We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Interplay Between Serotonin Transporter Signaling and Voltage-Gated Potassium Channel (Kv) 1.5 Expression

Christophe Guignabert

INSERM UMR 999, "Pulmonary Hypertension:
Physiopathology and Novel Therapies", Le Plessis-Robinson,
France

1. Introduction

The exact mechanisms of pulmonary arterial remodeling that lead to the onset and progression of pulmonary arterial hypertension (PAH) are still largely unclear. However, many disease-predisposing factors and/or contributing factors have been identified, including inflammation, endothelial cell dysfunction, aberrant vascular wall cell proliferation and mutations in the *bone morphogenetic protein receptor type II (BMPRII)* gene (Humbert *et al.*, 2004; Mandegar *et al.*, 2004; Chapman *et al.*, 2008; Rabinovitch, 2008; Hassoun *et al.*, 2009; Morrell *et al.*, 2009). During the last few years, the serotonergic system and voltage-gated potassium (Kv) channels have attracted special attention and substantial evidence now supports a close relationship between them in the physiopathology of PAH.

2. The serotonergic system in the pathogenesis of PAH

Serotonin (5-hydroxytryptamine or 5-HT) and its transporter (SERT or 5-HTT) have long been suspected of playing important roles in the pathogenesis of idiopathic PAH and have, for several reasons, been tightly linked to its etiology. 5-HT is an endogenous vasoactive indolamine found mainly in enterochromaffin tissue, brain and blood platelets. It promotes pulmonary arterial smooth muscle cell (PA-SMC) proliferation, pulmonary arterial vasoconstriction and local microthrombosis. Plasma 5-HT levels are elevated in patients with PAH and remain high even after lung transplantation, indicating that this condition is not secondary to the disease (Herve *et al.*, 1995). 5-HTT belongs to a large family of integral membrane proteins and is responsible for 5-HT uptake (e.g., by platelets, endothelial and vascular SMCs). Analysis of distal pulmonary arteries of patients with PAH and their cultured PA-SMCs indicates that 5-HTT is overexpressed and that the level of expression correlates with PAH severity (Eddahibi *et al.*, 2001; Eddahibi *et al.*, 2002; Marcos *et al.*, 2004; Marcos *et al.*, 2005). Tryptophan hydroxylase (TPH), the rate-limiting enzyme in 5-HT biosynthesis, is also expressed at abnormally high levels in pulmonary endothelial cells from patients with idiopathic PAH, and therefore raises 5-HT levels locally (Eddahibi *et al.*, 2006). There is evidence that alterations in platelet 5-HT storage and/or increased platelet

