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Review

A Systematic Review on the Role of Adrenergic Receptors in Angiogenesis Regulation in Health and Disease

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Abstract: Angiogenesis is essential during development or when tissue restoration and oxygenation is required. Limited or excessive formation of blood vessels is a hallmark of several pathologies, and many angiogenesis-related pathways are being studied to highlight potential targets for effective angiogenesis-stimulating or inhibiting therapeutic approaches. A few studies point to the adrenergic system as a significant regulator of angiogenesis, directly or indirectly. Functional adrenergic receptors are expressed on endothelial cells and affect their response to the adrenergic system. The latter can also upregulate the release of growth factors by mural cells of the vessel wall, blood cells or cancer cells, thus subsequently affecting endothelial cell functions and angiogenesis. In the present study we summarize up-to-date literature on the known effects of the adrenergic receptors on physiological and pathological angiogenesis.

Keywords: adrenergic receptors; agonists; angiogenesis; antagonists; blood cells; cancer cells; endothelial cells

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1. Introduction

1.1. Angiogenesis

Angiogenesis is the formation of new blood vessels from pre-existing ones. It is a complex process with many stages and mechanisms, which occurs throughout life in healthy conditions, such as embryo development and wound healing, but also in pathological ones, such as cancer and diabetes. During angiogenesis, vascular and predominantly endothelial cells play the most profound role. The onset of angiogenesis requires selective activation of endothelial cells from the pre-existing network of capillaries by pro-angiogenic growth factors. Among the latter, vascular endothelial growth factor A (VEGFA) is the most important, guiding various steps during new vessel sprouting. The newly formed vessels are stabilized by mural cell (pericytes and vascular smooth muscle cells) recruitment by platelet derived growth factor (PDGF) [1–3].

Blood cells may also affect angiogenesis by secreting various pro-angiogenic molecules. For example, in inflammation, monocytes that express VEGFA increase the permeability of the endothelial monolayer and thus initiate angiogenesis. Monocytes also express PDGF, which promotes the proliferation of both the endothelial and vascular mural cells [4].

A significant initiator of angiogenesis is hypoxia, which occurs in cancer and other pathologies. Hypoxia leads to upregulation of VEGFA secretion by cancer or other types of cells, which then activates endothelial cells to form new vessels [2,5].

1.2. Adrenergic Receptors

Adrenergic receptors (ARs) belong to the superfamily of G protein-coupled receptors, also referred to as receptors with seven transmembrane domains. They are divided into two distinct subtypes, α and β ARs. Alpha ARs are divided into α_1 and α_2 ARs, subdivided into α_{1A}, α_{1B}, α_{1D} and α_{2A}, α_{2B}, α_{2C} respectively, while beta ARs are classified as β_1, β_2 and β_3. Norepinephrine and epinephrine are the natural, endogenous ligands of ARs that

mediate the effects of the sympathetic nervous system. Agonist binding to ARs induces a conformational rearrangement that leads to the activation of the corresponding G proteins that differentially affect downstream signaling pathways (Table 1) [6,7].

Table 1. Distribution and functions of ARs.

AR	Expression	Signaling Pathway	Effect
α_1	vascular smooth muscle cells endothelial cells cardiomyocytes prostate smooth muscle cells brain	G_q/PLC/PKC and increased Ca^{2+}	vasoconstriction migration/proliferation positive inotropy/survival smooth muscle constriction complex cellular responses
α_2	autonomic ganglia sympathetic neurons central nervous system pancreas platelets kidneys tubular epithelium vascular smooth muscle cells GI smooth muscle cells	G_i/AC/decreased cAMP	neurotransmitter release suppression control of sympathetic flow sympathetic outflow modulation insulin release inhibition aggregation diuresis vasoconstriction decreased GI mobility
β_1	cardiomyocytes kidney smooth muscle cells adipocytes	G_s/AC/increased cAMP	positive inotropy and chronotropy renin release lipolysis
β_2	vascular smooth muscle cells endothelial cells GI smooth muscle cells lung smooth muscle cells cardiomyocytes uterus smooth muscle cells bladder smooth muscle cells adipocytes pancreas eyes (ciliary epithelium) liver skeletal muscle	G_s/AC/increased cAMP	vasodilation migration/proliferation decreased contractility bronchodilation increased contractility and heart rate relaxation relaxation lipolysis insulin and glucagon secretion decreased fluid production glycogenolysis/ contraction
β_3	cardiomyocytes endothelial cells adipocytes, brown adipocytes bladder smooth muscle cells gallbladder retina epithelial cells	G_s/AC/increased cAMP or G_i/AC/decreased cAMP	negative inotropy migration/proliferation lipolysis, thermogenesis relaxation contraction decreased protection

PLC, phospholipase C; PKC, protein kinase C; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate.

