REVIEW ARTICLE

Pharmacotherapy for Pulmonary Hypertension: Future Directions

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ABSTRACT

The elevated blood pressure produced in pulmonary artery, pulmonary veins, pulmonary capillaries and lung vasculature is collectively known as pulmonary hypertension. The prevalence of pulmonary hypertension has been gradually increasing in industrialized nations. Pulmonary hypertension is a rare lung disorder and it is associated with various stern symptoms such as shortness of breath, dizziness, fatigue, non-productive cough, lethargy, chest pain, angina pectoris, fainting and peripheral edema. No specific medications are available to treat pulmonary hypertension, however, pulmonary hypertension could be treated depending upon the origin and magnitude of hypertension using group of medications including endothelin receptor antagonists, long acting prostacyclin and its analogue, phosphodiesterase 5 inhibitor, calcium channel blockers, anticoagulants, diuretics etc. The ongoing research works revealed numerous potential pharmacological target sites to treat pulmonary hypertension efficiently. In this review, we discussed the molecular mechanisms involved in the pathogenesis of pulmonary hypertension and detailed account of current status of medications employed in the treatment of pulmonary hypertension including their therapeutic outcomes. Moreover, the newly identified potential target sites for managing pulmonary hypertension have been discussed.

Key words: Pathophysiology, pharmacological interventions, potential target sites, pulmonary hypertension, transforming growth factor-β (tgf-β), vascular endothelial dysfunction

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INTRODUCTION

Pulmonary hypertension is a severe diverse group of fatal disorders characterized by sustained increase in pulmonary artery pressure and vascular resistance due to pulmonary artery hyper-constriction.[1] It is a rare lung disorder in which the pulmonary artery becomes narrowed. The elevated blood pressure in pulmonary artery provides stress in the right ventricle of the heart, and as a result, the right ventricle gradually becomes enlarged, weaker and loses its ability to pump an adequate amount of blood to the lungs, which may develop right ventricular heart failure.[1] Pulmonary hypertension is a rare disorder and 15 cases have been reported per billion populations.[1] Pulmonary hypertension may be of either primary (familial and sporadic) or secondary (acquired) in which the primary pulmonary hypertension is relatively severe and rare, whereas the secondary pulmonary hypertension is common and less severe than primary pulmonary hypertension.[2] PH involves reduction in the production of vasodilator mediators, prostacyclin (PGI2) and nitric oxide (NO), and consequent increase in endogenous vasoconstrictors, endothelin-1 (ET-1) and thromboxane A2 in the pulmonary circulation.[3,4] In pulmonary hypertensive patients, the availability of NO was noted to be reduced due to impaired activation of endothelial nitric oxide synthase (eNOS) in the pulmonary circulation.[5] Serotonin elevates pulmonary artery smooth muscle cell (PASMC) proliferation, vasoconstriction and local micro thrombosis. [6] Patients with PH found high circulating levels of serotonin.[7] Preclinical studies on rats implicate the role of Rho-kinase in the pathogenesis of pulmonary hypertension.[8] Rho kinase plays an important role in PH. It suppresses myosin phosphatase activity and thus augments the PASMC contractility in rats.[9] The transient receptor potential channels (TRPC) involve in the process of PASMC proliferation and pulmonary vascular medial hypertrophy, and studies demonstrated the enhanced expression of TRPC in lungs of PH patients.[10,11] Oxidative stress produced by reactive oxygen species (ROS) contribute to PH in rats.[12] This disease is also caused by loss and mutation in the Bone morphogenetic protein type II receptor (BMPR-II).[13] The up-regulation of non-phagocytic nicotine amide adenine dinucleotide phosphate oxidase (NOX) subunit NOX4 in mice developed pulmonary hypertension by inducing vascular remodeling and medial hypertrophy of pulmonary artery.[14] The transforming growth factor-β (TGF-β), a fibrogenic cytokine, was found to be increased in lungs of pulmonary hypertensive patients.[15] Thus, the molecular mechanism involved in the pathogenesis of PH found to be complex, and not completely identified. Bosentan was the first endothelin receptor antagonist appear to be effective for the treatment of PH and it was approved by FDA in 2001, followed by sitaxsentan in 2006 and ambrisentan in 2007 for the management of PH.[16] Numerous prostacyclin analogues such as epoprostenol, iloprost, beraprost, treprosinil and cicaprost have been observed in experimental and clinical studies to have therapeutic potential in the treatment of pulmonary hypertension.[17] Various new interventions such as serotonin antagonists, vasoactive intestinal peptide, stimulators of soluble guanylate cyclase, tyrosine kinase inhibitors, Rho-kinase inhibitors, statins, potassium channel openers etc are under investigation [Figure 1 and Table 1]. The present review has been aimed to delineate the pathophysiology and drug therapy of pulmonary hypertension.

Pathophysiology of pulmonary hypertension

Pulmonary vascular wall remodeling is the result of changes in structural and functional components in the pulmonary arteries. The process of pulmonary vascular remodeling may occur as endothelial dysfunction which is a precursor for smooth muscle dysfunction of pulmonary arteries, which leads to pulmonary vasoconstriction. In pulmonary hypertension, smaller vessels of lungs are primarily affected and later-on entire pulmonary vascular tree undergoes histological alterations. The functions of pulmonary endothelium is to maintain blood vessels tone, fibrinolysis, homeostasis, neutrophil recruitment, production of growth factors.[18] Endothelial dysfunction is produced by the imbalance between vasoconstrictor peptides (serotonin and