consumption by the lung may trigger the development of PAH (Herve *et al.*, 1990; Herve *et al.*, 1995; Breuer *et al.*, 1996; Eddahibi *et al.*, 2000b; Kereveur *et al.*, 2000; Morecroft *et al.*, 2005). Furthermore, serotonergic appetite suppressant drugs have been associated with an increased risk of developing PAH (Douglas *et al.*, 1981; Gurtner, 1985; Loogen *et al.*, 1985; Brenot *et al.*, 1993; Abenhaim *et al.*, 1996; Souza *et al.*, 2008). Additionally, studies on animal models of pulmonary hypertension consolidate all these observations obtained from human subjects. Plasma 5-HT levels are elevated not only in rodents treated with the anorectic agent dexfenfluramine (Eddahibi *et al.*, 1998), but also in the progression of monocrotaline- and chronic hypoxia-induced pulmonary hypertension. The chronic infusion of exogenous 5-HT via osmotic pumps can potentiate the development of PH in rats exposed to chronic hypoxia (Eddahibi *et al.*, 1997). A bone morphogenetic protein type II receptor (BMPR-II) deficiency increases susceptibility to PH induced by 5-HT in mice (Long *et al.*, 2006). In the fawn-hooded rat, a strain with a genetic deficit in platelet 5-HT storage that causes elevated plasma 5-HT concentrations, PH develops when the animals are exposed to mild hypoxia but not in control rats (Sato *et al.*, 1992). An abnormally high level of 5-HTT in the lungs was reported for fawn-hooded rats (Sato *et al.*, 1992; Morecroft *et al.*, 2005). Furthermore, rodents engineered to constitutively express angiopoietin 1 in the lung develop PH. This effect was found to be directly related to the elevated production and secretion of 5-HT by stimulated pulmonary endothelial cells (Sullivan *et al.*, 2003). It has also been shown in the monocrotaline model that 5-HTT expression levels increased prior to the onset of PH, which strongly supports a role for 5-HTT overexpression in disease development (Guignabert *et al.*, 2005). Treatment with selective serotonin reuptake inhibitors (e.g. fluoxetine) abrogates the disease in chronically hypoxic mice and rats with monocrotaline-induced PH (Li *et al.*, ; Wang *et al.*, ; Marcos *et al.*, 2003; Guignabert *et al.*, 2005; Guignabert *et al.*, 2009; Zhai *et al.*, 2009; Zhu *et al.*, 2009). Furthermore, mice carrying null mutations at the 5-HTT locus are protected from developing PH induced by prolonged hypoxia (Eddahibi *et al.*, 2000a). Similarly, hypoxia-induced PH in mice lacking the *tph1* gene, which exhibit marked reductions in 5-HT synthesis rates and contents in their peripheral organs, was less severe than in wild-type mice (Izikki *et al.*, 2007).

More recently, direct evidence that elevated levels of 5-HTT gene expression can promote pulmonary vascular remodeling and spontaneous PH was obtained with the creation of two different types of transgenic mice: (1) SM22 5-HTT+ mice that selectively express the human 5-HTT gene in smooth muscle at levels close to that found in human idiopathic PAH; and (2) SERT+ mice that ubiquitously express high levels of the human 5-HTT gene from a yeast artificial chromosome (YAC) construct. SM22 5-HTT+ mice undergo pulmonary vascular remodeling, develop PH and exhibit marked increases in right ventricular systolic pressures (RVSPs), right ventricular hypertrophy (RVH), and muscularization of pulmonary arterioles (Figure 1). One major point is that PH in these mice developed without any alterations in 5-HT bioavailability, and therefore occurred as a sole consequence of the increased 5-HTT protein levels in SMCs. Compared to wild-type mice, SM22 5-HTT+ mice exhibited increases of three- to four-fold in lung 5-HTT mRNA & protein, together with increased lung 5-HT uptake activity. However, there were no changes in platelet 5-HTT activity or blood 5-HT levels. PH worsened as the SM22 5-HTT+ mice grew older (Guignabert *et al.*, 2006). Consistent with these observations, female SERT+ mice housed in normoxic conditions developed a three-fold increase in RVSP values compared to those of their wild-type controls (MacLean *et al.*, 2004).

Fig. 1. Development of pulmonary hypertension and vascular remodeling in SM22 5-HTT+ mice versus wild-type mice at 20 and 55 weeks of age under normoxic conditions. Right ventricular systolic pressure and representative pictures of in situ cell proliferation in muscularized vessels, shown by proliferating cell nuclear antigen (PCNA) immunohistochemistry. Scale bar = 50 μ m.