ARs have a wide distribution and affect numerous functions [6,7], as summarized in Table 1. Agonists and antagonists of ARs are clinically used in the treatment of various diseases, mostly of the cardiovascular and the respiratory systems. The most recent findings that are discussed in the following paragraphs suggest their involvement in the regulation of angiogenesis in health and disease.

2. Search Strategy

We searched the MEDLINE/PubMed and the Scopus databases focusing on areas of relevance to angiogenesis and the role of adrenergic receptors in new blood vessel formation. We excluded all items that were not in research journals. As keywords we used different combinations of the terms: *"angiogenesis"*, *"adrenergic receptors"*, *"endothelial cells"*, *and "adrenergic signaling"*. To be more focused, we used the criterion that the two terms coexist in the title and/or the abstract of the articles. When we used the combination "angiogenesis" and "adrenergic receptors", the search yielded 65 results, 25 of which were

published during the last five years. The combination "angiogenesis" and "adrenergic signaling" yielded 35 results, 15 of which were published during the last five years. The combination "endothelial cells" and "adrenergic signaling" led to 21 results, among which 10 were published in the last five years. Finally, the combination "endothelial cells" and "adrenergic receptors" led to 120 results, among which 26 were published in the last five years. Many of the publications appeared in more than one of the above-mentioned combinations and we finally chose 73 publications that were most relevant to the scope of this review, including all the relevant publications of the last five years (31 papers). We also included seven review papers in the Introduction of this review, in which the readers can look for more information on mechanisms of angiogenesis and on the physiology and pharmacology of the adrenergic receptors.

3. Expression of ARs in Endothelial Cells

ARs subtypes expression differs among endothelial cells of different origin. Human coronary artery endothelial cells express α_1 ARs, with the α_{1B} subtype being predominant [8]. Bovine aortic and bovine pulmonary artery endothelial cells [9], as well as human pulmonary artery and human umbilical vein endothelial cells (HUVEC) [10] express functional β ARs that are downregulated by hypoxia [10] and may belong to the β_2 subtype [11]. Cultured endothelial cells from the human iliac vein, human skin, and bovine fetal aorta also express β_2 ARs and respond to β_2 agonists [12,13]. Bovine brain capillary endothelial cells express both β_1 and β_2 ARs (relative proportion 42% and 58% respectively) [14]. Endothelial progenitor cells (EPCs) express β_2 ARs [15]. Human dermal microvascular endothelial cells express all subtypes of β ARs [13], while human retinal endothelial cells express both β_1 and β_3 but not β_2 ARs [16].

4. ARs and Physiological Angiogenesis

4.1. The Evidence on the Role of α ARs in Physiological Angiogenesis Is Limited and Contradictory

The α_1 AR agonist phenylephrine at very low doses that do not affect vascular contraction has been shown to stimulate α_{1D} ARs and promote NO-dependent endothelial cell migration and proliferation in vitro, an effect that was significantly enhanced under hypoxic conditions [17]. In the same line, the nonselective reversible antagonist of α_1 and α_2 ARs, phentolamine, suppresses endothelial cell proliferation, migration, and tube formation in vitro. Phentolamine decreases expression of VEGF receptor 2 (VEGFR2) and angiopoietins 1 and 2, without affecting the expression of VEGFA [18]. It also inhibits proliferation, migration, and secretion of VEGFA and angiopoietin 1 by pericytes in vitro [19]. The potent and selective α_1 AR antagonist doxazosin hinders the VEGFA-mediated proliferation and migration of HUVEC in vitro, prevents attachment on fibronectin and activates caspase-3-dependent apoptosis. It also hinders the action of fibroblast growth factor 2 (FGF2) on endothelial cells [20]. In the same line, the selective α_1 AR antagonist terazosin inhibits HUVEC proliferation, migration, and tube formation in vitro and blocks the stimulatory effects of VEGFA [21].

