frontiers in Cardiovascular Medicine

REVIEW
published: 17 December 2018
doi: 10.3389/fcvm.2018.00179

The Role of G Protein-Coupled Receptors in the Right Ventricle in Pulmonary Hypertension

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Pressure overload of the right ventricle (RV) in pulmonary arterial hypertension (PAH) leads to RV remodeling and failure, an important determinant of outcome in patients with PAH. Several G protein-coupled receptors (GPCRs) are differentially regulated in the RV myocardium, contributing to the pathogenesis of RV adverse remodeling and dysfunction. Many pharmacological agents that target GPCRs have been demonstrated to result in beneficial effects on left ventricular (LV) failure, such as beta-adrenergic receptor and angiotensin receptor antagonists. However, the role of such drugs on RV remodeling and performance is not known at this time. Moreover, many of these same receptors are also expressed in the pulmonary vasculature, which could result in complex effects in PAH. This manuscript reviews the role of GPCRs in the RV remodeling and dysfunction and discusses activating and blocking GPCR signaling to potentially attenuate remodeling while promoting improvements of RV function in PAH.

Keywords: right ventricle, G protein-coupled receptor, pulmonary hypertension, remodeling, dysfunction

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Specialty section:
This article was submitted to Heart Failure and Transplantation, a section of the journal Frontiers in Cardiovascular Medicine

Received: *12 September 2018*
Accepted: *30 November 2018*
Published: *17 December 2018*

Citation:
Viswanathan G, Mamazhakypov A, Schermuly RT and Rajagopal S (2018) The Role of G Protein-Coupled Receptors in the Right Ventricle in Pulmonary Hypertension. Front. Cardiovasc. Med. 5:179. doi: 10.3389/fcvm.2018.00179

INTRODUCTION

Right ventricular (RV) dysfunction and failure predict mortality in a number of cardiopulmonary diseases including pulmonary arterial hypertension (PAH) (1), heart failure (2–4) and chronic obstructive pulmonary disease (COPD) (5, 6). Initially, the RV undergoes favorable (adaptive) remodeling characterized by an increase in RV wall thickness, dilation and mass mediated by cardiomyocyte hypertrophy and moderate extracellular matrix deposition to maintain its contractility to the increased afterload (7, 8). At some point in the course of the disease, the compensatory mechanisms of the RV are exhausted and the RV undergoes maladaptive remodeling with RV dilation and dysfunction (9), which is characterized by insufficient angiogenesis (10), excessive inflammation (11), and fibrosis (12). Despite similar pulmonary hemodynamics across different causes of PAH, such as that due to congenital heart disease or scleroderma, there are wide variations in outcomes in PAH depending on the etiology (13). For example, survival and functional status of PAH patients due to congenital heart diseases (CHD) are better than those of IPAH patients (14, 15), which may be explained by the compensated RV function and favorable (adaptive) RV remodeling (increased wall thickness) due to longstanding PAH (16). For these reasons, many groups have postulated that the RV, and not the pulmonary circulation, should be the major target for treatment in PAH (17).

In left heart failure, after treatment of excess afterload (with systemic blood pressure targets of <130/80), treatments target the left ventricle itself. Many evidence-based therapies for left heart failure specifically target G protein-coupled receptors (GPCRs) expressed on cardiomyocytes (18). GPCRs represent the largest family of membrane receptors involved in signal transduction and ∼34% of FDA-approved drugs block or activate different GPCRs (19). Altered GPCR signaling pathways play crucial roles in the pathogenesis of major cardiovascular diseases such as systemic hypertension, coronary artery diseases (CAD), and left heart failure, and agents targeting these GPCRs serve as cornerstone treatment strategies in these diseases (20). Similarly, several GPCR signaling pathways are dysregulated in PAH and serve as targets for drugs, such as endothelin receptor antagonists (ERAs) and prostanoids (21). Many treatments for PAH have little effect on pulmonary artery pressure, as a meta-analysis reveals that in PAH patients, mPAP decreases only by 2.87 mmHg during 14.3 weeks of treatment (22). Apart from effecting pulmonary vasculature, some of these same treatments have been shown to have direct effect on the RV in preclinical studies. However, a meta-analysis of clinical trials showed that 12 week treatment with current PAH therapies do not have a favorable direct effect on right heart function (23). Moreover, some of these treatment strategies for PAH may even be detrimental to the right ventricle. For example, bosentan exerts negative inotropic effect on the hypertrophied RV in isolated perfused rat heart (24). Similarly, several synthetic prostanoids impair RV function in the hypertrophied heart while improving RV function in the healthy rat heart (25). Similarly, development of peripheral edema in patients taking PAH specific therapy may indicate the deterioration of RV failure due to the treatment (24, 26). Notably, right heart function is a critical prognostic determinant in patients with PAH, as patients with impaired RV performance despite a significant pulmonary vasodilatory effect of the therapy (27). Thus, developing therapies focusing on RV function in PAH may improve symptoms, quality of life, hemodynamics, and survival. In this review, we highlight GPCR drug targets in the RV, the effects of targeting them in preclinical and clinical studies, and the challenges around developing these therapeutics.

GPCR SIGNALING

GPCRs are the most common receptors encoded in the genome, comprising >1% of the coding human genome with ∼800 members and expressed within every organ system (28). GPCRs share a common architecture with an extracellular N-terminal sequence, seven transmembrane-spanning domains, and an intracellular C-terminal domain. GPCRs sense a wide range of extracellular stimuli, including proteins, small molecules, hormones, neurotransmitters, ions, and light. GPCR signaling is primarily controlled by three protein families: G proteins, G protein receptor kinases (GRKs), and β-arrestins. These proteins perform distinct functions at the receptor (29). Upon stimulation with an agonist, GPCRs activate heterotrimeric G proteins by catalyzing the exchange of GTP for GDP on Gα subunits of the heterotrimeric G-protein. This leads to dissociation of the heterotrimeric complex into Gα and Gβγ subunits. The dissociated subunits have different roles, with the Gα subunit regulating second messenger effectors such as cyclic adenosine monophosphate (cAMP—promoted by Gs and inhibited by Gi/o), inositol triphosphate (IP3—promoted by Gq/11), diacylglycerol (DAG—promoted by Gq/11), while the Gβγ subunit can modulate other receptors and channels, such as inward rectifying potassium channels. After ligand binding, the receptor is phosphorylated by a number of kinases, primarily by GRKs, on its C-terminus and cytoplasmic loops (30), which enhance β-arrestin binding to the receptor. β-arrestins mediate receptor desensitization (31), the process whereby repeated stimulation decreases the signaling response over seconds to minutes, and receptor internalization (32–34). This results in receptor downregulation, a decrease in receptor membrane expression over minutes to hours with trafficking of the receptors to proteasomes or lysosomes. In addition to acting as negative regulators of G protein signaling, β-arrestins also couple to numerous signaling mediators including kinases and transcription factors by acting as adaptors and scaffolds (35–41). These pathways are separate from classical G protein signaling, but can involve similar signaling cascades that are often temporally distinct.

THE RIGHT VENTRICLE IS NOT JUST A WIMPY LEFT VENTRICLE

The right ventricle is different from the left ventricle from the point of embryology (42), structure (43, 44), functionality (45) as well as sarcomere structure (46). The normal pulmonary circulation represents a low-resistance, high compliance load to the right ventricle (RV) and a low pressure is sufficient to pump blood to the lungs for oxygenation. RV function is reflected in its structure. The RV is thin-walled and crescent-shaped compared to the left ventricle (LV), which has a circular/ellipsoidal cross-section that combined with larger muscle mass can generate higher pressures (17). Similarly, at a molecular level, there are significant differences between the RV and LV in the expression of genes known to be involved in the response to pressure overload and failure (7), with different RV and LV responses to certain effectors. For example, α_1-adrenergic receptor (α_1AR) agonists increase LV contractility, but may decrease RV contractility (47). Chronic infusion of norepinephrine induces hypertrophy in LV but not in RV (48). miRNA profiling in hypertrophy to failure revealed several notable differences between RV and LV miRNAs. These include miRNAs that are linked to cell proliferation, metabolism, survival, extracellular matrix turnover, and impaired proteasomal function. For example, miRNA 93, miRNA 148a, and miRNA 28 were upregulated in RV hypertrophy/failure and downregulated or unchanged in LV hypertrophy/failure (49). Therefore, the findings from left heart physiology and pathophysiology cannot be simple extrapolated to the right heart (50, 51).

ROLE OF GPCRS IN RV REMODELING AND DYSFUNCTION

Many GPCRs have been studied in animal studies of RV hypertrophy and failure. We have summarized a non-comprehensive list of preclinical studies of RV hypertrophy and failure that quantified changes in GPCR expression in the RV (**Table 1**), changes in the expression of GPCR ligands in the RV (**Table 2**), and the effects of treatment with GPCR ligands (**Table 3**). Below we focus on a number of receptors that have been studied for their effects on RV function.

Endothelin Receptors

Endothelin-1 (ET-1) is produced by endothelial cells and acts on pulmonary artery smooth muscle cells (PASMCs) to induce vasoconstriction and cell proliferation, thus actively contributing to the pathogenesis of PAH (126). The effects of ET-1 on target cells are mediated with two distinct GPCRs, the endothelin type A (ET_AR) and type B (ET_BR) receptors (127). Notably, these receptors have distinct expression patterns and effects: ET_AR is expressed primarily on smooth muscle cells and promote vasoconstriction while ET_BR is expressed primarily on endothelial cells and promotes vasodilation (128). However, the effect of ET-1 is primarily vasoconstriction, as it is the most potent vasoconstrictor in the human cardiovascular system (128). Both ET_AR and ET_BR are coupled to Gi and Gq, as well as to β-arrestins (129). This results in the activation of a variety of signaling pathways downstream of the receptor (**Figure 1**). Activation of endothelin receptors by ET-1 results in the activation of Bcl2, the epidermal growth factor (EGF) receptor (EGF-R) (130), and mitogen-activated protein kinase (PK) cascades (131). These signaling pathways promote cardiomyocyte survival and hypertrophy in response to pressure overload (132). Circulating levels of ET-1 are increased in PAH patients (133, 134) and its levels correlate with pulmonary vascular resistance (PVR), right atrial pressure (RAP) and oxygen saturation in PAH (135). These findings led to the development and subsequent approval of both ET_AR-specific and dual $ET_{A/B}R$ ERAs for the treatment of PAH, including bosentan, ambrisentan, and macitentan (136).