Of the fourteen distinct 5-HT receptors, the 5-HT-2A, -2B, and -1B receptors are particularly relevant to the pathogenesis of PAH. High levels of 5-HT-1B, -2A, and -2B receptor immunoreactivity were reported in remodeled pulmonary arteries from patients with various forms of pulmonary hypertension, but only the 5-HTT was found to be overexpressed in pulmonary artery smooth muscle cells (Marcos *et al.*, 2005). Several lines of evidence support the notion that functional interactions exist between some of these 5-HT receptors and 5-HTT, and thus have encouraged studies to better understand these complex relationships (Lawrie *et al.*, 2005; Launay *et al.*, 2006). Antagonism of the 5-HT-2A receptor inhibits not only monocrotaline-induced pulmonary hypertension in mice (Hironaka *et al.*, 2003) but also the 5-HT-induced pulmonary vasoconstriction in vessels from normoxic and hypoxic rats (Morecroft *et al.*, 2005; Cogolludo *et al.*, 2006). However, the 5HT-2A receptor antagonist ketanserin is not specific for pulmonary circulation, and systemic effects have limited its use in PAH (Frishman *et al.*, 1995). 5-HT-2B knockout mice are resistant to hypoxia-induced pulmonary hypertension and administration of the specific 5-HT-2B receptor antagonist RS-127445 prevented an increase in pulmonary arterial pressure in mice challenged with hypoxia (Launay *et al.*, 2002). Furthermore, the 5-HT-2B receptor may control 5-HT plasma levels *in vivo* (Callebert *et al.*, 2006), and its functional loss may predispose humans to fenfluramine-associated PAH (Blanpain *et al.*, 2003). A very recent study showed that terguride, a potent 5-HT-2A/5-HT-2B receptor antagonist, inhibits the

proliferative effects of 5-HT on PA-SMCs and prevents the development and progression of monocrotaline-induced PH in rats (Dumitrascu *et al.*). The 5-HT-1B receptor mediates 5-HT-induced constriction in human pulmonary arteries (Morecroft *et al.*, 1999), and has been shown to be involved in the development of PH in rodents exposed to chronic hypoxia (Keegan *et al.*, 2001). Recently, Morecroft *et al.* have reported that co-inhibition of the 5-HT-1B receptor and 5-HTT with a combined 5-HT-1B receptor/5-HTT antagonist (LY393558) is effective at preventing and reversing experimental PH in animal models and 5-HT-induced proliferation in PA-SMCs derived from idiopathic PAH patients.

3. Expression and activity of the Kv1.5 channel in the pathogenesis of PAH

Potassium ion (K^+) channels play a crucial role in the immediate and long-term regulation of vascular smooth muscle function. They are integral membrane proteins that allow the selective passage of K^+ across biological membranes. Their activity determines and regulates cell membrane potential, which in turn, regulates the open state probability of voltage-gated calcium ion (Ca^{2+}) channels, Ca^{2+} influx, and intracellular Ca^{2+} levels. The increase in cytoplasmic free Ca^{2+} concentration in SMCs is an important trigger for cell contraction but also a stimulus for pulmonary SMC proliferation. Among the different types of K^+ channels, Kv channels are expressed at high levels in most vascular SMCs and are regarded as a major determinant of vascular tone and resting membrane potential (Post *et al.*, 1995; Yuan, 1995; Evans *et al.*, 1996; Ko *et al.*, 2008). There are four major families of Kv channels, Kv1.x to Kv4.x, with two to eight members in each family. Differential distribution of Kv channels exists in several types of SMCs and this contributes to the large functional diversity that has been noted for native Kv currents in different myocytes (Archer *et al.*, 1996; Coppock & Tamkun, 2001). Although Kv1.2, Kv1.5, Kv2.1, Kv3.1b and Kv9.3 play important roles in the hypoxia-inhibited K^+ current found in PA-SMCs, much attention has been attracted by the Kv1.5 channel (Archer *et al.*, 1993; Archer *et al.*, 1996; Patel *et al.*, 1997; Archer *et al.*, 1998; Osipenko *et al.*, 2000; Archer *et al.*, 2001; Coppock *et al.*, 2001; Coppock & Tamkun, 2001; Archer & Michelakis, 2002; Archer *et al.*, 2004a; Guignabert *et al.*, 2009). In addition to hypoxia, endothelin-1, thromboxane A₂, 5-HT, and anorectic drugs have been shown to inhibit Kv currents in PA-SMCs (Weir *et al.*, 1996; Archer *et al.*, 1998; Cogolludo *et al.*, 2003; Cogolludo *et al.*, 2006). Kv1.5 is widely represented in the cardiovascular system (Overturf *et al.*, 1994). In the human heart, the Kv1.5 channel is expressed predominantly in the atrial myocardium and is responsible for the ultra-rapid component of the delayed rectifier K^+ current, I_{Kur} (Fedida *et al.*, 1993; Wang *et al.*, 1993; Gaborit *et al.*, 2007). A familial form of atrial fibrillation has been attributed to a loss-of-function mutation in the Kv1.5 gene (Olson *et al.*, 2006). It is also expressed in the human ventricle where it possibly contributes to the K^+ current through formation of heteromultimeric K^+ channels with other Kv-alpha subunits (Mays *et al.*, 1995). In the human lung, Kv1.5 was shown to be expressed in SMCs, endothelial cells, macrophages, and dendritic cells. Importantly, the expression levels of Kv1.5 channel proteins are higher in distal pulmonary arteries than in proximal pulmonary arteries, thus making its involvement in PAH disease an attractive possibility (Archer *et al.*, 2004b).