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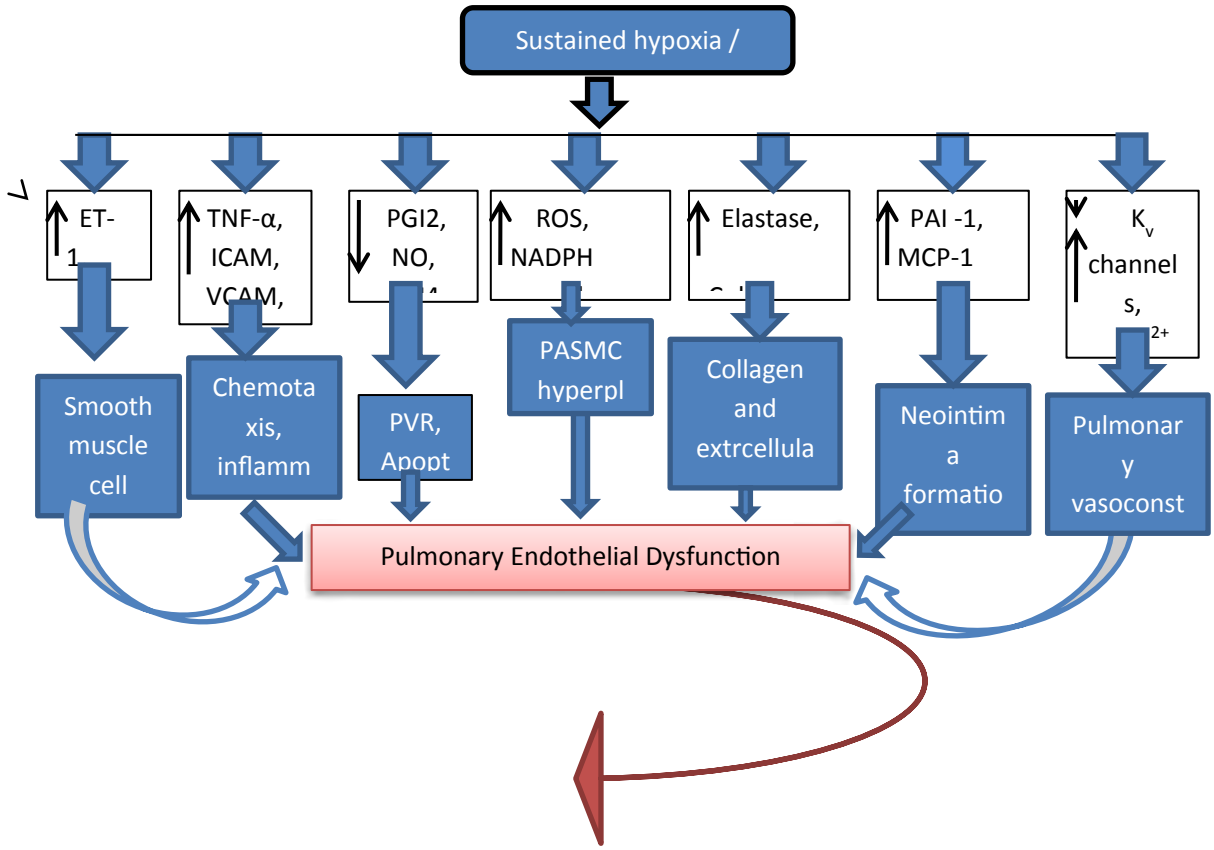

Figure 1: Path physiology of pulmonary hypertension

thromoboxane) and vasodilator peptides (NO, prostacyclin, EDHF (endothelial derived relaxing factor). Injury to pulmonary endothelium leads to produce PH by activating various coagulation pathways such as factor VIII antigen, von willebrand's factor (vWF), thrombomodullin, and plasminogen activator inhibitor type-1. Endothelium injury causes up-regulation of matrix metalloproteinases (MMP2, MMP9), collagenase, elastase and fibronectin. Quiescent cell line once activated in diseased state, the endothelial cell may express specific markers and proteins such as E-selectin, intracellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM), tissue factor, vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor (TGF-β) cause SMC and fibroblast proliferation.[18] In severe pulmonary hypertension there is an increased circulating level of pro- inflammatory cytokine IL-1 and IL-6, regulated on activation, normal T-cell expressed and secreted (RANTES) and fractaline.[19] Moreover there is an increased biosynthesis of polyamines and xanthine oxidoreductase which ultimately damage pulmonary vasculature.[20] The pulmonary vascular endothelial dysfunction induces apoptotic cell death and releases endothelial cells into circulation.[21] However, transplantation of endothelial progenitor cells reduced PAH in animals[22] Endothelial progenitor cells (EPCs) transfected with eNOS not only prevent but also reverse pulmonary arterial hypertension in rats.[23] Mesenchymal stem cells delivered intratracheally have been shown to prevent progression of PAH in rats.[24] BMPR-II is a receptor for transforming growth factor (TGF)-beta/ bone morphogenetic protein (BMP) superfamily is a member of TGF-β superfamily of growth factor receptors. Mutations in the BMPR-II can be found in the ligand-binding domain in the cytoplasmic tail which promotes the development of PH.[25] BMPR-II expressed ubiquitously and differentially activates various downstream signaling pathways such as pSmad1/5, p38 mitogen-activated protein kinase (p38MAPK), c-Jun N-terminal kinase (JNK) and Akt/PI3K which leads to PASMC proliferation and migration.[26] BMPR-II mutants and hypoxia lead to trapping of vesicle tethers, SNAREs and SNAPs in the Golgi of affected pulmonary arterial endothelial cells. Increased caveolin-1 expression further leads to decreased production of NO, thereby results in narrowing of pulmonary blood vessels.[27] In addition, a reduced expression of the co-receptor, BMPRIA is frequently observed in patient with PH. Impaired endothelial BMPR-II signaling causes proliferation of SMCs and involved in the pathogenesis of PAH. BMP involves in the activation of platelet-derived growth factor (PDGF), moreover it has been proved that imatinib (PDGF inhibitor) has been shown to reverse pulmonary hypertension[28] Treatment of apoe-/- mice with the PPARγ agonist rosiglitazone reverses pulmonary hypertension (PH) in rats[29] In addition, Activin like kinases (ALK-1) gene mutations have also been observed in pulmonary hypertension.[30]