However, in another study, doxazosin stimulates, while phenylephrine inhibits proliferation, migration, and tube formation by Wistar-Kyoto rat aortic endothelial cells in vitro [22]. This discrepancy may be due to the different origin of the endothelial cells studied but needs to be further researched.

During the vascular development of the labyrinth of fetal and maternal vessels, α_{2B} ARs hinder the expression of the anti-angiogenic soluble VEFG receptor 1 (VEGFR1). Targeted deletion of the α_{2B} AR gene leads to upregulation of soluble VEGFR1 and inhibition of embryonic vasculogenesis. Neutralization of soluble VEGFR1 by a specific antibody restored the number of vessels in α_{2B}-deficient placentae in vivo at embryonic day 10.5 [23].

In chick and quail models, it has been shown that sympathetic innervation promotes the differentiation and the arterial fate of endothelial cells through ERK1/2 activation downstream of both α_1 and α_2 ARs. The α_1 ARs stimulate PLC that activates the ERK

pathway, while the α_2 ARs inhibit the AC/protein kinase A (PKA) pathway and thus also activate ERK1/2 [24,25].

4.2. The Role of β ARs in Angiogenesis Regulation Is Better Evidenced Compared to That of α ARs but Contradicting Data Still Exist

It has been demonstrated that the β ARs in endothelial cells are highly associated with angiogenesis. Isoproterenol, a non-selective β AR agonist, as well as overexpression of β_2 ARs in human endothelial cells, increase endothelial cell proliferation, migration, and tube formation in vitro through ERK1/2 activation [26]. Activation of β_2 ARs in HUVEC activates both the cAMP/PKA and the cAMP/exchange proteins activated by cyclic AMP (Epac1) pathways. The former enhances VEGFA expression and secretion, and the latter increases VEGFR2 expression, thus upregulating a significant pro-angiogenic pathway [27]. Deletion of β_2 ARs in mouse aortic endothelial cells inhibits VEGFA expression and tube formation in vitro, an effect attributed to the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway inactivation downstream of the impaired cAMP-response element binding (CREB) phosphorylation [28]. The selective β_2 AR agonist terbutaline has been shown to stimulate bEnd.3 microvascular endothelial cells tube formation without affecting their proliferation rate. This effect is inhibited using specific AKT and ERK1/2 kinase inhibitors, suggesting that both kinases act downstream of the β_2 ARs. In vivo, terbutaline stimulates angiogenesis in the chick embryo chorioallantoic membrane assay [29]. In the immortalized human dermal microvascular endothelial cell line HMEC-1 and in primary human dermal endothelial cells, β_2 AR activation has been shown to increase IL-6 production [30], which may then stimulate angiogenesis [31].

EPCs express β_2 ARs and isoproterenol or overexpression of β_2 ARs stimulates EPCs proliferation, migration, VEGFA production and tube formation in vitro [32]. Activation of β_2 ARs in EPCs leads to activation of the Akt/endothelial nitric oxide (NO) synthase pathway to promote VEGFA secretion and enhance the reendothelialization capacity of EPCs in vivo [15]. Similarly, overexpression of β_2 ARs in infused peripheral blood-derived EPCs has been shown to increase their proliferation, migration, and NO production in vitro and in vivo, enhancing restoration of endothelium-related vascular injuries [33].

Enhancement of NO production downstream of β_2 ARs in mouse pulmonary artery endothelial cells has been shown to involve a $G_{i/o}$ protein, c-Src kinase, phosphoinositide 3-kinase and Akt kinase but to be independent of cAMP/PKA, ERK1/2, and 5′ AMP-activated protein kinase [34], thus questioning the involvement of ERK1/2 downstream of β_2 ARs in the regulation of angiogenesis. Involvement of ERK1/2 kinase in the regulation of angiogenesis by the β_2 ARs has been also questioned by a study showing that in rat aorta endothelial cells in vitro, the non-selective β AR agonist isoprenaline decreases and the non-selective β AR antagonist propranolol increases ERK1/2 activity [35].