Low levels of Kv1.5 gene expression and channel activity are hallmarks of human and experimental PH, including the chronic-hypoxia and monocrotaline models (Yuan *et al.*, 1998a; Yuan *et al.*, 1998b; Reeve *et al.*, 2001; McMurtry *et al.*, 2004; McMurtry *et al.*, 2005; Bonnet *et al.*, 2006; Guignabert *et al.*, 2006; Young *et al.*, 2006; Remillard *et al.*, 2007; Archer *et al.*, 2008; Guignabert *et al.*, 2009). However, the underlying mechanism of Kv1.5 in PH

pathology remains unclear even though there has been significant progress made in understanding how the expression of its gene is regulated. A variety of transcriptional factors, such as HIF-1 α (Bonnet *et al.*, 2006), c-Jun (Yu *et al.*, 2001), a signal-transducing transcription factor of the AP-1 family, and nuclear factor of activated T cells (NFAT) (Guignabert *et al.*, 2009) are involved in *Kv1.5* gene regulation. Several single nucleotide polymorphisms (SNPs) in the *Kv1.5* gene of idiopathic PAH patients have been reported, and these SNPs may correlate with altered *Kv1.5* gene expression or protein function in PA-SMCs (Remillard *et al.*, 2007). Restoring *Kv1.5* gene expression to normal levels in rats reduces PH induced by chronic hypoxia and restores hypoxic pulmonary vasoconstriction (Pozeg *et al.*, 2003). Taken together, all these observations strongly support the hypothesis that *Kv1.5* channel dysfunction and gene down-regulation represent predisposing factors that may operate in conjunction with other factors and/or genetic defects.

4. Connections between serotonin transporter signaling and Kv1.5 channel expression

During the last few years, direct evidence for a molecular interplay between 5-HTT signaling and *Kv1.5* expression/activity has emerged. Exogenous 5-HT has been shown to reduce *Kv1.5* mRNA levels in cultured human PA-SMCs, an effect totally abolished by a selective 5-HTT antagonist fluoxetine (Guignabert *et al.*, 2006). In normal rat PA-SMCs and in Ltk— cells stably transfected with the human *Kv1.5* gene, Kv currents were inhibited by 5-HT via activation of the 5-HT-2A receptor (Cogolludo *et al.*, 2006). Compared to wild-type mice, SM22 5-HTT+ mice exhibited a marked decrease in the levels of the *Kv1.5* channel protein in the lung (Figure 2), but no changes in the levels of expression in the lung were detected for endothelin-1, Tie2 receptor, prostacyclin synthase, or members of the bone morphogenetic protein (BMP) pathway (BMP-RII, BMP-RIA, BMP-RIB, BMP-2, and BMP-4). Furthermore, SM22 5-HTT+ mice show depressed hypoxic pulmonary vasoconstriction and greater severity to hypoxia- or monocrotaline-induced PH (Guignabert *et al.*, 2006). In contrast, 5-HTT knockout mice exhibit a potentiation of acute hypoxic hypoxic pulmonary vasoconstriction (Eddahibi *et al.*, 2000a).