The physiological effects of ERAs are complex and is likely mediated by effects both on the pulmonary circulation and the right ventricle. In monocrotaline (MCT)-induced PH rats, the dual ET receptor antagonist BSF 420627 doubled survival compared to untreated animals and increased survival by 10% compared to the ET_A-selective antagonist LU 135252 (98). A reduction of RV hypertrophy was only seen in the animals receiving the dual ET receptor antagonist, suggesting that blockade of both ET_AR and ET_BR is necessary to prevent all of the deleterious effects of ET-1 in the MCT model. A direct comparison of the dual ET receptor antagonist bosentan and the ET_A-selective antagonist ambrisentan in the MCT model demonstrated that, compared to bosentan, ambrisentan significantly increased prostacyclin synthase I expression (97). However, both antagonists similarly reduced RV systolic pressure, pulmonary vascular remodeling, and RV hypertrophy. Macitentan, an ET receptor dual antagonist, prevents RV hypertrophy and the development of PH at a dose 10 times lower than bosentan (137), which may simply reflect its higher potency at ET receptors. ET-1 up-regulates HIF-1 alpha, which can contribute to maladaptive remodeling and increased anaerobic metabolism (138). Macitentan treatment reduced PAH severity, lowered RV FDG uptake, and improved RV function in SUHX rats (106). In the Dahl-salt rat model of systemic hypertension, macitentan administered in addition to the maximally effective dose of bosentan further reduced mean arterial pressure (MAP) (97). These differences between ERAs is likely a combination of their different patterns of $ET_{A/B}R$ selectivity and different potencies, but some of it may also be due to their selective inhibition of different signaling pathways downstream of these receptors.

However, there are controversies regarding the role of ET-1 in RV failure and only a few studies have addressed this topic. ET-1 and ET_BR are upregulated in the RV myocardium in MCT-induced RV remodeling in rats (62). This is in contrast to the RV myocardium of PAH patients, where the density of ET_AR is increased, while ET_BR is decreased or unchanged (24, 52). Interestingly, while, ET-1 does not influence on contractility and calcium handling of isolated cardiomyocytes from remodeled RV (139), bosentan, an $ET_{A/B}R$ antagonist, exerts negative inotropic effect on the hypertrophied RV of MCT rats (24). However, long-term treatment with an ET_AR antagonist in MCT rats improved RV remodeling due to normalization of calcium handling (104). ET-1 may exert negative inotropic effect on the right ventricle of adults mice (140), or positive inotropic effect on right ventricle of neonatal mice (141) through ET_AR (140, 141). Thus, the effects of ERAs on the RV are complex and vary depending on the model system used.

Adrenergic Receptors

The adrenergic receptors (ARs) are a large family of receptors with three beta (β) ARs (β_1AR, β_2AR, and β_3AR), three alpha $(\alpha)_1$ ARs (α_{1A}-, α_{1B}-, and α_{1D}ARs) and three α_2ARs (α_{2A}-, α_{2B}-, and α_{2C}ARs). The βARs and α_1ARs are all expressed in the myocardium (142, 143), while the α_2ARs are expressed in the nervous system. β_1 and β_2ARs classically couple to Gs, but can also couple to Gi under certain conditions, while α_1ARs classically couple to Gq (**Figure 2**). Both groups of receptors also bind to β-arrestin adapters. These receptors are also tightly regulated by the activity of GRKs, as GRK2 uncouples βAR signaling and inhibition of GRK2 improves RV function in models of right heart failure (144). The development of RV remodeling in response to pressure overload is accompanied by the dysregulation of myocardial adrenergic receptors in several experimental models of RV remodeling in rodents including MCT-induced PAH (54, 55), SU5416-Hypoxia (SuHx)-induced PAH (144), Hypoxia (HOX)-induced PAH (58), and pulmonary artery banding (PAB) (144).

There are interspecies differences in adrenergic signaling changes in response to the pressure overload in the RV myocardium. For example, in a canine model of MCT-induced RV remodeling, RV function is maintained/compensated to the increased pressure overload, which is associated with increased surface expression of both α_1- and βARs (59). This is in contrast

TABLE 1 | Summary of studies evaluating GPCR expression in the RV in PAH patients or in different models of right heart hypertrophy/failure.

Disease model/disease	Species/subjects	Methods	GPCRs	References
PAH patients	Human	LBA	↑ endothelin-1 receptor type A (ET_RA)	(52)
PAH patients	Human	LBA	↓ endothelin-1 receptor type B (ET_RB)	(52)
PAH patients	human	IFS	↑ endothelin-1 receptor type A (ET_RA)	(24)
PAH patients	Human	WB	↑α-7nAchR	(53)
PAH patients	Human	WB	↔m2AchR	(53)
MCT induced RV remodeling	Rats	LBA	↓ β-adrenergic receptors (β-ARs)	(54)
MCT induced RV remodeling	Rats	WB	↓ β-adrenergic receptors (β1-AR, β2-AR)	(55)
MCT induced RV remodeling	Rats	LBA	↓ β-adrenergic receptors (β1-AR, β2-AR)	(56)
MCT induced RV remodeling	Rats	LBA	↓ β-adrenergic receptors (β-ARs)	(57)
HOX induced RV remodeling	Rats	PCR	↓ β1-adrenergic receptor (β1-AR)	(58)
HOX induced RV remodeling	Rats	PCR	↔ β2-adrenergic receptor (β2-AR)	(58)
HOX induced RV remodeling	Rats	LBA	↓ β-adrenergic receptors (β-ARs)	(58)
MCT induced RV remodeling	Dogs	LBA	↑ β-adrenergic receptors (β-ARs)	(59)
MCT induced RV remodeling	Dogs	LBA	↑α1-adrenergic receptor (α1-AR)	(59)
MCT induced RV remodeling	Rats	LBA	↓α1-adrenergic receptor (α1-AR)	(56)
MCT induced RV remodeling	Rats	IFS	↑ endothelin-1 receptor type A (ET_RA)	(24)
HOX induced RV remodeling	Rats	GeneChip analysis, PCR, WB	↑ endothelin-1 receptor type B (ET_RB)	(60)
MCT induced RV remodeling	Rats	LBA	↓ endothelin-1 receptor type A (ET_RA)	(52)
MCT induced RV remodeling	Rats	LBA	↑ endothelin-1 receptor type B (ET_RB)	(52)
MCT induced RV remodeling	Rats	PCR	↑ endothelin-1 receptor type A and B (ET_RB)	(61)
MCT induced RV remodeling	Rats	LBA	↑ endothelin-1 receptor type A and B (ET_RB)	(62)
HOX induced RV remodeling	Rats	PCR	↑ endothelin-1 receptors (ET_RA and ET_RB)	(63)
PAB induced RV remodeling	Rabbits	IFS	↑ endothelin-1 receptor type A and B (ET_RB)	(64)
HOX induced RV remodeling	Rats	PCR	↓ angiotensin-II receptor (AT_2R)	(65)
MCT induced RV remodeling	Rats	PCR	↑ angiotensin-II receptor (AT_1R) (at initial stages)	(65)
MCT induced RV remodeling	Rats	LBA	↑ angiotensin- II receptor (AT_2R)	(65)
MCT induced RV remodeling	Rats	LBA	↑ angiotensin-II receptor (AT_1R) (at initial stages)	(65)
MCT induced RV remodeling	Ovariectomized female rats	PCR	↑ angiotensin-II receptors (AT_1R, AT_2R)	(66)
HOX induced RV remodeling	Rats	WB	↑ angiotensin-II receptors (AT_1R)	(67)
PAB induced RV remodeling	Rats	PCR	↓ angiotensin-II receptors (AT_1R)	(68)
MCT induced RV remodeling	Rats	PCR	↔ angiotensin-II receptors (AT_1R and AT_2R)	(69)
MCT induced RV remodeling	Rats	LBA	↑ angiotensin-II receptor (AT_1R)	(70)
SuHx induced RV remodeling	Rats	PCR	↓ APJ-receptor	(71)
MCT induced RV remodeling	Rats	PCR	↓ APJ-receptor	(72)
HOX induced RV remodeling	Rats	GeneChip analysis	↑ chemokine receptor (CXCR4)	(60)
PAB induced RV remodeling	Dogs	PCR	↑ chemokine receptor (CCR2)	(73)
PE model	Rats	PCR	↑ chemokine receptor (CCR1 and CXCR4)	(74)
MCT induced RV remodeling	Rats	LBA	↔ muscarinic receptors	(57)

PAH, pulmoinary arterial hypertension; MCT, monocrotaline; HOX, hypoxia; SuHx, sugen plus hypoxia; LBA, ligand binding assay; PCR, polymerase chain reaction; WB, western blot; IFS, immunofluorescent staining.

to what is observed in the remodeled RV myocardium in MCT rats (54, 56–58) and HOX rats (58), where the surface expression of both β_1AR and β_2AR are decreased. This finding is likely related to sympathetic hyperactivity and subsequent downregulation of adrenergic receptors in the RV myocardium (145), which is also observed clinically in PAH (146) and in other preclinical disease models such as HOX rats (145). Similarly, MCT rats have increased levels of plasma norepinephrine along with increased content of both epinephrine and norepinephrine in the remodeled RV tissue (147). Moreover, plasma levels of norepinephrine in PAH patients with severe RV failure are correlated with the parameters of pulmonary hemodynamics and cardiac function (135).