In contrast to positive regulation of angiogenesis by β_2 ARs, it has been reported that activation of β_2 ARs that are highly expressed in human dermal microvascular endothelial cells (HDMEC) delays HDMEC migration and tube formation and decreases secretion of the pro-angiogenic growth factors FGF2 and VEGFA in vitro. Moreover, β_2 AR activation decreases angiogenesis in murine skin wounds in vivo. These effects have been attributed to a cAMP/EPAC1-dependent mechanism [13]. In the same line, antagonism, or gene deletion of the β_2 AR can increase VEGFA secretion from keratinocytes in vitro and angiogenesis in vivo [36]. Moreover, the selective β_2 AR agonist salbutamol inhibits angiogenesis in the in vivo chick embryo chorioallantoic membrane assay and decreases the number of vessels in a rat model of skin wound healing [37]. There are also data showing that norepinephrine via β_2 ARs [38] and cAMP via PKA [39–41] induce endothelial cell apoptosis and inhibit angiogenesis.

Another function of endothelial cells that may be related to angiogenesis initiation and seems to be affected by β_2 ARs is endothelial cell layer permeability. It has been shown that the selective β_2 agonist formoterol decreases vascular permeability in the rat trachea by inhibiting endothelial gap formation [42]. Isoproterenol and formoterol also

decrease endothelial cell permeability in cultures of bovine aortic and retina endothelial cells, possibly via cAMP production [43].

The first data that supported an (indirect) role of β_3 ARs in angiogenesis were obtained in cultures of brown adipocytes that synthesize and release VEGFA in response to catecholamines [44]. It was later shown that the selective β blocker nebivolol stimulates endothelial NO release through the β_3 AR expressed in HUVEC [45] and that activation of β_3 ARs by catecholamines in bovine aortic endothelial cells may lead to an increase in NO release through the small G protein Rac1 that is upstream of PKA and Akt kinase activation [46].

An interesting observation in rat pulmonary microvascular endothelial cells is that the effect of β ARs could be manipulated by regulating their transport from the endoplasmic reticulum to the Golgi, mediated by the Ras-like GTPase Rab1, thus affecting their cell surface expression. Decreased cell surface expression of β ARs coincides with increased endothelial cell permeability following stimulation of cells with lipopolysaccharide [47]. In the same line, it has been shown that β_2 ARs can form oligomeric complexes with VEGFR2 on the surface and in intracellular endosomes of endothelial cells. These complexes can co-internalize and increase in number in response to both β_2 AR and VEGFR2 agonists. Treatment of endothelial cells with VEGFA can also prolong the β_2 AR agonist-stimulated association between the β_2 AR and β-arrestin 2, thus potentially affecting their subcellular distribution and signaling [48].

5. Role of ARs in Non-Neoplastic Pathological Angiogenesis

5.1. The Role of α_1 ARs in Heart Failure and Ischemia and Their Correlation to Angiogenesis

Induction of angiogenesis may prove beneficial in cases such as heart failure caused by chronic myocardial infarction. Stimulation of α_1 ARs has promising results in heart failure, not only due to their increased inotropic properties, but also due to the induction of a paracrine mechanism that results in angiogenesis stimulation and inhibition of cardiac remodeling. Overexpression of α_{1A} ARs in cardiomyocytes in a transgenic mouse model led to reduced cardiac remodeling after chronic myocardial infarction that has been attributed to the induction of angiogenesis. The latter is the result of crosstalk signaling between the cardiomyocyte and the endothelial cell. Cardiomyocytes that overexpress the α_{1A} ARs secrete VEGFA downstream of the MEK/ERK1/2 pathway. VEGFA then acts on endothelial cells resulting in their proliferation, migration, and activation of the angiogenic process [49].

On the other hand, the density of α_1 ARs has been shown to increase in a model of hindlimb ischemia in Wistar-Kyoto rats and treatment of the rats with doxazosin seems to promote neo-angiogenesis without affecting systemic blood pressure, suggesting an anti-angiogenic effect of α_1 ARs stimulation [22].

5.2. Involvement of β ARs in Angiogenesis-Related Pathologies—Evidence Supports a Positive Regulation of Angiogenesis by β ARs Stimulation

Based on the observations that β_2 AR overexpression or activation enhances angiogenic activities of EPCs in vitro [15,32,33], in a mouse model of induced ischemia, injection of isoproterenol-treated wildtype EPCs has been shown to significantly improve blood density and blood flow compared to non-treated or β_2 AR knockout EPC-treated mice [32].

Chronic stress has been implicated in the development of endometriosis through activation of the β_2 ARs, expressed in ectopic endometrium, by the released catecholamines. The downstream cAMP/PKA signaling pathway, followed by the activation of CREB, seem to positively affect angiogenesis, thus accelerating endometriosis [50]. In a rat model of surgically induced endometriosis, propranolol has been shown to decrease expression of VEGFA, MMP2 and MMP9 and suppress endometrial tissue development [51].