Fig. 2. *Kv1.5* expression is lower in the lung tissues of SM22 5-HTT+ mice than in the lungs of wild-type mice.

A representative immunohistochemistry slide shows strong *Kv1.5* staining in the SMCs of distal pulmonary arteries from wild-type mice and weak staining in the arterial SMCs of SM22 5-HTT+ mice.

Scale bar= 50 μ m.

A recent study has provided the first evidence that 5-HT, via 5-HTT, decreases Kv1.5 expression by inhibiting nuclear NFATc2 translocation *in vitro* & *in vivo* (Guignabert *et al.*, 2009). In the first part of this study, chronic dichloroacetate administration (an inducer of Kv1.5 expression, apoptosis, and depolarization of mitochondrial membranes) vs. saline limited the progression of pulmonary vascular remodeling and PH in SM22 5-HTT+ mice by progressively and markedly reducing hemodynamic values, right ventricular hypertrophy and the pulmonary vessel remodeling. Furthermore, oral fluoxetine (a selective 5-HTT antagonist) therapy totally reversed the established PH in these mice. Interestingly, the authors found that Kv1.5 expression progressively normalized in the lungs of SM22 5-HTT+ mice treated with either dichloroacetate or fluoxetine, which contrasted with the persistently low levels of Kv1.5 expression detected in control SM22 5-HTT+ mice treated with vehicle (Figure 3).

Fig. 3. Changes in Kv1.5 expression in the lungs of SM22 5-HTT+ and wild-type mice treated for 21 days with dichloroacetate (DCA; 80 mg/kg/day) or fluoxetine (Fluox; 10 mg/kg/day) or vehicle (saline). Representative western blots of Kv1.5 and β-actin proteins in SM22 5-HTT+ and wild-type mice treated with an active drug or vehicle.

Due to the finding that dichloroacetate upregulated Kv1.5 expression by an NFAT-dependent mechanism (Bonnet *et al.*, 2007b) and to the demonstrated interrelationships between 5-HT signaling, Ca²⁺/calcineurin signaling activation, and cardiac muscle cell hypertrophy (Bush *et al.*, 2004), the hypothesis that NFAT may be a major molecular link between 5-HTT signalling and Kv1.5 expression/activity was tested. Consistent with this theory, 5-HT treatment of human PA-SMCs *in vitro* induced significant nuclear translocation of NFATc2, which led to a subsequent and significant decrease in Kv1.5 protein expression (Figure 4). NFATc2 nuclear translocation was greater and Kv1.5 protein expression was significantly lower in PA-SMCs from idiopathic PAH patients than in control PA-SMCs under basal conditions. In addition, dichloroacetate, 11R-VIVIT (a selective inhibitor of NFAT translocation), cycloporine A (an indirect inhibitor of NFAT activation) and fluoxetine markedly inhibited the elevated nuclear NFATc2 translocation and normalized the low Kv1.5 levels in PA-SMCs from idiopathic PAH patients (Guignabert *et al.*, 2009).

In addition, Guignabert *et al.* also clearly showed by [³H]-thymidine incorporation that dichloroacetate (5 × 10⁻⁴ M), 11R-VIVIT (4 × 10⁻⁶ M), cycloporine A (10⁻⁶ M) and fluoxetine (10⁻⁶ M) markedly inhibited the growth of PA-SMCs from idiopathic PAH patients and the growth of normal PA-SMCs treated with the highest dose of 5-HT (10⁻⁶ M). All these *in vitro* findings confirm and extend previous evidence obtained by Bonnet *et al.* (Bonnet *et al.*, 2007b) and clearly demonstrated that NFAT serves as a link between 5-HTT activation and Kv1.5 downregulation.