Pharmacotherapy for pulmonary hypertension

Prostanoids

Prostanoids: Prostacyclins represent a newest and most important therapeutic approach in the treatment of pulmonary hypertension. Prostacyclin-I2 (PGI2) is the strongest pulmonary vasodilator with potent aggregation-inhibitory, anti-inflammatory and anti-proliferative properties. Main target of prostanoid is the Gs coupled IP proteins and activates adenylate cyclase, leading to increased cyclic adenosine monophosphate (cAMP)-dependent pathways. In addition the effect of prostanoids may be mediated by the activation of the peroxisome proliferator- activated receptor δ, a mechanism that may be important for anti-remodeling effect of prostanoids.[31]

PGI2 analogues have been shown to decrease chemokine secretion, suppress neutrophil adhesion, respiratory burst and elastase

Table 1: Pharmacological interventions for pulmonary hypertension

S. No.	Target sites	Therapeutic interventions
1	Calcium channel blockers	Nifedipine, Diltiazem, Amlodipine
2	Prostanoids	Epoprostenol, Treprostinil, Iloprost, Beraprost, ONO-1301
3	ET_A receptor antagonist	Sitasentan, Ambrisentan, BQ-123, ABT-627, BMS-182874, CI-1020, LU-135272, SPP301, TBC 11251,TBC 3711, YM-598, WS009A
4	$ET_{A/B}$ receptor antagonist	Bosentan, CPU0213, CPUO507, BSF420627
5	Phosphodiesterase V inhibitor	Sildenafil
6	Phosphodiesterase ¾ inhibitor	Pumafentrine
7	Soluble gunanyl cyclase stimulator	BAY 41-2272, BAY-58-2667, YC-1
8	Rho kinase inhibition	Fasudil, SB-772077-B
9	Inhibition of PDGF	Imatinib
10	Ligands of PPAR-γ	Pioglitazone, Rosiglitazone, Troglitazone
11	Inhibition of HMG- CoA-reductase	Simvastatin, Atorvastatin, Rosuvastatin, Pravastatin
12	Multikinase inhibitor	Fluvastatin
13	Steroids and immunosuppressive therapy	Sorafenib
14	Mitochondrial pyruvate dehydrogenase kinase inhibitor	Testosterone, Progesterone, Prednisolone, 2-methoxyestradiol, Dehydroepiandrosterone, cyclosporine dichloroacetate
15	Inhibition of Nuclear factor of activated T-cells	Peptide V1VIT, Cyclosporine
16	$5HT_{2A}$ receptor antagonist	Sarprogelate, Ketanserin
17	5HT transporter inhibition	Fluoxetine, Paroxetine, Citalopram
18	Vasodilator peptide	Adrenomedullin
19	Elastase inhibition	ZD-0892
20	Activin receptor -like kinase-5 inhibition	IN-1233
21	Inhibition of store operated calcium channel	SKF-96365, Nickel and La^{3+}
22	Diuretics	Furosemide
23	Anticoagulants	Warfarin sodium
24	Inotropic agents	Digoxin
25	κ- opioid receptor agonist	U50, 488H
26	Potassium channel opener	Dichloroacetate, Iptakalim, Levcromakalin, JTV-506
27	Phosphodiesterase-4 inhibitor	Roflumilast
28	P38 MAPK inhibitor	SB-203580
29	Vasoactive intestinal peptide	Aviptadil

secretion[32] Thus, various prostacyclin analogues such as Epoprostenol, Iloprost, Beraprost, Treprostinil, cicaprost have been observed in numerous experimental and clinical studies to have proming agent in the treatment of pulmonary hypertension. Epoprostenol was the first drug approved for by the food and drug administration (FDA) in 1984 for the management of PH.[33] Long term administration of intravenous Epoprostenol requires a permanent central venous catheter and a portable infusion pump. Inhaled Iloprost is more intrapulmonary selectivity avoidance of right to left shunt blood flow.[34] However, inhalation of Iloprost has been shown to attenuate PAH and vascular structural remodeling in MCT-treated rats.[34] Inhaled Iloprost was noted to retard the pulmonary hypertension in patients by suppressing neutrophil adhesion, respiratory burst and elastase secretion.[35] Inhaled Iloprost has been shown functional improvement in some children with PAH.[36] Beraprost was noted to inhibit the development of pulmonary hypertension through vasodilation, antiplatelet aggregation and through anti-inflammatory action in MCT injected rats.[37] Beraprost sodium prolongs the life of PH patients by improving exercise capacity and ventilator efficiency.[38] Treprostinil, a novel prostacyclin analogue has been noted to reduce the expression of NFκB nuclear translocation, tumor necrosis factor-alpha, interleukin-1beta, interleukin-6, and granulocyte macrophage colony-stimulating factor in human alveolar macrophages.[39] It has been demonstrated that inhaled Treprostinil was found to be effective in pulmonary hypertensive patients by increasing exercise tolerance and pulmonary vasodilation.[40] Cicapost, was found to be effective in preventing pulmonary hypertension in rats.[41] Cicaprost has been shown to inhibit endogenous ET-1 release from human pulmonary artery SMCs.[42] The combination of inhaled Treprostinil with sildenafil produced additive effect in pulmonary vasodilation in pulmonary hypertensive patients.[43] The combination of sildenafil with long term intravenous Epoprostenol has been found to delay the worsening of pulmonary hypertension rather than treatment with either drug alone.[44] The combined effect of Treprostinil and Bosentan were found to be safe and shows significant improvement in PH.[45]