Chronic ischemia in Wistar Kyoto Rats leads to decreased vascular density within the ischemic hindlimb. Overexpression of β_2 ARs restores capillary density and improves hindlimb perfusion. Similarly, the impaired angiogenesis observed in the spontaneously

hypertensive rat model was significantly ameliorated following overexpression of β_2 ARs [26].

Despite the observation that terbutaline promotes physiological angiogenesis in vitro and in vivo [29], it has no effect on revascularization following spinal cord injury in a mouse model [29]. It needs to be clarified by further studies whether stimulation of the β_2 ARs may prove beneficial in central nervous system injuries that would benefit from angiogenesis stimulation.

Antagonism of β ARs has shown beneficial effects in several pathologies that may benefit from angiogenesis inhibition, as evidenced by several studies that have used propranolol. First, propranolol has been suggested as a treatment for infantile hemangiomas, significantly reducing their extent. Propranolol treatment decreases the anti-apoptotic Bcl-2 protein expression and increases expression of the pro-apoptotic Bax protein in infantile hemangioma tissues in vivo. Propranolol also hinders the expression of PDGF-BB in vivo and downregulates expression of the angiopoietin-like protein 4 in endothelial cells [52–54]. Hemangioma-derived endothelial cells express β_1 and β_2 ARs. Isoprenaline increases intracellular cAMP levels leading to increased VEGFA expression and VEGFR2 phosphorylation. Activation of VEGFR2 leads to ERK1/2 phosphorylation and cell proliferation through activation of several cell cycle regulators. The stimulatory effects of isoprenaline are VEGFR2-dependent and are inhibited by both β_1 and β_2 AR antagonists, with the effects of the β_2 AR antagonists being more prominent [55]. Many β blockers, such as propranolol, have high affinities for β_3 ARs and accumulating evidence suggests that the β_3 ARs may play a major role in the pathophysiology of infantile hemangioma [56].

Propranolol has been also used in the therapy of choroidal neovascularization (CNV), which is an ischemic complication of various eye diseases such as Stargardt disease, degenerative myopia, and choroidal hemangioma. CNV occurs in the choroid that forms the middle layer of the eyeball and is characterized by loss of homeostasis between the expression of angiogenic factors, such as VEGFA, FGF2 and PDGF, and anti-angiogenic factors such as pigment epithelium-derived factor (PEDF) and thrombospondin-1 (TSP1). The enhanced angiogenesis in the choroidal space gradually leads to blindness [57]. Mononuclear macrophages that express all three types of β ARs appear to be the major inflammatory component of this condition, releasing pro- and anti-angiogenic agents depending on their polarization [58]. Propranolol seems to limit CNV by decreasing the expression of the inflammatory mediators IL-6 and TNFα and increasing the expression of the anti-inflammatory IL-10 and the anti-angiogenic PEDF by the mononuclear macrophages [59].

Propranolol has been also studied in retinopathy of prematurity (ROP), an eye disease that leads to blindness caused by delayed vascular growth, retinal ischemia, and abnormal angiogenesis. In oxygen induced ROP models, propranolol decreases VEGFA expression and retinal angiogenesis, while it enhances pericyte apoptosis via the inhibition of the Akt signaling pathway [60]. The effect seems to be mainly due to β_2 but not β_1 or β_3 AR antagonism [61].

Propranolol can be also beneficial in diabetic foot ulcers, as evidenced in mouse models, in which topical use of propranolol in the wounded area promotes keratinocyte proliferation and migration. Dermal and epidermal regeneration is enhanced via the increased levels of epidermal growth factor and MMP9, while the expression of VEGFA and endothelial cell proliferation are decreased. Pericytes and mural cell proliferation is enhanced, and this may explain the increased density of functional blood vessels in diabetic wounds following propranolol treatment [62]. Like the effects of topical application, in an in vivo model of cutaneous wound healing in streptozotocin-induced diabetic rats, oral administration of propranolol improves wound healing by enhancing cell proliferation, collagen deposition, NO levels and blood vessel density [63].