For many years in left heart failure, it was unclear as to whether to treat with βAR agonists or β-adrenergic blockers (beta-blockers) until the discovery that beta-blockers improved mortality in chronic systolic heart failure by improving βAR expression on cardiomyocytes (148). At this time, it is unclear as to whether targeting the RV with beta-blockers will have similar protection in the setting of high afterload in PAH. This equipoise has encouraged scientists to perform studies evaluating the effects of both βAR agonists and beta-blockers on

TABLE 2 | Summary of studies evaluating the expressions of GPCR ligands and ligand modulators in the RV in different models of right heart hypertrophy/failure.

Disease model	Species/ subjects	Method	GPCR modulator/ligand	References
MCT induced RV remodeling	Rats	HPLC	↑ epinephrine	(54)
MCT induced RV remodeling	Rats	HPLC	↑ norepinephrine	(54)
MCT induced RV remodeling	Rats	HPLC	↓ norepinephrine	(75)
MCT induced RV remodeling	Rats	Endothelin RIA assay	↓ endothelin-1	(76)
HOX induced RV remodeling	Rats	PCR	↔ endothelin-1	(63)
MCT induced RV remodeling	Rats	PCR	↑ endothelin-1	(61)
MCT induced RV remodeling	Rats	PCR	↑ endothelin-1	(77)
MCT induced RV remodeling	Rats	Endothelin RIA assay	↑ endothelin-1	(62)
MCT induced RV remodeling	Rats	PCR	↑ endothelin-1	(78)
MCT induced RV remodeling	Rats	IFS	↑ endothelin-1	(24)
MCT induced RV remodeling	Rats	ACE activity assay	↑ ACE activity	(79)
PAB induced RV remodeling	Dogs	ACE activity assay	↔ ACE activity	(80)
MCT induced RV remodeling	Rats	PCR	↑ renin	(69)
MCT induced RV remodeling	Rats	PCR	↑ angiotensinogen	(69)
HOX induced RV remodeling	Rats	Apelin content assay	↑ apelin	(81)
SuHx induced RV remodeling	Rats	PCR	↓ apelin	(82)
MCT induced RV remodeling	Rats	PCR	↓ apelin	(71)
MCT induced RV remodeling	Rats	PCR	↓ apelin	(72)
SuHx induced RV remodeling	Rats	PCR	↓ apelin	(83)
PAB induced RV remodeling	Mice	PCR	↑ CXCL10, CXCL6, CCL8, CX3CL1, CCL5, CXCL16, CCL2, CCL3	(73)
PE model	Rats	PCR	↑ CXCL1 and CXCL2	(84)
PE model	Rats	PCR	↑ CXCL1, CXCL2	(85)
PE model	Rats	PCR	↑ CC-chemokine genes (CCL2, 3, 4, 6, 7, 9, 17, 20, 27), CXC-chemokine genes (CXCL1, 2, 9, 10, 16)	(74)
PAB induced RV remodeling	Pigs	Microarray	↑ CCL2, CXCL6, CXCL2	(86)
PE model	Rats	PCR	↓ XCL-1 and CXCL-12	(74)

PAH, pulmonary arterial hypertension; PAB, pulmonary artery banding; MCT, monocrotaline; SuHx, sugen plus hypoxia; HOX, hypoxia; PE, pulmonary embolism; PCR, polymerase chain reaction; IFS, immunofluorescent staining; HPLC, high performance liquid chromatography.

pulmonary hemodynamics and RV function in different animal models. Carvedilol, a non-selective beta-blocker targeting β1-AR, β2-AR, and α1-AR, improves RV function and fibrosis without effecting on pulmonary vasculature in MCT-treated rats (149) as well as in SuHx rats (150). The beneficial effect of carvedilol is mediated through the modulation of TGFβ1-CTGF signaling (149) as well as signaling pathways involved in cardiac hypertrophy, protein ubiquitination and mitochondrial function (111). Similarly, another beta-blocker, metoprolol improves the remodeling and function of the pressure overloaded RV in MCT rats (110, 151), mainly by improving RV metabolism (110) and calcium handling (151). In contrast, bisoprolol does not exert beneficial effects on the RV in PAB-operated rats (90). In line with this research, treatment with pyridostigmine (PYR), an oral acetylcholinesterase inhibitor, an activator of parasympathetic system, in the SuHx rats, delays progression to RV failure and improves load-independent indices of RV function mainly due to decreased RV inflammation through the reduced leukocyte infiltration and reduced indices of pulmonary vascular remodeling (53). Interestingly, the density of muscarinic acetylcholine receptors, another GPCR, is not changed in RV remodeling in MCT rats (57). In addition, the effect of adrenergic signaling on cardiac function changes depending on whether RV is remodeled or not. For example, activation of α_1AR causes negative inotropic healthy RV, while in the failing RV myocardium, stimulation of α_1AR exerts positive inotropic effect (152, 153). Following this findings, a recent study showed that a selective α_1AR A type agonist A61603 ameliorates RV remodeling in bleomycin-induced RV remodeling by improving RV antioxidant system and RV fibrosis (154).

Serotonin Receptors

PAH can be caused by exposure to specific drugs, and serotonin 5-HT_{2B} agonists (155), such as Fen-Phen, have a "definite" association with the development of PAH (136). Consistent with this, disturbed serotonin metabolism contributes to the development and progression of PAH (156) and antagonists of serotonin receptors are beneficial in the preclinical models of PAH (157). There are multiple serotonin receptors, including the 5-$HT_{1A,B,D,E,F}$ (which couple to Gi), 5-$HT_{2A,B,C}$ (which couple to Gq), and the 5-$HT_{4,6,7}$ (which couple to Gs) (129). Many of these receptor subtypes are expressed in the RV and pulmonary circulation (21). PAH patients display increased levels of circulating serotonin (158, 159). Serotonin effects on the

TABLE 3 | Summary of studies evaluating the effects of treatment with GPCR ligands in preclinical models of right heart hypertrophy/failure.

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
Captopril	ACE-1 inhibitor	Preventive	HOX rats (14 days)	Osmotic minipump, 20 mg/kg/day (days 0–14)	- Prevented the rise in PAP (↓ mPAP) - Prevented RV hypertrophy (↓RV/BW) - Prevented PA remodeling (↓muscularized PAs)	(87)
Captopril	ACE-1 inhibitor	Preventive	MCT rats (25 days)	Oral gavage, 30 mg/kg/day (days 1–25)	- Did not prevent the rise in PAP (↔PAP) - Preserved RV function (↑TAPSE) - Prevented the changes of modulators of RV ECM (↓MMP2 and MMP9 expressions, ↓MMP2 and MMP9 activities)	(88)
Enalapril	ACE-1 inhibitor	Preventive	MCT rats (28 days)	Oral gavage, 25 mg/kg/day (days 1–28)	- Did not prevent the rise in PAP (↔RVSP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Prevented the rise in plasma markers of hypertrophy (↓ANP) - Prevented the change in RV norepinephrine content (↑NE) - Decreased mortality - Preserved RV enzymatic activity (↑CK activity, ↑LD-1 activity)	(75)
Enalapril	ACE-1 inhibitor	Preventive	MCT rats (5 weeks)	Drinking water, 4.4 mg/kg/day (5 weeks)	- Prevented RV hypertrophy [↓RV/(LV+S)]	(89)
Ramipril	ACE-1 inhibitor	Preventive	PAB rabbits (21 days)	Injection (i.p.), 37.5 mg/kg (1 hour after surgery), further in drinking water (1 mg/kg/day) (21 days)	- Did not prevent the rise in PAP (↔RVSP) - Did not prevent RV hypertrophy (↔RV/BW) - Preserved papillary cardiomyocyte contractility - Preserved RV enzymatic activity (↓Gαq, ↓Gαi1/2)	(70)
Losartan	AT_1R blocker	Curative	PAB rats (7 weeks)	Oral gavage, 20 mg/kg/day (6 weeks)	- Did not have influence on any of the measured parameters of RV	(90)
Losartan	AT_1R blocker	Preventive	PAB rabbits (21 days)	Injection (i.p.), 0.25 mg/kg, 1 h after surgery, then 50 mg/kg/d in the drinking water	- Did not prevent the rise in PAP (↔RVSP) - Did not prevent RV hypertrophy (↔RV/BW) - Preserved papillary cardiomyocyte contractility - Preserved RV enzymatic activity (↓Gαq, ↓Gαi1/2)	(70)
Losartan	AT_1R blocker	Curative	MCT rats (25 days)	Vanilla pudding, daily, 20 mg/kg	- Reduced PAP (↓RVSP) - Reduced PVR (↓PVR) - Reduced RV dilation (↓RVEDD) - Did not decrease RVWT - Did not improve RV function (↔CO, ↔TAPSE) - Did not increase RV contractility (↔Ees) - Improved RV diastolic function (↓Eed) - Reduced RV afterload (↓Ea) - Reduced PA remodeling (↔ wall thickness) - Did not decrease RV cardiomyocyte hypertrophy (↔RV CSA)	(91)
Losartan	AT_1R blocker	Preventive	HOX rats (14 days)	Osmotic minipump, 20 mg/kg/day (days 0–14)	- Prevented the rise in PAP (↓ mPAP) - Prevented RV hypertrophy (↓RV/BW) - Prevented PA remodeling (↓muscularized PAs)	(87)
Candesartan	AT_1R blocker	Preventive	PAB dogs (60 days)	Oral, 1 mg/kg/day (60 days)	- Prevented thickening RV wall thickness - Decreased RV fibrosis - Decreased RV cardiomyocyte diameter - Increased circulating levels of RAAS members (↑renin, ↑angI, ↑AngII)	(80)

(Continued)