Endothelin receptor antagonists

ET-1 was discovered in 1988 and was found to be important vasoconstrictor and abundantly expressed in the lung and directed attention towards pulmonary hypertension. ET-1 binds with two types of receptor; ETA receptor and ETB receptor.[4] ETA receptor located on SMCs and cardiac myocytes, whereas ETB receptor predominantely expressed on both endothelial and SMCs. Endothelin receptor binds with phospholipase C, which further increases inositol triphosphate, diacylglycerol (DAG) and intracellular calcium, finally leads to vasoconstriction.[46] Whereas, the activation of ETB receptor was found to increases the release of NO and prostacyclins. It also exhibit antiapoptotic and antiproleiferative property. This also mediates the pulmonary clearance of circulating ET-1 and reuptake of ET-1 by endothelial cells.[47] ET-1 exhibits vasoconstriction, mitogenic, proinflammatory actions and induces platelet aggregation.[48,49] At present, three different ERAs have been developed for PAH: Bosentan, sitasentan and ambrisentan.

Bosentan was the First endothelin receptor antagonist approved by food and drug administration in 2001. The clinical study named Bosentan Randomized trial of Endothelin Antagonist Therapy (BREATHE-1) improved exercise capacity as assessed in terms of 6-min walking distance.[50] In a recent study, bosentan combined with sildenafil decrease PVR, normalizes cardiac output, RV shortening and increases right ventricular mitochondrial capacity in MCT- induced pulmonary hypertensive rats.[51,52] The long term randomized, double-blind, placebo-controlled showed that combination of Bosentan with sildenafil was found to be more effective in the treatment of pulmonary hypertension as compared to monotherapy.[53] Sitaxsentan was the second drug approved in 2006 for the pulmonary hypertensive patients.[54] Moreover, it has been demonstrated that sitaxsentan attenuates the right ventricular systolic pressure, improved exercise capacity and pulmonary vascular remodeling and the associated cardiac hypertrophy by blocking the increased level of ET-1 in hypoxia induced pulmonary hypertensive rats.[55] However, treatment with sitaxsentan was noted to inhibit the cytokines levels such as IL-1, TNF- activation in PH patients.[56] Ambrisentan was approved in the USA in 2007 for PAH patients and shows improved exercise capacity and less adverse effects (aminotransferase abnormalities).[56,57] However, treatment with ambrisentan was noted to reduce right ventricular systolic pressure (RVSP), pulmonary vascular resistance (PVR) by increase in prostacyclin synthase expression-1, improved exercise capacity as compared to bosentan in experimental rats[58] Endothelin receptor antagonists CPU0507, is reported to restore altered pulmonary vasoconstriction in rats.[59] CPU0123, a novel endothelin receptor antagonist has been shown to suppress excessive ET-ROS pathway in pulmonary hypertensive rat.[60] Inhalation of the Endothelin A receptor antagonist LU-135252 not only improves mean arterial pressure, cardiac output but also attenuates hypoxic pulmonary vasoconstriction.[61] Preventive effect of BQ123 (ETA receptor antagonist) has been reported in pulmonary hypertension in broilers.[62] Further, CI-1020 and C1-1034 endothelin-A receptor antagonist were noted to reverse hypoxic pulmonary hypertension in perinatal lamb.[63] Furthermore, treatment with WS009A ETA antagonist reverses PVR and pulmonary hypertension in experimental pulmonary hypertension in rats.[64,65] Moreover, novel and selective endothelin-A receptor antagonist YM598 suppresses the increase in pulmonary arterial hypertension and decrease right ventricular hypertrophy in experimental model of pulmonary hypertension in rats[66] Macitentan was noted to reduce pulmonary arterial hypertension in patients.[67] Bosentan was shown to reduce nitrosative and oxidative stress and attenuates the progression of pulmonary hypertension in patients.[68]

Phosphodiesterase (PDE) inhibitors

Phosphodiesterase level was found to be increase in the pulmonary vessel and it plays a considerable role in the progression of pulmonary hypertension[69] Phosphodiesterase-1 (PDE-1) has three isoforms which are regulated by calcium-calmodulin and can hydrolyze both cAMP and cGMP although PDE-1A /B receptor have higher affinity for cGMP. The treatment with PDE1 inhibitor 8-methoxymethyl-isobutyl-1-methylxanthine (8MM-1BMX) reduced PVR and right ventricular hypertrophy by inhibiting SMC proliferation in rats with MCT-induced pulmonary hypertension.[70] Pumafentrine, PDE-3/4 inhibitor (mixed) reversed small pulmonary arterial muscularisation, media hypertrophy in MCT-induced pulmonary hypertension in rats.[71] However, sildenafil was shown to produce a significant improvement in exercise capacity in pulmonary hypertensive patients.[72] Moreover, Sildenafil inhibits proliferation of PASMC and down-regulation of capacitative calcium entry (CCE) and transient receptor potential gene expression in human pulmonary artery SMCs.[73] Further, treatment with tadalafil has a beneficial effect in patients with pulmonary artery hypertension has a better therapeutic agent than sildenafil because it has no effect on PDE1.[74] Previous studies documented that treatment with rosuvastatin, sildenafil and their combination reduce pulmonary hypertension by decreasing right ventricular pressure, right ventricular mass in monocrataline induced pulmonary hypertension in rats.[8]