6. Role of ARs in Cancer Angiogenesis

The induction of angiogenesis has been characterized as one of the most important hallmarks of cancer and is a crucial process for tumor growth. As tumors increase in

size, tumor parenchyma due to insufficient blood supply becomes hypoxic, secretes pro-angiogenic growth factors, such as VEGFA, and stimulates angiogenesis. In contrast to physiological angiogenesis, the cancer blood vessels are usually abnormal, leaky, and misshapen, characterized by a lack of auxiliary pericytes and high permeability [64,65].

Besides a direct effect of ARs on endothelial cells as described in previous paragraphs, tumor angiogenesis may be regulated indirectly, following activation or inhibition of ARs expressed in cancer cells. Human lung adenocarcinoma A549 cells [66], human breast cancer MDA-MB-231 cells [67], human colon cancer HCT116 cells, human ovarian carcinoma OVCAR8 cells [68] and epidermoid carcinoma cell line A-431 [69] are examples of cancer cell lines that express functional β ARs. To the best of our knowledge, there are limited data on the involvement of the α ARs in the regulation of cancer angiogenesis.

In line with an indirect role of β ARs in the stimulation of cancer angiogenesis are data showing that nebivolol suppresses mitochondrial respiration and ATP synthase in colon and breast cancer cell lines. Even though treatment with nebivolol does not affect cancer cell proliferation and apoptosis in vitro, in mice carrying colon carcinomas, treatment with nebivolol results in delayed tumor growth and decreased angiogenesis with less well-structured basal lamina and fewer pericytes. In addition, although VEGFA levels remain unaffected, nebivolol significantly decreases VEGFR2 expression and impedes normal endothelial cell proliferation [68].

A mechanism through which ARs in cancer cells may enhance cancer angiogenesis involves the peroxisome proliferator-activated receptor gamma (PPARγ). In animal models of breast cancer, activation of β ARs by chronic stress-produced catecholamines suppresses PPARγ expression and enhances the production of VEGFA and FGF2 by cancer cells, resulting in highly vascularized tumors. Treatment with the PPARγ synthetic agonist pioglitazone results in almost avascular tumors and abolishes the effects of chronic stress. The effect of chronic stress and norepinephrine on PPARγ downregulation and angiogenesis stimulation is mediated by the β_2 ARs [70].

The β_2 AR seems to also affect breast cancer metastasis to the bone. Isoproterenol or chronic stress following injection of an osteotropic variant of MDA-MB-231 breast cancer cells in mice increases VEGFA-positive osteoblasts, bone vessel density and incidence of bone metastatic lesions, effects that are abrogated by global or osteoblast-specific genetic loss of β_2 ARs [67]. The effect of isoproterenol on the VEGFA expression by osteoblasts is independent of the presence of cancer cells and can be inhibited by blocking the interaction of VEGFA with VEGFR2 [67], similarly to what has been observed in hemangioma-derived endothelial cells [55].

Treatment of human lung adenocarcinoma A549 cells that express β_2 ARs with isoproterenol results in increased phosphorylation of ERK1/2 and CREB, and increased mRNA levels of MMP2, MMP9 and VEGFA. Gene silencing of CREB inhibits isoproterenol-induced production of MMP2, MMP9 and VEGFA [66]. Similar results are obtained from an in vivo model of repeated social defeat stress-induced lung cancer, where it has been shown that stress exposure enhances expression of VEGFA, VEGFR2, MMP2 and MMP9, thus enabling tumor vasculature formation and cancer progression [71]. The mammalian C-terminal Eps15-homology domain 1-containing protein (EHD1), which regulates β_2 AR recycling from the endocytic compartment to the plasma membrane, has recently been shown to promote non-small-cell lung cancer progression by positively regulating angiogenesis through β_2 AR signaling in lung cancer cell lines [72].

Ultraviolet B (UVB)-irradiated murine skin keratinocytes express β_2 ARs. Angiogenesis, as well as the number of skin tumors and the tumor burden, are significantly decreased in UVB-irradiated mice following treatment with two selective β_2 AR antagonists that decrease VEGFA expression through inhibition of CREB phosphorylation [69]. In the same line, in prostate cancer cells in vitro and in a prostate cancer xenograft model in vivo, isoproterenol and chronic stress respectively, through β adrenergic signaling, enhance the phosphorylation of CREB, which induces the expression of histone deacetylase C2 (HDAC2) and suppresses TSP1 production by epigenetic modification [73]. Signal-

ing through β_2 ARs in prostate cancer endothelial cells enhances endothelial oxidative phosphorylation and prostate cancer angiogenesis; targeting this pathway may improve prostate cancer therapeutic approaches [74]. In prostate cancer, selective α_1 AR antagonists may have both anticancer and anti-angiogenic effects. This is based on the observation that terazosin not only directly inhibits prostate cancer cell proliferation, but also inhibits angiogenic functions of endothelial cells in vitro and VEGFA-induced angiogenesis in nude mice in vivo [21].