TABLE 3 | Continued

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
Telmisartan	AT_1R blocker	Preventive	MCT rats (25 days)	Oral in distilled water, 3 mg/kg/day (24 days)	- Prevented RV hypertrophy (↓RV/Tibia) - Preserved RV function (↑TAPSE) - Prevented the changes of regulators in RV ECM remodeling (↓MMP2, ↓MMP9, TGF-β1)	(92)
Valsartan	AT_1R blocker	Preventive	MCT rats (21 days)	Oral gavage, 20 mg/kg/day (21 days)	- Prevented the rise in PAP (↓RVSP) - Preserved RV function (↑RVEF, ↑TAPSE) - Prevented PA remodeling (↓wall thickness) - Prevented RV hypertrophy [↓RV/(LV+S)] - Did not prevent RV fibrosis (↔RV collagen area) - Prevented RV cardiomyocyte apoptosis (↓TUNEL positive cells, ↓Fas, ↓caspase-3, ↓bax, ↑bcl-1) - Decreased mortality	(93)
C21	AT_2R agonist	Curative	MCT rats (4 weeks)	Injection (i.p.), daily, 0.03 mg/kg/day (2 weeks)	- Decreased PAP (↓RVSP) - Decreased RV hypertrophy [↓RV/(LV+S)] - Decreased RV fibrosis (↓ fibrosis area)	(94)
PD-123319	AT_2R blocker	Curative	MCT rats (4 weeks)	Injection (i.p.) 3 $mg{\cdot}kg^{-1}{\cdot}day$ (2 weeks)	- Did not decrease PAP (↔RVSP) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Did not decrease RV fibrosis (↔ fibrosis area)	(94)
A779	Mas antagonist	Curative	MCT rats (4 weeks)	Injection (s.c.) 0.5 mg/kg/day (2 weeks)	- Did not decrease PAP (↔RVSP) - Did not decrease RV remodeling [↔RV/(LV+S)] - Did not decrease RV fibrosis (↔ fibrosis area)	(94)
Macitentan	ET_RA/ET_RB blocker	Preventive	PAB rabbits (31 days)	Oral gavage, 10 mg/kg/day (days 1–31)	- Preserved RV function (↑RV S') - Prevented RV cardiomyocyte hypertrophy (↓myocyte size) - Prevented RV fibrosis (↓collagen volume) - Preserved RV gene expressions (↓CTGF, ↑endothelin-1, ↑PDGF, ↑MMP2, ↑MMP9) - Prevented RV apoptosis (↓ TUNEL positive cells, ↓caspase-3, ↓caspase-8)	(64)
SB 217242	ER_RA blocker	Preventive	HOX rats (14 days)	Osmotic minipump, 10.8 mg/day, (days 0–14)	- Prevented the rise in PAP (↓PAPs) - Did not decrease PA remodeling (↔ wall thickness) - Reduced RV hypertrophy [↓RV/(LV+S)]	(95)
SB 217242	ER_RA blocker	Curative	HOX rats (28 days)	Osmotic minipump, 10.8 mg/day, (days 14–28)	- Reduced PAP (↓PAPs) - Reduced PA remodeling (↔ wall thickness) - Did not decrease RV hypertrophy [↔RV/(LV+S)]	(95)
A-192621	ET_RB blocker	Preventive	MCT rats (4 weeks)	Oral gavage, twice daily, 30 mg/kg/d (days 1–28)	- Augmented the increase in PAP (↑RVSP) - Worsened RV hypertrophy [↑RV/(LV+S)] - Did not prevent PA remodeling (↔medial wall thickness)	(96)
ABT-627	ET_RA blocker	Preventive	MCT rats (4 weeks)	Oral gavage, twice daily, 10 mg/kg/d (days 1–28)	- Prevented the rise in PAP (↓RVSP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Decreased PA remodeling (↔medial wall thickness)	(96)

(Continued)

TABLE 3 | Continued

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
Bosentan	ET_RA/ET_RB blocker	Preventive	MCT rats (4 weeks)	Oral gavage, daily, 100 mg/kg (days 1–28)	- Prevented the rise in PAP (↓RVSP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Prevented PA remodeling (↓medial area)	(97)
Ambrisentan	ET_RA blocker	Preventive	MCT (4 weeks)	Oral gavage, daily, 35 mg/kg (days 1–28)	- Prevented the rise in PAP (↓RVSP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Decreased PA remodeling (↓medial area)	(97)
LU135252	ET_RA blocker	Curative	MCT rats (5 weeks)	Chow, 50 mg/kg/d (3 weeks)	- Decreased PAP (↓RVSP) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Improved RV diastolic function (↓RVEDP)	(98)
BSF420627	ET_RA/ET_RB blocker	Curative	MCT rats (5 weeks)	Chow, 50 mg/kg/day (2–3 weeks)	- Decreased PAP (↓RVSP) - Decreased RV hypertrophy [↓RV/(LV+S)] - Improved RV diastolic function (↓RVEDP) - Decreased mortality	(98)
Macitentan	ET_RA/ET_RB blocker	Curative	MCT rats (7 weeks)	Oral gavage, daily, 30 mg/kg/day (6 weeks)	- Improved RV function (↑ RVFAC, ↑TAPSE) - Improved RV remodeling (↓RVID, ↓RVWT) - Decreased RV hypertrophy (↓RV/(LV+S) - Decreased RV fibrosis (↓fibrosis area)	(99)
Macitentan	ET_RA/ET_RB blocker	Curative	MCT rats (3 weeks)	Chow, 30 mg/kg/day, (20 days)	- Improved RV remodeling (↓RVWT) - Decreased RV fibrosis (↓fibrosis area) - Improved cardiac electrical activity (↓ QT_C)	(100)
Bosentan	ET_RA/ET_RB blocker	Preventive	HOX rats (3 weeks)	Oral gavage, daily (100 mg/kg/day) (3 weeks)	- Did not prevent the rise in PAP (↔RVSP) - Prevented RV hypertrophy (↓RV/(LV+S), ↓RV/BW) - Did not prevent RV wall thickness (↔RVWT) - Did not preserve RV function (↔TAPSE) - Prevented RV fibrosis (↓collagen-1)	(101)
TA-0201	ET_RA blocker	Preventive	MCT rats (19 days)	Oral gavage, daily (0.5 mg/kg/day) (19 days)	- Prevented the rise in PAP (↓RVSP/LVSP) - Did not prevent RV dilatation (↔RV/LV) - Prevented RV hypertrophy (↓RV/BW)	(102)
Bosentan	ET_RA/ET_RB blocker	Curative	MCT rats (25 days)	Oral gavage, daily (100 mg/kg/day) (14–25 days)	- Did not decrease PAP (↔RVSP) - Worsened PVR (↑PVR) - Did not decrease RV dilation (↔RVESD, ↔RVEDD) - Decreased RV function (↓RVFS, ↓CO) - Increased RV cardiomyocyte hypertrophy (↑CSA)	(103)
PD155080	ET_RA blocker	Preventive	MCT rats (9 weeks)	Chow, 50 mg/kg/day (9 weeks)	- Prevented the rise in PAP (↓RVSP) - Preserved RV diastolic function (↓RVEDP) - Prevented RV hypertrophy (↓RV/BW)	(104)
BMS-193884	ET_RA blocker	Preventive	MCT rats (20 days)	Chow, 100 mg/kg/day (19 days)	- Prevented the rise in PAP (↓RVSP) - Prevented RV hypertrophy (↓RV weight) - Normalized gene expression (↓ANP)	(105)

(Continued)

TABLE 3 | Continued

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
Macitentan	ET_RA/ET_RB blocker	Curative	SuHx rats (8 weeks)	Oral gavage, 30 mg/kg/day (3 weeks)	- Did not decrease PAP (↔RVSP) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Improved RV function (↑RVEF) - Reduced PA remodeling - Improved RV metabolism (↓RV FDG uptake)	(106)
Macitentan	ET_RA/ET_RB blocker	Preventive	PAB rabbits (6 weeks)	Oral gavage, 20 mg/kg/day (6 weeks)	- Prevented RV fibrosis (↓ fibrosis area) - Prevented RV cardiomyocyte hypertrophy (↓CSA) - Prevented upregulation of proteins driving disease progression (↓CTGF, ↓TGF-β, ↓pSMAD3, pSMAD2) - Prevented the activation of ECM regulators (MMP2 and MMP9) - Prevented RV cardiomyocyte apoptosis (↓TUNEL positive cells) - Preserved RV dysfunction (↓RV S', ↓TAPSE, ↓RVFAC, ↑CO) - Preserved RV contractility (↓Ees)	(107)
Macitentan	ET_RA/ET_RB blocker	Curative	PAB rabbits (6 weeks)	Oral gavage, 20 mg/kg/day (3 weeks)	- Decreased RV fibrosis (↓ fibrosis area) - Decreased RV cardiomyocyte hypertrophy (↓CSA) - Decreased the expression of proteins driving disease progression (↓CTGF, ↓TGF-β, ↓pSMAD3, pSMAD2) - Decreased the activities of ECM regulators (MMP2 and MMP9) - Decreased RV cardiomyocyte apoptosis (↓TUNEL positive cells) - Preserved RV dysfunction (↓RV S', ↓TAPSE, ↓RVFAC, ↑CO) - Preserved RV contractility (↓Ees	(107)
Macitentan	ET_RA/ET_RB blocker	Preventive	Bleo rats (4 weeks)	Oral gavage, 100 mg/kg/day (4 weeks)	- Prevented a decrease in RV function (↑RV CO) - Prevented RV hypertrophy [↓RV/(LV+S)] - Prevented RV cardiomyocyte hypertrophy (↓cardiomyocyte diameter) - Prevented PA remodeling (↓pulmonary vascular hypertrophy) - Prevented gene expression changes (↓Col1a1, ↓Fn1, ↓Lgals3, ↓Lox, ↓Nppa, ↓Nppb, ↓timp1, ↓fst, ↓inhba)	(108)
Bosentan	ET_RA/ET_RB blocker	Prevented	Bleo rats (4 weeks)	Oral gavage, 300 mg/kg/day (4 weeks)	- Prevented a decrease in RV function (↑RV CO) - Did not prevent RV hypertrophy [↔RV/(LV+S)] - Did note prevent RV cardiomyocyte hypertrophy (↔cardiomyocyte diameter) - Did not prevent PA remodeling (↔pulmonary vascular hypertrophy) - Did not prevent gene expression changes (↔Col1a1, ↔Fn1, ↔Lgals3, ↔Lox, ↔Nppa, ↔Nppb, ↔timp1, ↔fst, ↔inhba)	(108)
Bisoprolol	β1-AR blocker	Curative	MCT rats (31 days)	Oral gavage, daily (10 mg/kg) (10–31 days)	- Did not reduce PAP (↔RVSP) - Improved RV remodeling (↓RVEDD, ↔RVWT) - Improved RV systolic function (↑CO, ↑TAPSE) - Improved RV diastolic function (↓RVEDP) - Improved RV contractility (↑Ees, ↑Ees/Ea) - Reduced RV fibrosis (↓fibrosis area) - Reduced RV inflammation (↓CD45+ cells) - Restored βAR signaling (↑troponin-I phosphorylation, ↑myosin binding protein C phosphorylation)	(109)