Soluble gunanyl cyclase stimulator

Soluble gunanyl cyclase is an attractive target for treating pulmonary hypertension.[75] The decreased level of endogenous NO plays a important role in the progression of pulmonary hypertension. NO is a potent vasodilator and inhibitor of vascular SMC proliferation and platelet aggregation which exerts most of physiological action by the activation of soluble guanylyl cylase and subsequent enhance the level of cGMP. The increase in cGMP levels cause pulmonary vasodilation by mechanism involving modulation of Ca^{2+} homeostasis and sensitivity of contractile apparatus to $[Ca^{2+}]$.[75] In NO biavailibility was found to reduce in pulmonary hypertensive patients.[76] In pulmonary hypertension there is reduced pulmonary levels of eNOS, which result in decreased synthesis of NO.[77,78] The plasma concentrations of the endogenous L-arginine analog, asymmetric dimethylarginine (ADMA), was found to be increase in pulmonary hypertensive patients, which inhibits both the transport of L-arginine and the synthesis of NO in PH patients.[79] Moreover, the expression of dimehylaminohydroxylase (DDAH) enzyme responsible for breakdown of ADMA is reduced in pulmonary hypertension.[80] In PH patients, increased activity of arginase II leads to the decreased production of NO by competing with NOS for L-arginine substrate. The expression of phosphodiesterase-5 (PDF5), the principal enzyme responsible for the degradation of cGMP in the pulmonary vascular smooth muscle cell has been shown to be increased in case of pulmonary hypertension.[81] The deficiency of cofactor tetrahydrobiopterin is required for substrate binding and stabilization of dimeric structure of eNOS to facilitate biosynthesis of NO in pulmonary hypertension.[82] Further, the oxidative stress may deactivate sGC because the oxidized form of enzyme (sGC-Ox) is not capable of forming cGMP[83] sGC stimulators act on the non-oxidized Fe II heme whereas sGC activators act preferentially on the Fe III heme have a pathogenic role to induce pulmonary vasodilation in the absence of NO. It has been documented that administration of novel BAY 41-2272 (sGC activator) reduces PVR, right ventricular hypertrophy chronic model of pulmonary hypertension in neonatal rats.[84] In a recent study, Riociguat (BAY 63-2521), guanyl cyclase stimulator is well tolerated and superior to NO therapy, currently being investigated in phase III clinical trial for the treatment of PH.[85-87] Some soluble guanyl cyclase stimulators such as BAY 41-2272, BAY 41-8543 and riociguat (BAY 63-2521), CFM-1571, BAY 60-4552, vericiguat (BAY 1021189) has been noted to reduce mean pulmonary arterial pressure and reverse vascular remodeling and right heart hypertrophy in several experimental models of PH.[75]

Rho-kinase inhibitors

Rho kinase is a novel therapeutic target is involved in the pathogenesis of pulmonary hypertension.[88] Involvement of intracellular signaling pathways by GTP-binding proteins, such as Rho, Ras, Rab and Ran families.[89] Rho- kinase suppresses myosin phosphatase activity by phosphorylating the myosin binding subunit of the enzyme and thus augments VSMC contraction.[88] Up regulation Rho kinase inhibition involved in decrease eNOS expression and activates inflammatory cell migration in PH. Rho kinase has a important role in PH. It activates various mediators such monocyte chemoattractant protein-1 (MCP-1), PAI-1 and NADPH oxidase and finally cause vascular remodeling in patients.[90] Oral treatment with rho kinase inhibitor, Fasudil is also effective to inhibit the development of pulmonary arterial hypertension induced by experimental mice.[51,91] Furthermore, combined treatment

of Fasudil (Rho kinase inhibitor) with beraprost (prostacyclin analogue) was found to improve right ventricular hypertrophy and median thickness in pulmonary vessels of MCT-induced pulmonary hypertensive rats.[92] This suggests that rho kinase inhibitor could be combined with prostanoids as a future treatment of PAH. SB-772077-B, a novel aminofurazan based Rho-kinase inhibitor which has been shown to produce ameliorative effect in monocrotaline- induced pulmonary hypertension in rats.[93] Statins was found to reduce MCT-induced pulmonary hypertension in rats through inhibition of Rho, Ras, Rac pathways.[94] Further, administration or inhalation of Rho-kinase inhibitors promotes pulmonary vasodilation in patients with PAH.[95] Moreover, treatment with Y-27632 attenuates pulmonary hypertension in hyperoxia-exposed newborn rats by decreasing right ventricular hypertrophy and pulmonary arterial remodeling.[96] Previous studies documented that treatment with fasudil, sildenafil and their combination reduce pulmonary hypertension by decreasing right ventricular pressure and improve exercise capacity in MCT-induced pulmonary hypertension in rats.[97] Thus, Rho-kinase is a novel target and Rho-kinase inhibitiors can be used for the treatment of pulmonary hypertension.

Serotonin (5-HT) receptor antagonist and Serotonin transporter (5-HTT) blockers

Serotonin system has been implicated in the pathophysiology of pulmonary hypertension. Serotonin level was found to be elevated in patients with PAH.[98] Serotonin mediates pulmonary arterial proliferation, vasoconstriction and local micro-thrombosis.[99,100] Further, the transgenic SM22-LacZ (+) mice overexpressing the 5- hydoxytryptamine transporter gene exhibit marked pulmonary hypertension.[101,102] Moreover, 5-HT2A receptor antagonist, sarpogrelate has been reported to reduce PAH in rats through anti-inflammatory and anti-proliferative properties.[103] Sarpogrelate was beneficial to suppress PAH and pulmonary vascular remodeling and prolong survival in a rat model of PH. In addition, nordexfenfluramine can cause severe pulmonary hypertension than dexfenfluraminre though the activation of 5-HT (2) receptors and increase the influx of extracellular Ca^{2+} and release of Ca^{2+} from the sarcoplasmic reticulum in PASMC.[104]