Fig. 4. Representative micrographs showing immunoreactivity for the active form of NFAT in cultured PA-SMCs isolated from patients with idiopathic PAH (IPAH PA-SMCs) and normal subjects (Control PA-SMCs) treated with serotonin (10^{-6} M) or vehicle (phosphate buffered saline or PBS) with or without one of the following: PBS, fluoxetine (10^{-6} M), or dichloroacetate (5×10^{-4} M). Scale bar= 20 μ m.

Furthermore, an abnormal level of activated NFAT was found in the lungs of SM22 5-HTT+ mice, which gradually decreased over time with oral dichloroacetate and fluoxetine therapy. To further study the importance of NFAT activation and its downstream effects on disease progression, separate experiments were performed in SM22 5-HTT+ and wild-type mice with an indirect inhibitor of NFAT, the calcineurin inhibitor: cyclosporine A (1 mg/kg/day, *per os*, daily for three weeks). Cyclosporine A treatment reduced the pulmonary levels of active NFAT and increased Kv1.5 protein levels in SM22 5-HTT+ mice, but yielded no beneficial effects on pulmonary hemodynamics or arterial structures. In contrast, a similar cyclosporine A treatment for two weeks partially reversed monocrotaline-induced PH in rats (Bonnet *et al.*, 2007b). Several possible explanations have been proposed for this discrepancy. First, NFAT regulates many cytokines known to be central in the pathogenesis of PAH (Macian, 2005), and inflammation is an important component of PAH in the monocrotaline rat model but not in SM22 5-HTT+ mice. Second, normalization of Kv1.5 expression in vitro neither completely inhibited PA-SMC proliferation induced by 5-HT nor completely abolished the differences between idiopathic PAH and control PA-SMCs. These observations suggest that inhibition of NFAT activation alone was not sufficient to counteract all the effects induced by 5-HT via its transporter in SM22 5-HTT+ mice, which exhibit constant and sustained 5-HTT activation in SMCs. Such activation induces cellular proliferation by activating several other intracellular signal transduction pathways (Figure 5), including: tyrosine phosphorylation of GTPase-activating protein (Lee *et al.*, 1997), rapid formation of superoxide (O_2^-); and activation of Rho/Rho kinase (ROCK) (Liu *et al.*, 2004; Guilluy *et al.*, 2009), extracellular signal-regulated kinase 1 (ERK1)/ERK2, and mitogen-activated protein (MAP) kinase (Lee *et al.*, 1998; Lee *et al.*, 2001). Intracellular accumulation of 5-HT has also been found to interact with other intracellular signal transduction pathways including the transcription factor GATA-4 (Suzuki *et al.*, 2003; Lawrie *et al.*, 2005), the platelet-derived growth factor receptor (PDGF-R) (Ren *et al.*, ; Liu *et al.*, 2007), and the serine/threonine protein kinase, Akt (Liu & Fanburg, 2006).

Fig. 5. Diagram of the link between 5-HTT activation and Kv1.5 downregulation. Intracellular accumulation of 5-HT induces arterial SMC proliferation via activation of several intracellular signal transduction pathways, including reactive oxygen species (ROS) production and activation of Rho-kinase (ROCK), which lead to phosphorylation and nuclear translocation of extracellular-regulated kinase 1 (ERK1)/2 and to dephosphorylation and nuclear translocation of NFATc2. NFATc2 remains in the cytoplasm when phosphorylated. Following intracellular accumulation of 5-HT or activation by calcium (Ca^{2+}), NFAT is dephosphorylated by the phosphatase calcineurin. Once in the nucleus, NFATc2 can regulate gene expression in coordination with ERK, leading to Kv1.5 downregulation and changes in the balance between proliferation and apoptosis.