In addition to an effect on tumor cells, catecholamines may indirectly induce angiogenesis and neoplasia progression by activating ARs in tumor stroma cells, such as macrophages. In in vivo mouse models of lung cancer, chemical depletion of norepinephrine delays tumor growth, which seems to result from a decrease in the percentage of polarized M2 macrophages compared to M1 macrophages, as well as a decrease in the concentration of VEGFA in the tumors. Following stimulation with epinephrine or norepinephrine, M2 polarized macrophages secrete VEGFA and enhance angiogenesis in vitro, effects that are prevented by their pretreatment with propranolol [75]. Similarly, in a mouse model of breast cancer, stress-induced epinephrine and norepinephrine lead to the polarization of macrophages to the M2 phenotype and increased tumor weight and volume. The effect of epinephrine on the polarization of macrophages towards the M2 phenotype has been verified in vitro and occurs through β_2 ARs [76]. In an ovarian cancer cells/macrophages co-culture system in vitro, long-term exposure to epinephrine and norepinephrine increases the expression of numerous angiogenic molecules, including VEGFA, PDGF-AA and angiogenin. In an orthotopic ovarian cancer model in vivo, stress conditions also lead to enhanced PDGF-AA production, infiltration of $CD68^+$ macrophages in tumors, and increased ovarian cancer growth [77].

7. Conclusions and Future Directions

It is evident that both α and β ARs modulate angiogenesis (Figure 1) and their many agonists and antagonists, which are already in clinical use, can be exploited for their use in the control of angiogenesis. This has already been the case in pathologies, such as in infantile hemangiomas, where the use of propranolol is already established [78,79]. There are, however, many unanswered questions that, so far, have led to unclear and sometimes conflicting data, as mentioned in this review, and need to be clarified by future studies. The AR subtype(s) expressed by different endothelial cells should be clearly identified and verified by both in vitro and in vivo studies. The exact pathways downstream of each subtype in each case should be also elucidated. This task is very difficult due to homologies of these receptors at the level of effector binding sites and the common downstream signaling pathways. An example that is indicative of this complexity is the accumulating evidence suggesting that many β (especially selective β_1) AR antagonists are linked to β_3 AR activation [80], and some of their effects may not be due to β (β_1) antagonism, but rather result from β_3 activation, as described in this review for the pro-angiogenic effects of nebivolol. Future studies will clarify the missing points and will help expand the therapeutic indications of AR agonists and antagonists to regulate angiogenesis-related pathologies.