In a recent study, the administration of Fluoxetine was found to have ameliorative effect on pulmonary arterial hypertension by diminished the expression of Bcl- 2, Bcl-x (L) and increases the expression of cleaved caspases-3 and Kv 1.5 channels in MCT-induced pulmonary hypertension in rats.[105] Moreover, citalopram (5-HT inhibitors) and GR127935 (5-HT 1B/1D receptor antagonist) have been reported to reduced pulmonary vascular remodeling in hypoxia-induced pulmonary hypertensive mice.[106] The use of selective serotonin reuptake inhibitors such as paroxetine, sertraline, fluoxetine has been found to reduce 50% reduction of death risk in PH patients.[107] Recently, a phase II randomized, Placebo-controlled study on PRX-08066, 5-HT2B receptor antagonist as well as 5-HTT transporter inhibitor has been noted to attenuate pulmonary hypertension in different experimental models. A PRX-08066 can consider a novel therapy to treat pulmonary hypertensive patients. Previous studies documented that treatment with fluxetine reduce pulmonary hypertension in MCT treated rats by inhibiting RhoA-ROCK and Akt signaling pathways.[108] Thus, the serotonin receptor antagonist and serotonin transporter inhibitor has been suggested to produce a unique agent in the treatment of pulmonary hypertension.

Statins

Statins play a crucial role in the therapy of pulmonary hypertension. The clinical and experimental evidence suggest that statins decreases the Rho-kinase activation, P38 MAP kinase expression, restores eNOS expression, prevent apoptosis and improved medial wall thickness.[109,110] Treatment with pravastatin, HMG-CoA reductase inhibitor has been noted to down-regulate the expression of stromal-cell derived factor (SDF-1), CXC chemokine receptor 4 and ICAM-1/ CD18 pathway in hypoxia induced-pulmonary hypertension in rats.[111] Further, a placebo-controlled study rosuvastatin has been noted to decrease the level of P-selectin, tissue plasminogen activator in patients with pulmonary hypertension.[112] However, the treatment with simvastatin was shown to retard pulmonary vascular remodeling by inhibiting RhoA/ROCK pathway in cultured PASMCs.[91] Moreover, treatment with fluvastatin was shown to reduce right ventricular pressure, right ventricular remodelling and muscularization of pulmonary artery in rats by increasing the eNOS activity in experimental pulmonary hypertension.[113] In a recent study, combination of atorvastatin and sildenafil produced high reduction in PVR, RVP as compared to treatment with either drug alone in a rat model of pulmonary hypertension.[111] Co-administration of statin with imatinib was found to be more effective treatment of pulmonary hypertension by decreasing arterial blood pressure, ventricular hypertrophy in MCT-induced pulmonary hypertension in rats.[114] In addition, combined therapy (beraprost plus simvastatin) also found to be beneficial in PH.[115] Hence, statins might be the potential agents for the management of pulmonary hypertension.

Peroxisome proliferator activated receptor

Peroxisome proliferator activated receptor belongs to the nuclear family of ligand activated transcriptional factors.[116,117] PPAR have been implicated in various disorder including cancer, diabetes, cardiomyopathy and pulmonary hypertension.[118,119] PPARγ agonist has been shown to prevent development of pulmonary hypertension in rats.[120] PPARγ agonist exhibits beneficial effect in pulmonary hypertension through several antiproliferative, anti-inflammatory and antiapoptotic mechanisms.[118] PPARγ agonist has been noted to decrease the expression of NADPH oxidase, PAI-1 production and stimulates NO production.[121] PPARγ ligands reduce iNOS expression, platelet derived growth factor signaling production, macrophage recruitment and inflammatory mediator production in pulmonary hypertension.[122] PPARγ activation was noted to inhibit the Rho/Rho kinase pathway and helps in delaying the progression of disease.[123] Further, PPARγ Agonists was found to reduce the production of ET-1, potent vasoconstrictor and plays a protective role in pulmonary hypertension. Treatment with pioglitazone, PPARγ ligand reduces proliferation of PVSMC, PVR and induces apoptosis in experimental pulmonary hypertension in rats.[124] Recently it has been demonstrated PPARγ agonist rosiglitazone ameliorates PH in Apoe-/-mice[29] PPARβ /δ agonist could be a novel target for the treatment of PH. In addition, GW0742 (PPARβ /δ agonist) has been noted to improve to right ventricular pressure in hypoxia-induced pulmonary hypertensive rats.[125] Rosiglitazone was noted to attenuate ET-1 induced pulmonary vasoconstriction and reduce pulmonary hypertension in Sprague-Dawley rats.[126] Thus, further experiments are needed to investigate the role PPARβ/γ in pulmonary hypertension.

Calcium channel blockers

The increased level of intracellular calcium plays a significant role in the pathogenesis of pulmonary hypertension. Calcium channel blockers are the heterogenous class of vasodilators and found to be effective for the treatment of pulmonary hypertension.[127] Various calcium channel blockers such as nifidipine, diltiazem were shown to have therapeutic potential in management of pulmonary hypertension. The treatment with nifedipine was shown to be effective in pulmonary hypertensive patients by sustained reduction in pulmonary artery pressure and

PVR.[128] The administration of amlodipine was shown to prevent the pulmonary vascular remodeling by restore eNOS expression in the lung tissue of MCT- induced pulmonary hypertensive rats.[129] However, the blockers of store operated Ca^{2+} such as SKF-9 and nickel attenuates hypoxic pulmonary vasoconstriction.[130] Recently, it was documented T-type calcium channel blockers may also be involved in the treatment of pulmonary hypertension.[131]