In contrast to cyclosporine A, dichloroacetate elicits a wide spectrum of beneficial effects able to ameliorate dysfunctions related to abnormal NFAT activation, production of reactive oxygen species, fragmentation and/or hyperpolarization of the mitochondrial reticulum, and changes in the apoptosis/proliferation ratio (Bonnet *et al.*, 2007a; Archer *et al.*, 2008; Michelakis *et al.*, 2008). In addition, dichloroacetate treatment led to rapid and marked decreases in anti-apoptotic factor B-Cell Lymphoma 2 (BCL2) expression and in the BCL2/Bax ratio compared to vehicle, which suggests that down-regulation of BCL2 by dichloroacetate might be an important mechanism in the reversal of pulmonary vascular remodeling in SM22 5-HTT⁺ mice and chronic hypoxia- or monocrotaline-induced pulmonary hypertension.

In addition to the effects of intracellular accumulation of 5-HT, activation of HIF-1 α and c-Jun are two other major drivers of Kv1.5 down-regulation (Yu *et al.*, 2001; Bonnet *et al.*, 2006). c-Jun is a nuclear protein that serves as a nuclear signal transduction intermediate in cell growth and differentiation. Overexpression of c-Jun downregulates expression of Kv1.5 and upregulates expression of the β -subunit (Kv β 2) in PA-SMCs (Yu *et al.*, 2001). Thus, c-Jun modulates Kv current, influences the resting membrane potential and affects the SMC proliferation. Abnormal activation of HIF-1 α has been reported in the PA-SMCs of patients with idiopathic PAH and in those from fawn-hooded rats. Inhibition of HIF-1 α restores Kv1.5 expression and normalizes Kv current in experimental PH (Bonnet *et al.*, 2006). The presence of an evolutionarily conserved and functional consensus NFAT binding site in the HIF-1 α promoter at position 728 bp suggests that NFAT and HIF-1 α , either individually or via cooperative effects, are also two key players in Kv1.5 down-regulation (Walczak-Drzewiecka *et al.*, 2008). In addition to the serotonergic system, other NFAT activators have been identified that include the transcription factor signal transducer and activator of transcription 3 (STAT3), peroxisome proliferator-activated receptor γ (PPAR γ), Pim1, vasoactive intestinal peptide (VIP) and miR-204 (Courboulin *et al.*, ; Paulin *et al.*, ; Bao *et al.*, 2008; Said, 2008).

5. Conclusion

In summary, multiple downstream signaling pathways are activated following 5-HTT activation and a better understanding of this complex network of interactions will be crucial for developing methods to limit its potential pathogenic role. Recent evidence has demonstrated that 5-HTT activation and Kv1.5 downregulation are connected via a NFAT-dependent mechanism (Guignabert *et al.*, 2009). Although chronic dichloroacetate, cyclosporine A or fluoxetine administration returned the Kv1.5 level to normal in SM22 5-HTT+ mice, only dichloroacetate and fluoxetine treatments substantially diminished pulmonary artery pressure, right ventricular hypertrophy, and pulmonary arterial muscularization in this experimental model. These findings suggest that inhibition of NFAT alone with cyclosporine A is not sufficient to counteract all the effects induced by 5-HT via its transporter. Thus, pharmacological inhibition of the upstream components of the serotonergic pathway or the use of dichloroacetate with pleiotropic effects are very attractive as therapeutic strategies for treating pulmonary hypertension.

6. Acknowledgments

The author thanks Saadia Eddahibi, Marc Humbert, Elie Fadel, Michel Hamon, Serge Adnot, Bernard Maître, Gerald Simonneau, and Phillipe Hervé for valuable discussions.

7. References

- Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G & Begaud B (1996) Appetite-suppressant drugs and the risk of primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. *N Engl J Med* 335, 609-616.