(Continued)

TABLE 3 | Continued

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
Metaprolol	β1-AR blocker	Curative	MCT rats (31 days)	Oral gavage, daily (10 mg/kg) (15–31 days)	- Did not decrease PAP (↔RVSP) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Improved RV contractility (↑ ESPVR/Ea) - Improved RV cardiomyocyte contractility (↓sarcomere shortening)	(110)
Carvedilol	β1-AR blocker	Curative	SuHx rats (8 weeks)	Oral gavage, daily (15 mg/kg) (4–8 weeks)	- Restored gene expression changes (↑PGC-1α, ↑CD36, ↑ CPT1α, ↑CPT2, ↑ACADM) - Reduced protein degradation system (↓20S proteosome activity, ↓ubiquitinated protein)	(111)
Bisoprolol	β1-AR blocker	Curative	PAB rats (7 weeks)	Oral gavage, 10 mg/kg/day (6 weeks)	- Did not have influence on any of the measured parameters of RV	(90)
Arotinolol	α/β-AR blocker	Preventive	MCT rats (2 weeks)	Osmotic minipump, 0.25 mg/kg/day (2 weeks)	- Prevented the increase in PAP (↓RVSP, ↓sPAP, ↓mPAP, ↓dPAP) - Prevented RV diastolic dysfunction (↓RVEDP) - Prevented RV hypertrophy (↓RV/BW)	(112)
Metoprolol	β1-AR blocker	Curative	MCT rats (21 days)	10 mg/kg1/day (days 14–21)	- Did not decrease PAP (↔RVSP, ↔mPAP) - Decreased PVR (↓PVR) - Improved RV function (↑CO) - Decreased RV hypertrophy [↓RV/(LV+S)] - Decreased PA remodeling (↓PA muscularization)	(113)
Metoprolol	β1-AR blocker	Curative	MCT rats (21 days)	10 mg/kg/day (days 14–21)	- Did not decrease PAP (↔RVSP, ↔mPAP) - Decreased PVR (↓PVR) - Improved RV function (↑CO) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Decreased PA remodeling (↓PA muscularization)	(113)
Nebivolol	β1-AR blocker	Curative	MCT (21 days)	100 mg/kg1/day1 (days 14–21)	- Did not decrease PAP (↔RVSP, ↔mPAP) - Did not decrease PVR (↔PVR) - Did not improve RV function (↔CO) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Did not decrease PA remodeling (↔PA muscularization)	(113)
Sarpogrelate	5-HT_{2A}R antagonist	Preventive	MCT rats (21 days)	50 mg/kg/day, intraperitoneally (21 days)	- Prevented the rise in PAP (↓mPAP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Prevented PA remodeling (↓medial wall thickness) - Decreased mortality	(114)
Sarpogrelate	5-HT_{2A}R antagonist	Curative	MCT rats (6 weeks)	50 mg/kg/day, intraperitoneally (21 days)	- Did not decrease PAP (↔mPAP) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Did not reduce PA remodeling (↔medial wall thickness)	(114)
Sarpogrelate	5-HT_{2A}R antagonist	Preventive	HOX rats (14 days)	Oral gavage, 50 mg/kg/day (14 days)	- Preventive the rise in PAP (↓mPAP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Prevented PA remodeling (↓PA muscularization, ↓medial wall thickness)	(115)
C-122	5-HT_{2B}R antagonist	Preventive	MCT rats (21 days)	Oral gavage, 10 mg/kg/day (21 days)	- Prevented the rise in PAP (↓mPAP, ↓sPAP) - Prevented RV hypertrophy (↓RV/BW) - Prevented PA remodeling (↓PA muscularization)	(116)

(Continued)

TABLE 3 | Continued

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
SB204741	5-HT_{2B}R antagonist	Curative	PAB (21 days)	Injection (i.p.), 5 mg/kg/d for	- Did note reduce PAP (↔RVSP) - Decreased RV hypertrophy (↓RV/tibia) - Decreased RV fibrosis (↓total collagen area) - Improved RV function (↑CO)	(117)
Terguride	5-HT_{2A}R/5-HT_{2B}R antagonist	Curative	PAB (21 days)	Injection (i.p.), 0.2 mg/kg/d	- Did note reduce PAP (↔RVSP) - Decreased RV hypertrophy (↓RV/tibia) - Decreased RV fibrosis (↓total collagen area) - Improved RV function (↑CO)	(117)
Sarpogrelate	5-HT_{2A}R antagonist	Preventive	HOX rats (14 days)	Oral gavage, 50 mg/kg/day	- Preventive the rise in PAP (↓mPAP) - Prevented RV hypertrophy (↓RV/TLV+S) - Prevented PA remodeling (↓remodeled vessels)	(118)
GR127935	5-$HT_{1B/1D}$R antagonist	Preventive	HOX rats (14 days)	Oral, 3 mg/kg/day in distilled H_2O	- Preventive the rise in PAP (↓mRVP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Prevented PA remodeling (↓PA muscularization, ↓medial wall thickness)	(119)
Fluoxetine	5-HTT	Preventive	HOX rats (15 days)	Oral gavage, (10 mg/kg/day)	- Preventive the rise in PAP (↓RVSP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Did not prevent PA remodeling (↓PA muscularization, ↓medial wall thickness)	(120)
Citalopram	5-HTT	Preventive	HOX rats (15 days)	Oral gavage, (10 mg/kg/day)	- Preventive the rise in PAP (↓RVSP) - Prevented RV hypertrophy [↓RV/(LV+S)] - Did not prevent PA remodeling (↔PA muscularization)	(120)
Ketanserin	5-HT_{2A}R receptor antagonist	Preventive	HOX rats (14 days)	Injection (i.p.) 2 mg/kg/day	- Did not prevent the rise in PAP (↔RVSP) - Did not prevent RV hypertrophy [↔RV/(LV+S)] - Did not prevent PA remodeling (↔PA muscularization)	(120)
GR127935	5-$HT_{1B/1D}$R antagonist	Preventive	HOX rats (15 days)	Injection (i.p.) 2 mg/kg/day	- Did not prevent the rise in PAP (↔RVSP) - Did not prevent RV hypertrophy [↔RV/(LV+S)] - Did not prevent PA remodeling (↔PA muscularization)	(120)
Treprostinil	Prostanoid	Curative	SuHx rats (7 weeks)	Osmotic minipumps, 100 ng/kg/min (3 weeks)	- Reduced PAP (↓RVSP) - Decreased RV hypertrophy [↓RV/(LV+S)] - Improved RV function (↑CO, ↑TAPSE) - Decreased RV remodeling (↓RVID/LVID, ↓RVWT) - Did not reduce PA remodeling (↔medial wall thickness, ↔occluded vessels)	(121)
Treprostinil	Prostanoid	Preventive	HOX mice (28 days)	Osmotic minipump, 70 ng/kg/min (28 days)	- Prevented PAP increase (↓RVSP) - Did not prevent RV hypertrophy [↔RV/(LV+S)] - Prevented PA remodeling (↓PA muscularization, ↓wall thickness)	(122)
Iloprost	Prostanoid	Curative	MCT rats (42 days)	Nebulization, 6.0 μg/kg/day, 15-min nebulisations were repeated 12 times per day for 2 weeks	- Decreased PAP increase (↓RVSP) - Decreased PA remodeling [↓RV/(LV+S)] - Reduced PVR (↓PVRI) - Decreased PA remodeling (↓PA muscularization, ↓wall thickness)	(123)

(Continued)

TABLE 3 | Continued

Agent	Mechanism of action	Treatment option	Study design	Agent application details	Main effects of the drug on PA and the RV	References
Iloprost	Prostanoid	Curative	SuHx rats (6 weeks)	Nebulization, 0.1 μg/kg, 15-min nebulisations were repeated three times daily for 2 weeks	- Decreased PAP (↓mPAP) - Did not decrease RV hypertrophy [↔RV/(LV+S)] - Did not decrease PA remodeling (↔PA muscularization) - Restored RV function (↑CO, ↑TAPSE, ↑running time) - Decreased RV fibrosis (↓ fibrosis area) - Decreased the change of gene expressions (↓CTGF, ↓Cola1a, ↓Cola3, MMP2, MMP9, TIMP2)	(83)
Treprostinil	Prostanoid	Curative	PAB (7 weeks)	Osmotic minipump, 300 ng/kg/minute or 900 ng/kg/minute (6 weeks)	- Did not have effects of any of the measured RV parameters	(124)
Beraprost	Prostanoid	Preventive	MCT rats (19 days)	Oral gavage, daily (100 μg/kg/day) (19 days)	- Prevented the rise in PAP (↓RVSP/LVSP) - Did not prevent RV dilatation (↔RV/LV) - Prevented RV hypertrophy (↓RV/BW)	(102)
Cefminox	IP and PPARγ agonist	Preventive	HOX rats (28 days)	Injection (tail i.v.), 160 mg/kg daily (28 days)	- Prevented the rise in PAP (↓mPAP) - Prevented RV hypertrophy [↓RV/(LV+S)]	(125)
Cefminox	IP and PPARγ agonist	Preventive	HOX rats (28 days)	Injection (tail i.v.), 320 mg/kg daily (days 1–28)	- Prevented the rise in PAP (↓mPAP) - Prevented RV hypertrophy [↓RV/(LV+S)]	(125)
Apelin	Exogenous apelin	Curative	MCT rats (25 days)	Injection (i.p.), daily, 200 μg/kg/day (days 11–24)	- Reduced PAP (↓RVSP) - Reduced RV hypertrophy [↓RV/(LV+S)] - Reduced RV cardiomyocyte hypertrophy (↓cardiomyocyte diameter) - Reduced RV fibrosis (↓fibrosis) - Did not decrease PA remodeling (↔wall thickness) - Normalized gene expressions (↑apelin, ↑APJ, ↓endothelin-1, ↓angiotensin-II, ↑MAS)	(71)

RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure; Ees, end-systolic elastance; Ea, arterial elastance; Eed, end-diastolic elastance; PAP, pulmonary artery pressure; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; BW, body weight; RV, right ventricle; LV, left ventricle; S, septum; PA, pulmonary artery; TAPSE, tricuspid annular plane systolic excursion; PAB, pulmonary artery banding; MCT, monocrotaline; HOX, hypoxia; SuHx, sugen plus hypoxia; Bleo, bleomycin; CO, cardiac output; RVWT, right ventricular wall thickness; RVESD, right ventricular end-systolic diameter; RVEDD, right ventricular end-diastolic diameter; RVID, right ventricular diameter at end-diastole; RVFAC, right ventricular fractional area change; RVEF, right ventricular ejection fraction; RV S', lateral systolic velocity of the tricuspid annulus; PVR, pulmonary vascular resistance; i.p., intraperitoneal; s.c., subcutaneous; CSA, cardiomyocyte cross sectional area.

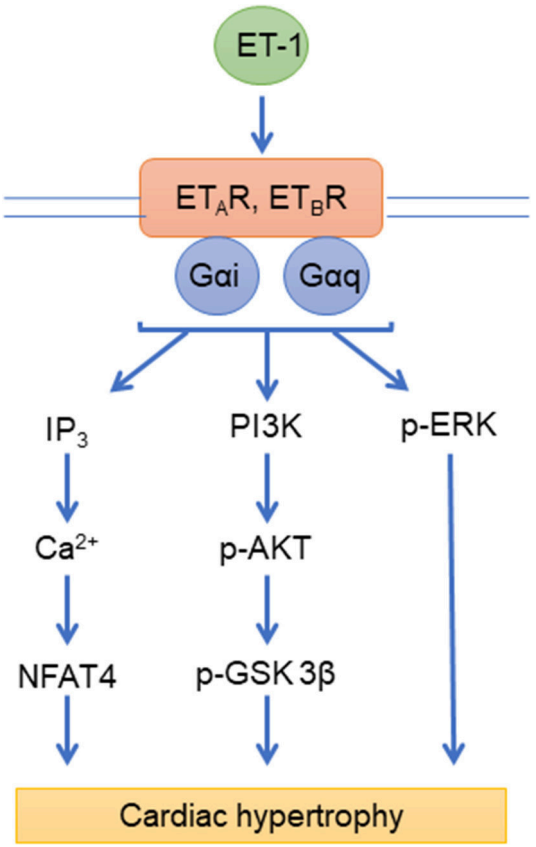

FIGURE 1 | Endothelin signaling pathways. ET_AR, ET_BR, endothelin receptors; ET-1, endothelin; IP_3, inositol 1,4,5-trisphosphate; Ca^{2+}, Calcium; NFAT4, nuclear factor of activated T cells 4; PI3K, Phosphatidylinositol -4,5-bisphosphate 3-kinase; p-AKT, phospho-Protein kinase B; p-ERK, phospho- extracellular signal-regulated kinases; Gαi, Gαq, G-proteins.

target cells using its GPCRs and some of its receptors have been found to be upregulated in the remodeled pulmonary arteries. Several serotonin receptor antagonists have been studied in animal models of PAH and RV remodeling and some of them have been found to be efficacious to reverse or prevent the disease (114–120). However, little is known about the effect of serotonin on the RV remodeling and only few studies have focused specifically on the RV using PAB models. The expression of serotonin receptor 5-HT_{2B}R is increased in the remodeled RV myocardium in PAB-operated mice (117) and treatment with serotonin receptor antagonists terguride or SB204741 reduce RV fibrosis and improve RV function in PAB-operated mice, a beneficial effect mediated through diminished TGF-β1 induced collagen synthesis by RV cardiac fibroblasts (117). Moreover, the serotonin system works in concert with adrenergic and angiotensin systems to induce cardiac hypertrophy (160).

Prostanoid Receptors

Prostanoids are a group of lipid-based molecules that modulate vascular tone, platelet function, inflammation, cell proliferation and cardiac function (161). Prostanoids exerts their effects with GPCR prostanoid receptors including DP_{1-2}, EP_{1-4}, FD, IP, and TP (162) and majority of them are present on cardiomyocytes (163). The prostacyclin receptor (IP) is abundantly expressed in blood vessels, leukocytes, and platelets, and is activated by binding of the prostacyclin and its analogs. IP receptors are coupled to Gs and Gq proteins (**Figure 3**). The activated IP stimulates adenyl cyclase activity via Gs proteins, increasing cAMP levels in the cells. IP can also activate vasoconstrictive pathways via Gq coupling under certain circumstances (164, 165). The ligands for IP receptors (prostacyclin and its analogs) also bind and activate EP receptors (166); these receptors are not only expressed on the cell membrane but also in the nucleus (167, 168). IP receptor activation leads to the activation of peroxisome proliferator-activated receptor alpha and delta (PPARα and PPARδ) via IP receptor-dependent PKA activation (169). The enzyme prostaglandin-I synthase (PGI) produces prostacyclin, which can activate apoptosis through PPARδ (170). There is evidence that PPARδ is also involved in the acute signaling in prostacyclin-induced vasodilatation (171).

Several synthetic prostanoids have been developed and approved for the treatment of PAH including epoprostenol (IP receptor agonist), treprostinil (IP and EP2 receptor agonist), and iloprost (IP, EP1, EP3, and EP4 receptor agonist) (162). Although, prostanoids reverse/prevent pulmonary artery remodeling and pulmonary hemodynamics in a number of animal models of PAH including MCT, SuHx, and HOX rats (172), only few studies have specifically focused on the effect of prostanoids on RV function. For instance, in MCT and aortocaval-shunting models of RV remodeling, iloprost treatment improves RV capillary-to-myocyte ratio and RV fibrosis with no effect on pulmonary hemodynamics (173). Similarly, treatment with inhaled iloprost of SuHx rats, improves RV function and exercise performance without influencing on RV pressure overload, RV hypertrophy, RV capillarization, and PA remodeling (83). In addition, inhaled iloprost treatment of PAB-operated rats normalizes the expressions of ECM components in RV myocardium (83). The cardiac effect of prostanoids may have chamber specific effects on cardiomyocyte contractility as it was shown that beraprost, a synthetic prostanoid does not influence on RV cardiomyocyte contractility, while increasing the contractility of atrial cardiomyocytes (174).

The Angiotensin System

Both right and left heart failure is associated with neurohormonal activation of the renin-angiotensin-aldosterone system (RAAS), which is associated with disease progression and prognosis in PAH (91). Pulmonary endothelial cells are a rich source of angiotensin converting enzyme (ACE), which converts angiotensin I (Ang-I) to angiotensin-II (Ang-II) (175). Ang-II exerts its effects on target cells with two subtypes of angiotensin GPCRs, Ang-II type 1 receptor (AT_1R) and Ang-II type 2 receptor (AT_2R). These receptors have distinct effects, as the AT_1R promotes vasoconstriction through Gq/11 while AT_2R promotes vasodilation through Gi (**Figure 4**). The main effect of Ang-II physiologically is proliferation, hypertrophy, migration, and vasoconstriction of vascular cells through AT_1R, which promotes pulmonary vascular and RV