Potassium channel openers

Potassium channels may play a significant role in the pathogenesis of pulmonary artery hypertension. The decreased expression of Kv channels in pulmonary hypertension leads to inhibition of apoptosis and promotes pulmonary hypertrophy.[132,133] However, Kv1.5 is down-regulated in PASMCs in humans with PH.[134] Kv channel inhibition which results in membrane depolarization, activation of voltage dependent Ca^{2+} channel in rats.[135] Intracellular Ca^{2+} causes PASMC contraction by promoting myosin and actin interaction and PASMC proliferation.[136] Further, kv channel inhibition decelerates apoptotic volume decreases (AVD) and inhibits apoptosis.[137] Furthermore, kv channel openers like dichloroacetate (DCA) have been observed to prevent pulmonary hypertension in experimental animals.[138] Moreover, iptaklim, a novel KATP channel opener, have been shown to reduce right ventricular hypertrophy, pulmonary remodeling in hypoxic pulmonary hypertensive rats[139,140] However, appetite suppressants dexfenfluramine and aminorex directly inhibits potassium channel in rats.[141] Moreover, treatment with JTV-506 (KATP opener) attenuates pulmonary smooth muscle proliferation and vascular remodeling in MCT-induced pulmonary hypertensive rats.[142] In addition, levcromakalim have been noted to decrease right ventricular pressure in hypoxia-induced pulmonary hypertension in piglets.[143] Thus potassium channel opener may be a attractive target as it play a important role cell apoptosis, survival and proliferation.[137] Further, iptakalim, potassium channel opener was shown to reduce pulmonary hypertension in rats by decreasing pulmonary arterial smooth muscle cell proliferation by down-regulating PKC-α.[144]

Tyrosine kinase inhibitors

Recent developments have been made in pulmonary hypertension by class of the drugs acting to inhibit transmembrane receptor tyrosine kinases. Platelet-derived growth factor (PDGF), which acts via receptor tyrosine kinases, have a significant role in PH[145] Further, treatment with imatnib, PDGF receptor antagonist have been shown to reduce right ventricular pressure, pulmonary proliferation by suppressing activation of downstream signaling pathways in MCT-induced pulmonary hypertension in rats.[34] Furthermore, in clinical study treatment with imatininib showed improvement in six minute walk test, hemodynamics in pulmonary hypertensive patients.[146] In addition, treatment with multikinase inhibitor, sorafenib reduced right ventricular remodeling and pulmonary arterial masculinization by inhibition of Raf kinase and ERK1/2 signaling pathway in experimental pulmonary hypertension.[147] Erlotinib and imatinib aerosols can be a novel target for the treatment of pulmonary hypertension.[148] In a recent study, imatinib attenuates MCT-induced pulmonary hypertension by increasing vasodilation in pulmonary vascular beds.[28] Thus, tyrosine kinase may be a potential target and tyrosine kinase inhibitors may be used for the treatment of pulmonary hypertension.

Future directions

For the past couple of years, tremendous efforts have been made in the identification of novel target sites and potential future agents have been explored to have therapeutic potential in treatment of pulmonary hypertension. Elastase was found to be elevated in pulmonary hypertension.[149] Treatment with ZD-0892 elastase inhibitor completely reverses the MCT- induced pulmonary hypertension in rats[150] Adrenomedullin has a vasodilatory effect on pulmonary vasculature. ADM cause dose dependent increase in NO release and plays a protective role in PH.[151] Moreover, exogenous ADM prevents and reverse pulmonary hypertension in ovine endotoxaemia of rats.[152] Caveolin-1 plays a major role in pulmonary hypertension.[153] Reduced expression of caveolin-1 and 2 have been observed in the plexiform lesions formed in pulmonary hypertension[154] Cav-1 have been noted to increase cell growth and apoptosis in rats.[155]

Moreover, there is an inverse relationship between loss of cav-1 and various promitogenic and antiapoptotic IL-6/ STAT 3 and ERK1/2 signaling. Hypoxia leads to decrease in production of vasorelaxant proteins such as caveolin and nitric oxide intereaction and play a important role in PH.[156] However, treatment with cell-permeable cav -1 peptide prevents right ventricular pressure and hypertrophy in MCT -induced pulmonary hypertensive rats[157] Moreover, cav-1 rescue is associated with the inhibition of STAT-3 activation and attenuation of pulmonary hypertension.[158] Estrogens are critically involved in the acute activation of endothelial nitric oxide synthetase and SMC growth. Treatment with 2-ethoxyestradiol is antimitogenic and attenuates PH in experimental rats.[159] In addition, Dehydroepiandrosterone increase expression of soluble guanylate cyclase and inhibits pulmonary hypertension.[160] Treatment with mycophenolate mofetil is noted to attenuates right ventricular hypertrophy, reduce vascular wall thickening and vascular remodeling by preventing smooth muscle cell proleiferation, fibrobast activation MCT-induced pulmonary hypertension in rats.[161] Treatment with roflumilast, phosphodestrase 4 inhibitor attenuates pulmonary vascular remodeling by decreasing the level of inflammatory mediators in experimental pulmonary hypertensive rats.[162] P38 MAPK may prove to be a identical approach in the treatment of pulmonary hypertension. P38 MPK activation has been shown to mediate pulmonary hypertension by stimulation of superoxide production. Treatment with p38MAPK inhibitor SB-203580 was noted to reduce PH in experimental rats by increasing NO generation and reducing superoxide generation.[163] Treatment with κ -opioid receptor agonist U50, 488H inhibits the remodeling of pulmonary artery, ET-1, Ang-II and increase the production of NO in pulmonary hypertensive rats.[164]

