrane, as integrin activation can occurs by intracellular or extracellular stimuli through ligand binding to extracellular domain or by the changes on the cytoplasmic domains **(Mezu-Ndubuisi and Maheshwari, 2021).**

3,5,3′,5′ tetraiodothyroacetic acid (tetrac, TA4)

3,5,3′,5′ tetraiodothyroacetic acid (tetrac, TA_4) is a naturally occurring, analogue of thyroid hormone (L-thyroxine, T_4) that accounts for less than 1% of circulating thyroid hormones **(Moreno et al., 2008).** For 30 or more years, tetrac has been known to be taken up by pituitary cells that secrete thyrotropin (TSH) and to inhibit endogenous human TSH release by the pituitary gland. This action has been considered potentially useful in the clinic in the setting of TSH-dependent thyroid cancer **(Davis et al., 2013).**

Tetrac is a deaminated analogue of T4, with low hormone activity because of removal of an amine resulting in the conversion of thyroid hormone to tetrac **(Davis et al., 2011).** Tetrac has low affinity for the nuclear thyroid hormone receptors, through which the classical genomic actions are initiated by the thyroid hormone **(Cheng et al., 2010; Gellrich et al., 2020).**

Studies focused on the non-genomic actions of thyroid hormone revealed that such actions are independent of the nuclear thyroid hormone receptor and gene transcription **(Cheng et al., 2010)**, but mediated through cell surface receptor on the plasma membrane of cells that has been found to be expressed on integrins protein **(Davis et al., 2011; Davis et al., 2013).** The cell surface receptor site for the thyroid hormone was not identified until **Bergh et al. (2005)** described the existence of a thyroid hormone receptor on plasma membrane integrin αvβ3.

At the cell surface αvβ3 integrin receptor, tetrac was shown to acts as an antagonist of T_4 actions by binding to the extracellular domain of integrin αvβ3 blocking it and displacing thyroid hormones, resulting in anti-angiogenesis, anti-inflammation effect and reduced cell proliferation in cancer cells **(Davis et al., 2015; Davis et al 2021).**

As tetrac may undergo nuclear uptake and, in the nuclear compartment, tetrac has low-grade thyromimetic activity, a nano-formulation of tetrac called nanotetrac or nano-diamino-tetrac (NDAT) is formed by covalently bonding tetrac to a 150–200 nm poly lactic-co-glycolic acid (PLGA) nanoparticle **(Chang et al., 2018; yang et al., 2021).** NDAT has been shown to act primarily at the cell surface and does not enter the nucleus when it enters the cell **(Chang et al., 2018; Cheng et al., 2021).** NDAT can block the binding of thyroid hormones and competes with T4 for the integrin αvβ3 cell surface receptor **(Cheng et al., 2021).**

Effects of Tetrac:

1- Anti-angiogenic activity of tetrac

Tetrac has been described as an anti-angiogenic agent as it blocks the proangiogenic action of thyroid hormones on integrin αvβ3 **(Davis et al., 2015)**. But even in the absence of T4 and T3, tetrac and its nano-formulation also block the pro-angiogenic effect of different growth factors-mediated angiogenesis as vascular endothelial growth factor (VEGF), basic fibroblast growth factor-2 (bFGF-2) and platelet-derived growth factor via integrin αVβ3 antagonism **(Mousa et al., 2014; Rajabi et al.,2018)**.

Tetrac also was found to be an effective inhibitor for the pro-angiogenic effect of both erythropoietin (EPO) and VEGF on retinal endothelial cells **(Yoshida et al., 2012)**. The mechanism of tetrac involved in anti-angiogenesis is thought to involve disorganization of crosstalk between the integrin and nearby receptors for VEGF **(Davis et al., 2011)** and bFGF-2 **(Mousa et al., 2008)** and inhibition of local release of bFGF **(Davis et al., 2013)**. Inhibition of mitogen-activated protein kinase (MAPK) activity by tetrac alters activity of bFGF-2 and other factors **(Davis et al., 2013)**.

Tetrac also has shown to decrease abundance of angiopoietin-2 (Ang-2) mRNA in endothelial cells. Ang-2 protein production in tumor vasculature synergizes with vascular growth factor action to support tumor angiogenesis **(Thomas and Augustin 2009)**. Certain cytokines involved in the inflammatory process, such as IL-1, are also proangiogenic **(Voronov et al., 2007)**. Nanotetrac inhibits transcription of the IL-1α and IL-1β genes. Thus, a component of the anti-angiogenic properties of Nanotetrac in the setting of inflammation is vested in suppression of expression of interleukin genes **(Davis et al., 2013)**.

Also, Tetrac can induce the expression of thrombospondin-1, an endogenous suppressor of angiogenesis that is almost invariably unexpressed in cancer cells **(Bridoux et al., 2010)**. Tetrac may negatively affect endothelial cell motility that is important to neovascularization **(Davis et al., 2013)**.

2- Antioxidant activity of tetrac

Tetrac has shown to have antioxidants effect. Tetrac reveals high free radical scavenging capacities greater than those of T3 and protects LDL from peroxidation **(Oziol, 2001)**.

3- Anti-inflammatory activity of tetrac

Tetrac has shown to have anti-inflammatory effects through regulation of the expression of some inflammation-related genes **(Davis et al., 2013)**. Analysis of the gene signature of tetrac treatment in relatively chemoresistant human breast cancer cells has revealed an important set of actions on inflammation related genes **(Glinskii et al., 2009; Lin et al., 2012)**. IL-6 and IL-1α, are down-regulated by tetrac while a suppressor of cytokine signaling (SOCS) gene is up-regulated by tetrac (**Lin et al., 2012**). Expression of interferon response pathway genes and chemokine genes is decreased by tetrac **(Davis et al., 2011)**.

No Conflict of interest.

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