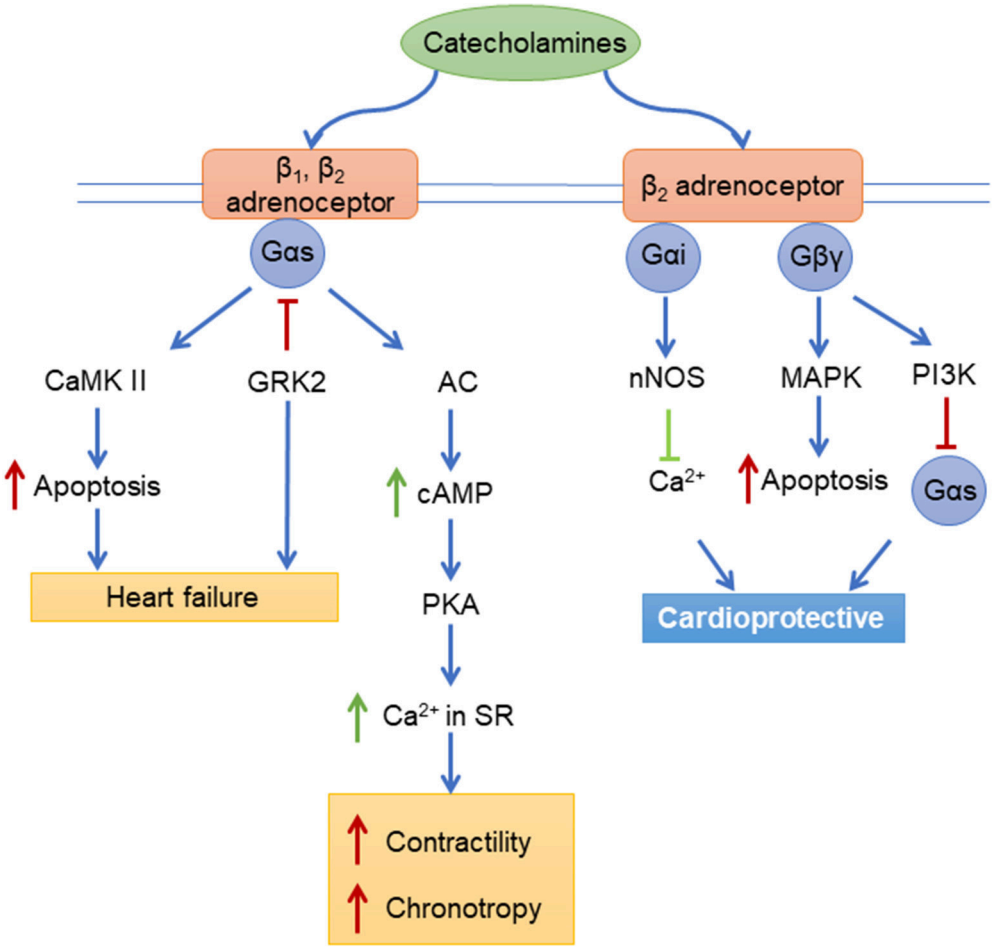

FIGURE 2 | Adrenergic receptors signaling pathways. CaMK II, Ca^{2+}/Calmodulin-Dependent Protein Kinase II; GRK2, beta-adrenergic receptor kinase 1; AC, Adenylyl cyclase; cAMP, Cyclic adenosine monophosphate; PKA, protein kinase A; Ca^{2+}, Calcium; nNOS, neuronal nitric oxide synthases; MAPK, mitogen-activated protein kinase; P13K, Phosphatidylinositol-4,5-bisphosphate 3-kinase; Gαs, Gαi, Gβγ, G-proteins.

remodeling. Through the AT_1R, Ang-II activates mitogen-activated protein kinases (MAPK), receptor tyrosine kinases (RTK), and non-receptor tyrosine kinases. Ang-II also promotes hypoxia inducible factor-1α (HIF-1α) accumulation and activates cyclin-dependent kinase p27 (Kip1) to promote cell hypertrophy and increased oxidative stress (176, 177) through reactive oxygen species generated by NADPH oxidase, which leads to vasoconstriction and inflammation (178). Increased ACE activity and Ang-II production augments pulmonary smooth muscle cell proliferation through AT_1R signaling (91, 179). Evidence suggests that RAAS is involved in the progression of pulmonary artery remodeling, and agents that inhibit RAAS are beneficial for the RV to cope better with the pressure overload (180).

AT_1R and AT_2R are upregulated in the RV myocardium in several animal models of RV remodeling including in MCT rats (55). Receptor expression changes over the course of hypoxia exposure in rats, with increased AT_1R lower AT_2R expression in the initial stages (65). However, there are studies indicating that expression of Ang-II receptors in the RV tissue are not changed in MCT rats (65) or even downregulated in PAB rats (68). Moreover, the activity and expression of ACE are increased in the fibrotic areas of the RV myocardium in HOX rats (79) suggesting its involvement in RV remodeling. In a rabbit PAB model, Ang-II increased RV collagen volume to ∼3-fold and increased expression of the profibrotic mediators transforming growth factor-β1, connective tissue growth factor, and ET-1 were noticed in this model (181). However, cardiomyocyte specific angiotensinogen overexpressing mice spontaneously develop RV and LV hypertrophy without cardiac fibrosis (182).

Multiple studies have tested the effects of ACE-1 inhibitors and Ang-II receptor blockers on the RV in models of right heart failure and hypertrophy. Several Ang-II receptor blockers including losartan (70, 90, 91), candesartan (80), telmisartan (92), and PD-123319 (94) have been studied in several animal models of RV remodeling such as MCT rats (91–94), PAB rats (90), PAB rabbits (70), and PAB dogs (80). The majority of these agents have demonstrated beneficial effects of RAAS inhibition on RV remodeling and function in several models

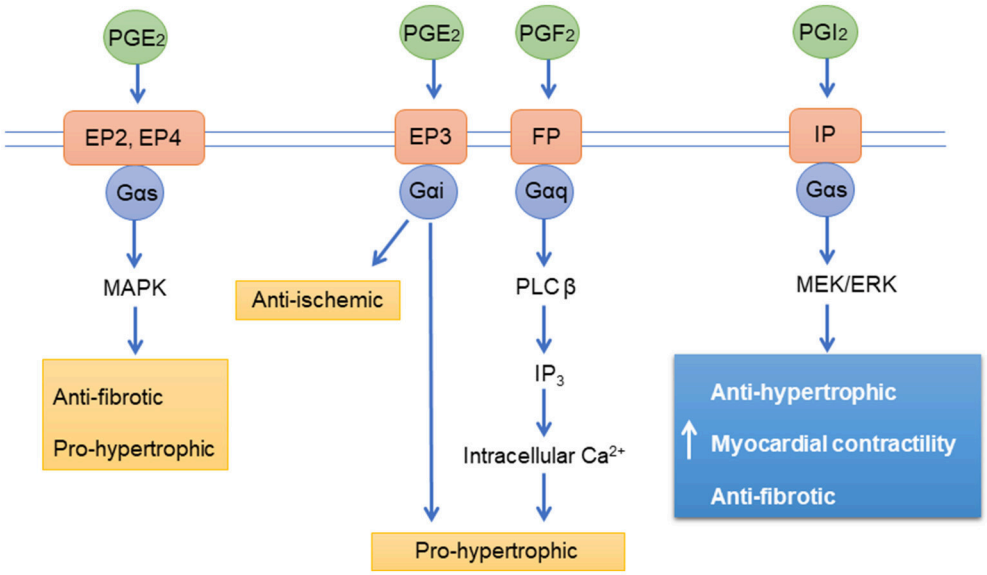

FIGURE 3 | Prostanoid receptors signaling pathways. PGE_2, Prostaglandin E2; PGF_2, Prostaglandin F2; PGI_2, Prostaglandin I2 (Prostacyclin); EP, Prostaglandin receptors; FP, Prostanoid receptors; IP, Prostacyclin receptor; PLC β, 1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-1; ERK, extracellular signal-regulated kinases IP3, inositol 1,4,5-trisphosphate; Ca^{2+}, Calcium; MAPK, mitogen-activated protein kinase; Gαs, Gαi, Gαq, G-proteins.

(70, 80, 91–94). However, a lack of effect of RAAS inhibition on the RV also has been reported (90). In addition, in preclinical studies, inhibition ACE-1 activity with enalapril (75, 89), captopril (87, 88), or ramipril (70) delivered direct beneficial effect on the RV without reducing PAP. Consistent with this, renal denervation (modulating both sympathetic and RAAS activity) improves pulmonary hemodynamics along with attenuation of RV fibrosis and diastolic stiffness (183). However, the aldosterone antagonist eplerenone does not exert beneficial effects on the RV in PAB models in mice (184) and rats (68).

Alternative processing of angiotensin yields peptides that have opposing effects to Ang-II. Angiotensin converting enzyme-2 (ACE2) cleaves Ang-I and Ang-II to yield angiotensin-(1–7) [Ang-(1–7)], angiotensin-(1–9), and angiotensin-(1–5) (185, 186). These peptides reduce pulmonary vascular and RV remodeling through the Mas receptor and AT_2R in PAH (187–189) (**Figure 4**). In pulmonary vascular and RV remodeling, cell proliferation, hypertrophy and pro-fibrotic signaling pathways are inhibited by ACE2/Ang-(1–7)/Mas receptor activation (190). Also, ACE2 inhibits ERK 1/2 and JAK2-STAT3 signaling, thereby reducing PASMC proliferation and migration (191). ACE2/Ang-(1–7) has also been shown to decrease cellular oxidant stress through downregulation of NADPH oxidase and improves pulmonary NO synthesis (190). ACE2/Ang-(1–7) exert antifibrotic effects by reducing oxidant stress, transforming growth factor-β levels and collagen production (190). In the RV, ACE2/Ang-(1–7) maintains NO levels, enhance cardiomyocyte calcium handling and improve myocardial contractility (186). Therefore, ACE2/Ang-(1–7)/Mas signaling holds therapeutic potential in RV and PAH.

Chemokine Receptors

Increased circulating levels of several chemokines have been observed in PAH patients including CXCL10 (192–194), CXCL12 (193), CXCL13 (195), and CXCL16 (193) and some of them were correlated with NT-pro-BNP and the parameters of the RV function such as TAPSE and RV EF (193). Since, chemokines have diverse biological functions, some of them may be beneficial in PAH, as it was shown that elevated levels of CXCL10 are associated with improved survival of patients (192). Notably, CXCL10 decreases proteoglycan synthesis by cardiac fibroblasts (73) thus potentially improving the remodeling extracellular matrix. However, some chemokines may simply be bystanders with no direct effect on the pulmonary vasculature or RV, or may have a yet-discovered role in PAH. For instance, despite of increased circulating levels of CXCL13 in PAH and CTEPH patients, its levels are not correlated with disease severity and outcome (195). Apart being expressed in the pulmonary vasculature, the expressions of several chemokines have been increased in the RV myocardium in both acute (74, 84, 85, 196) and chronic RV failure (73).