Nuclear factor of activated T-cells inhibits both apoptosis and expression of Kv 1.5 in myocardial cells of rats.[165] However, peptide VIVIT (NFAT Inhibitor) has been reported to decrease PH by restoring the expression of Kv1.5 and decreasing Bcl-2 in PASMCs.[166] Moreover, treatment with cyclosporine-A, (calcium/calmodulin-dependent protein inhibitor) has been noted to decrease right ventricular hypertrophy, HIF-1 levels in hypoxia-induced pulmonary hypertension in rats.[167,168] The protein kinase-C (PKC) pathway plays an important role in chronic pulmonary hypertension. Recent studies indicate the therapeutic potential PKC inhibitors in treating pulmonary hypertension.[169,170] Administration of xylitol, PKC inhibitors noted to reduce pulmonary artery smooth muscle cell proliferation in rat exposed to chronic hypoxia.[169] However, it has been reported that experimental pulmonary vasoconstriction is attenuated in PKCε null mice and that PKCζ appears to be important determinant of susceptibility to chronic hypoxic pulmonary hypertension.[171] The experimental and clinical study demonstrated that therapeutic prospective of vasoactive intestinal peptide in treating pulmonary hypertension. VIP also help to induce the synthesis of tetrahydrobiopterin[172] a critical cofactor in endothelial nitric oxide production.[173] Thus, the lack of VIP knock out (VIP-/-) mice develop PAH, right ventricular hypertrophy and pulmonary vascular remodeling.[174] Treatment with inhaled aviptadil (VIP agonist) was noted to exhibit pulmonary vasodilating effect and

improved oxygenation in patients with PH.[175] Vasoactive intestinal peptide get cleaved in the lungs by proteolytic cleavage, hence the use of this peptide is limited. So polymer- grafted Liposomal -based method of VIP administration has been developed for the treatment of PH.[176]

Herbal interventions

Recently, numerous potential herbal interventions have been developed to attenuate the progression of pulmonary hypertension. Resveratol, an antioxidant has been noted decrease right ventricular pressure, pulmonary artery resistance, right ventricular hypertrophy and decreasing expression of inflammatory cytokines (TNFα, IL- 1a, IL-6, PDGF) in MCT-induced pulmonary hypertension in rats.[177] Resveratol was observed to decrease oxidative stress by increases expression of eNOS, NADPH oxidase and improve endothelial function in experimental rats. The treatment with radix astragali has been shown to decreases mean arterial blood pressure, pulmonary vascular remodeling by inhibiting the type III collagen deposition, SMC proliferation and increases the tolerance of myocardium in hypoxia induced PH in rats.[178] Treatment with Panax ginseng has been noted to attenuate RVH, by inhibiting the calcineurin signal transduction pathway, increasing NO release in MCT-induced pulmonary hypertension in rats.[179] Genistein, a phytoestrogen was noted to reduce RVH, medial wall thickness of pulmonary arteries in pulmonary hypertensive rats by increasing the expression of endothelial NO synthase.[180] Treatment with Erigeron breviscapus has been noted to decreases mPAP, RVH and proliferation by inhibiting Fractalkine expression in pulmonary hypertensive rats.[181,182] The administration of San-Huang- Xie-Xin-Tang, traditional Chinese herbal preparation, composed of Coptidis rhizome, Scutellariae radix and Rhei rhizome has been noted to treat pulmonary hypertension by down regulating the expression of phosphodiesterase type 5, Rho-kinase (ROCK) II, cyclooxygenase -2 (COX-2), and up-regulated expression of soluble guanylyl in U46619-induced pulmonary hypertension in rats.[183,184] Treatment with garlic (Allium sativum) has been shown to attenuate RVH, right ventricular pressure in rats.[185] The administration of traditional Naofeikang, Chinese herb has been noted to lower pulmonary hypertension by preserving vessel endothelial cells and lessen the inflammatory reaction and inhibiting PVR in hypoxia induced pulmonary hypertension in hamsters.[186] In a clinical study, Parental preparation of Angelica was noted to decrease pulmonary hypertension in patients by decreasing the levels of ET-1, angiotensin-II (AT- II).[187] Treatment with Salvia miltiorrhiza, has been noted to inhibit structural remodeling of pulmonary arteries by decreasing the level of heme oxygenase-1 and iNOS and enhance the level of eNOS in animal model of PH.[188] The administration of tetrandrine was noted to decrease MPAP, PVR and b-FGF expression in the lung tissues of chronic hypoxic pulmonary hypertensive rats.[189] Treatment with total Ginsenosides has been shown ameliorative effect on RVH, MABP by enhancing the release of NO and decrease intracellular free calcium and decrease the expression of ERK-1 and Mitogen activated protein kinases in MCT-induced pulmonary hypertension in rats.[190,191] Treatment with various flavanoids Luteolin, Rhoifolin has been noted to decrease PAP, pulmonary artery wedge and aortic pressure and pulmonary vascular resistance in hypoxia induced pulmonary hypertensive dogs.[192] The administration of Plumbagin, a natural product found in the plants of the Plumbaginaceae, Droseracea, Ancestrocladaceae and Dioncophyllaceae families has been noted to lower pulmonary hypertension by decreasing pulmonary artery remodeling, mean pulmonary artery pressure, right ventricular remodeling in hypoxia induced pulmonary hypertension in rats.[193] Treatment with Ruscogenin, a traditional Chinese herb Radix ophiopogon Japonicus has been noted to decrease pulmonary hypertension by decreasing inflammatory cytokines, macrophage infiltration in MCT induced pulmonary hypertensive rats.[194]

CONCLUSION

Pulmonary hypertension is a serious health problem. This review will aid in providing better understanding of new ideas about the pathophysiology and new treatment strategy of pulmonary hypertension. The present article reviewed multiple pharmacological agents such as prostanoids, endothelin receptor antagonist, phosphodiesterase inhibitors, soluble guanyl cyclase stimulator, rho-kinase inhibitors, serotonin receptor antagonist, statins, PPARs agonist, calcium channel blockers, potassium channel openers, tyrosine kinase inhibitors, which can be used as interventional targets for the treatment of PH.

Conflict of interest

The authors declared no conflict of interest.

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