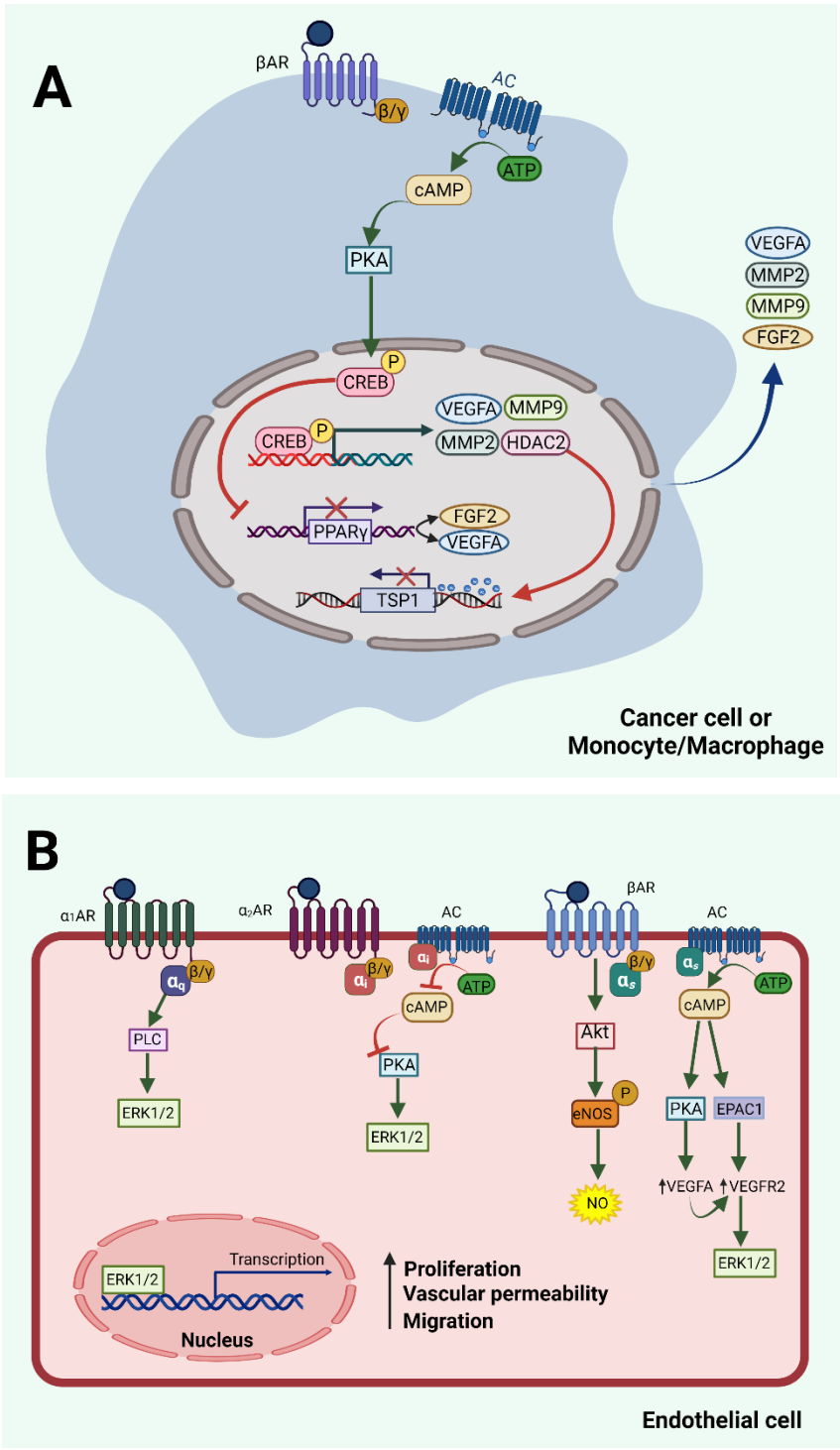

Figure 1. Adrenergic signaling in endothelial and other cells that regulate angiogenesis. (**A**) Indirect regulation. Norepinephrine and/or epinephrine reach the microenvironment of cancer or blood or other cells through the local sympathetic nerves or the bloodstream and bind to β ARs, thus activating the AC/cAMP/PKA pathway. PKA phosphorylates the transcription factor CREB, which induces the transcription of multiple pro-angiogenic factors, such as MMP2 and MMP9, VEGFA, and HDAC2. Secreted MMPs destabilize the extracellular matrix, releasing growth factors and allowing cancer cell metastasis and angiogenesis. Secreted VEGFA binds to VEGFR2 on neighboring endothelial cells and enhances their pro-angiogenic phenotype. Similarly, FGF2 and other secreted proangiogenic growth factors stimulate endothelial cells through their specific receptors. HDAC2 epigenetically inhibits the

production of the antiangiogenic TSP1. The CREB transcription factor also inhibits PPARγ, leading to further enhancement of VEGFA and FGF2 production. (**B**) Direct regulation. Endothelial cells express α and β ARs that affect the process of angiogenesis. Activation of α_1 and α_2 ARs triggers angiogenesis through ERK1/2 activation by different pathways. However, there is limited evidence and conflicting data related to the role of α ARs, as discussed in the text. Activation of β ARs leads to activation of AC/cAMP/PKA or EPAC1-dependent pathways that seem to transactivate the VEGFA/VEGFR2 pathway, also leading to ERK1/2 and endothelial cell activation. The Akt/eNOS pathway which leads to release of NO has been described downstream of β_3 ARs, and in the case of EPCs downstream of β_2 ARs, stimulating angiogenic properties of endothelial cells. The figure was created with BioRender.com (accessed on 29 November 2021).

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