The chemokine expressions in the RV myocardium may be independent of pulmonary vasculature and be solely driven by excessive mechanical stress imposed on the RV wall. In a mouse model of PAB-induced RV remodeling, several members of the chemokines have been upregulated in the RV myocardium, including CCL2, CCL5, CXCL16, CXCL10, and CX3CL1 (73). Moreover, acute RV remodeling in pulmonary embolism models in rats are also associated the upregulation of several chemokines including CC-chemokines (CCL2, 3, 4, 6, 7, 9, 17, 20, 27) and CXC-chemokine genes (CXCL1, 2, 9, 10, 16) (74, 84, 85). Similarly, in acute RV remodeling in PAB pigs CCL2, CXCL6,

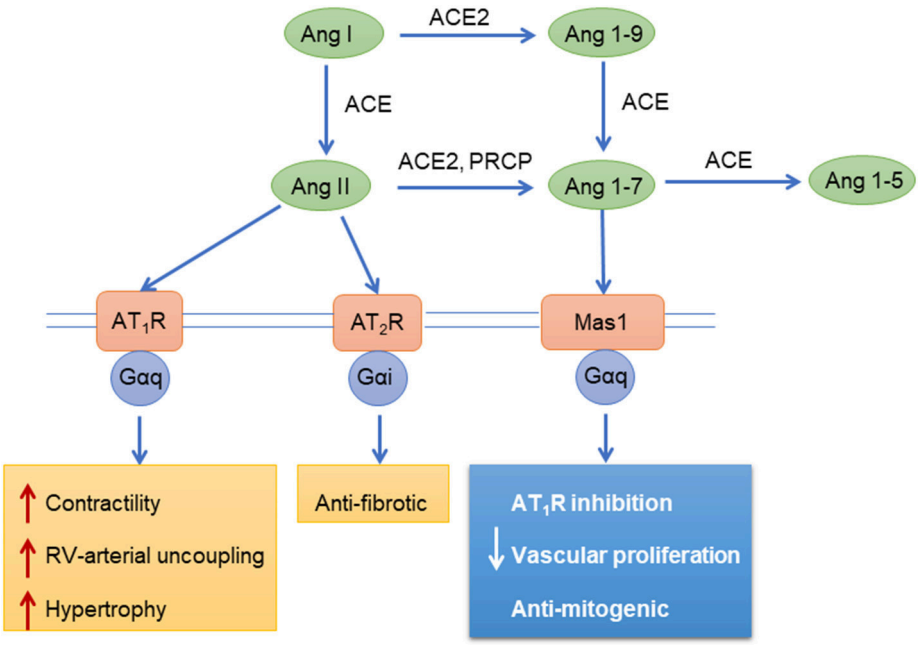

FIGURE 4 | Angiotensin mediated signaling pathways. Ang, angiotensin; ACE, Angiotensin-converting enzyme; AT_1R, Angiotensin II receptor type 1; AT_2R, Angiotensin II receptor type 2; Mas1, Proto-oncogene Mas; PRCP, Lysosomal Pro-X carboxypeptidase; Gαi, Gαq, G-proteins.

and CXCL2 chemokines are upregulated (86). However, other chemokines such as XCL-1 and CXCL-12 are downregulated in the acutely remodeled RV myocardium (74). The detrimental effect of upregulated chemokines on the RV may be due to their contribution to the cardiac fibrosis mediated by the upregulation of several proteoglycans by cardiac fibroblasts (73, 197). However, the roles of chemokine receptors have not been studied specifically in RV remodeling models and only few studies showed that some of them are upregulated in the remodeled RV myocardium such as LCR1 in HOX mice (60), CCR2 in PAB mice (73), and CCR1 and CXCR4 in rat model PE (74).

Apelin Receptor

Apelin and elabela/toddler are endogenous ligands for the apelin receptor APJ, which has been shown to play a beneficial role in normal physiology and its dysregulation is associated with several cardiopulmonary diseases (198), including PAH (199). Depending on the disease model and species used, apelin expression in the lung tissue has been noted unchanged (81), or upregulated in HOX mice (200). Nevertheless, apelin-KO mice develop more severe PAH upon exposure to hypoxia (200) suggesting the beneficial role apelin in PAH. In line with findings of preclinical studies, circulating levels of apelin are decreased in PAH patients (200), which may be due to decreased expression of apelin in endothelial cells of remodeled pulmonary arteries (201, 202). Moreover, in endothelial cell specific PPAR-γ deficient mice, which spontaneously develop pulmonary hypertension, treatment with apelin reverses PAH (201). RV myocardial expressions of apelin and its receptor APJ are dysregulated differently depending on the severity of pressure overload imposed on the RV wall. Apelin and its receptor are downregulated in maladaptive RV remodeling models such as SuHx rats (82), MCT rats (71, 72) while their expression is increased in adaptive RV remodeling models such as HOX rats (81). Moreover, treatment with pyroglutamylated apelin-13 (200 μg/kg/day, ip) of MCT rats attenuates RV cardiomyocyte hypertrophy and RV fibrosis along with restoration of apelin-AJP signaling in the RV without effecting on PA remodeling (71). Similarly, treatment with Elabela/Toddler, an endogenous analog of apelin, of MCT rats attenuates RV hypertrophy and PA remodeling (72). Importantly, similar to apelin, elabela/toddler exerts positive inotropic effects on both LV and RV (72). These findings have led to clinical trials with APJ agonists as a treatment option for PAH. For instance, in patients with PAH, 5-min intravenous infusions of increasing doses of (Pyr1) apelin-13 at 10, 30, and 100 nmol/min reduced PVR and increase CO without effecting on systemic hemodynamics (203).

Human Studies With GPCR Agonists and Antagonists

We refer readers to the following excellent review articles summarizing clinical trials with GPCR agonists or/and antagonists in PH patients including endothelin receptor antagonists (204), prostacyclin receptors agonists (205), and beta-blockers (206). Here we briefly discuss clinical studies evaluating the effects of above-mentioned drugs on the RV in PH patients. As discussed above, promising effects of GPCR agonists/antagonists on the pressure-overloaded RV in animal studies have led to several clinical trials focusing not only on

pulmonary hemodynamics but also on RV performance in PH patients.

Recent trials showed that initial upfront combination treatment with ERAs and PDE5 inhibitors improved RV remodeling and function in patients with scleroderma associated PAH (207) as well as in IPAH patients (208). Similar to animal studies, adrenergic receptors of the in the RV in human PAH are dysregulated (144, 209, 210). Despite the beneficial effects of beta-blockers in some models of PAH and RV remodeling, it is still unclear as to the potential beneficial effects of these drugs on the RV in patients with PAH. Bisoprolol (a selective β1AR-blocker) treatment for 6 months in 18 IPAH patients was associated with a reduced cardiac output and a trend toward reduced 6-min walk distance (211). Another study showed that in PH patients with different etiologies, carvedilol treatment was well tolerated and associated with maintenance of cardiac output and no improvement in 6-min walk distance with beneficial effect on RV metabolism (212).

Initially, the cardiac effects of prostanoids were studied in patients with heart failure and were found to be beneficial in these patients (213). Similarly, in PAH patients, prostanoids improve RV performance, functional and hemodynamic outcomes, and survival (214–218). A meta-analysis revealed that despite the fact that all forms of prostanoids improve hemodynamics and functional outcomes, only intravenous prostanoids provide significant survival benefit in PAH (218). However, in patients with left heart failure, treatment with epoprostenol is associated with increased mortality at 6 months, despite an early improvement in exercise capacity (219). Some have speculated that these early improvements in exercise performance and cardiac output after prostanoid therapy may be due to increased RV contractility, which subsequently may lead to increased myocardial oxygen consumption and may therefore be detrimental (220). Recently in a study of PAH patients, treprostinil treatment was associated with a decrease in afterload with no increase in inotropy (221). Therefore, it is still unclear as to the degree of which a direct effect of prostacyclins on the RV plays in the treatment of PAH.

One of the consequences of activated RAAS is increased levels of circulating aldosterone in PAH patients (222). In PAH patients, combination treatment with an aldosterone inhibitor, spironolactone and an ERA, ambrisentan lead to more significant improvements in functional status and cardiac performance compared to ambrisentan alone (223). The results of a randomized controlled trial (Clinicaltrials.gov NCT01468571) evaluating the safety and tolerability in PAH patients showed that it is safe and well tolerated (224). Another trial assessing the effects of the aldosterone inhibitor spironolactone in PAH is expected to complete in 2021 (Clinicaltrials.gov NCT01712620). In addition, clinical trials have shown that the use of agents modulating RAAS does not seem to be beneficial for the right ventricle of patients with congenital heart diseases (225). Taken together, despite the well-established beneficial effects of some of the GPCR agonists and antagonists on pulmonary hemodynamics in PAH, their direct effects on the RV are still somewhat controversial and require further study.

CONCLUSIONS

A number of GPCRs are differentially regulated in the RV myocardium in response to pressure overload in both PAH patients and preclinical models of RV remodeling (**Table 1**). In addition, levels of endogenous ligands targeting GPCRs are changed in the remodeled RV myocardium (**Table 2**). In preclinical studies of RV failure, some pharmacological agents targeting GPCRs have been shown to be beneficial while others do not appear to have any effects or are even detrimental (**Table 3**). However, the majority of preclinical studies have been performed using afterload-dependent models such as MCT-, hypoxia-, and SuHx-induced PAH models in which any changes in RV function are confounded by changes in the pulmonary vasculature. This is not true in PAB models, which allow the study of GPCRs and their endogenous and exogenous agonists or antagonists independent from direct effects on the pulmonary vasculature; however, such models have rarely been used. Taken together, the evidence is clear that several GPCRs are dysregulated in the RV myocardium in response to pressure overload are associated with RV remodeling and dysfunction. However, the underlying mechanisms that underlie GPCR function in the RV have not been fully elucidated, which must be addressed in future studies which could lead to novel therapies for right heart failure.

AUTHOR CONTRIBUTIONS

SR conceived the review. GV and AM drafted the manuscript. GV, AM, RS, and SR revised the manuscript critically for important intellectual content. RS and SR approved the final version of the manuscript submitted.

FUNDING

This work was supported by a Burroughs Wellcome Career Award for Medical Sciences and American Heart Association (grant 33670458) (SR) and CRC1213 (Collaborative Research Center 1213) (RS).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.