- Archer S & Michelakis E (2002) The mechanism(s) of hypoxic pulmonary vasoconstriction: potassium channels, redox O₂ sensors, and controversies. *News Physiol Sci* 17, 131-137.
- Archer SL, Gomberg-Maitland M, Maitland ML, Rich S, Garcia JG & Weir EK (2008) Mitochondrial metabolism, redox signaling, and fusion: a mitochondria-ROS-HIF-1 α -Kv1.5 O₂-sensing pathway at the intersection of pulmonary hypertension and cancer. *Am J Physiol Heart Circ Physiol* 294, H570-578.
- Archer SL, Huang J, Henry T, Peterson D & Weir EK (1993) A redox-based O₂ sensor in rat pulmonary vasculature. *Circ Res* 73, 1100-1112.
- Archer SL, Huang JM, Reeve HL, Hampl V, Tolarova S, Michelakis E & Weir EK (1996) Differential distribution of electrophysiologically distinct myocytes in conduit and resistance arteries determines their response to nitric oxide and hypoxia. *Circ Res* 78, 431-442.
- Archer SL, London B, Hampl V, Wu X, Nsair A, Puttagunta L, Hashimoto K, Waite RE & Michelakis ED (2001) Impairment of hypoxic pulmonary vasoconstriction in mice lacking the voltage-gated potassium channel Kv1.5. *Faseb J* 15, 1801-1803.
- Archer SL, Souil E, Dinh-Xuan AT, Schremmer B, Mercier JC, El Yaagoubi A, Nguyen-Huu L, Reeve HL & Hampl V (1998) Molecular identification of the role of voltage-gated K⁺ channels, Kv1.5 and Kv2.1, in hypoxic pulmonary vasoconstriction and control of resting membrane potential in rat pulmonary artery myocytes. *J Clin Invest* 101, 2319-2330.
- Archer SL, Wu XC, Thebaud B, Moudgil R, Hashimoto K & Michelakis ED (2004a) O₂ sensing in the human ductus arteriosus: redox-sensitive K⁺ channels are regulated by mitochondria-derived hydrogen peroxide. *Biol Chem* 385, 205-216.
- Archer SL, Wu XC, Thebaud B, Nsair A, Bonnet S, Tyrrell B, McMurtry MS, Hashimoto K, Harry G & Michelakis ED (2004b) Preferential expression and function of voltage-gated, O₂-sensitive K⁺ channels in resistance pulmonary arteries explains regional heterogeneity in hypoxic pulmonary vasoconstriction: ionic diversity in smooth muscle cells. *Circ Res* 95, 308-318.
- Bao Y, Li R, Jiang J, Cai B, Gao J, Le K, Zhang F, Chen S & Liu P (2008) Activation of peroxisome proliferator-activated receptor gamma inhibits endothelin-1-induced cardiac hypertrophy via the calcineurin/NFAT signaling pathway. *Mol Cell Biochem* 317, 189-196.
- Blanpain C, Le Poul E, Parma J, Knoop C, Detheux M, Parmentier M, Vassart G & Abramowicz MJ (2003) Serotonin 5-HT_{2B} receptor loss of function mutation in a patient with fenfluramine-associated primary pulmonary hypertension. *Cardiovasc Res* 60, 518-528.
- Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, Lee CT, Lopaschuk GD, Puttagunta L, Bonnet S, Harry G, Hashimoto K, Porter CJ, Andrade MA, Thebaud B & Michelakis ED (2007a) A mitochondria-K⁺ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. *Cancer Cell* 11, 37-51.

- Bonnet S, Michelakis ED, Porter CJ, Andrade-Navarro MA, Thebaud B, Bonnet S, Haromy A, Harry G, Moudgil R, McMurtry MS, Weir EK & Archer SL (2006) An abnormal mitochondrial-hypoxia inducible factor-1 α -Kv channel pathway disrupts oxygen sensing and triggers pulmonary arterial hypertension in fawn hooded rats: similarities to human pulmonary arterial hypertension. *Circulation* 113, 2630-2641.
- Bonnet S, Rochefort G, Sutendra G, Archer SL, Haromy A, Webster L, Hashimoto K, Bonnet SN & Michelakis ED (2007b) The nuclear factor of activated T cells in pulmonary arterial hypertension can be therapeutically targeted. *Proc Natl Acad Sci U S A* 104, 11418-11423.
- Brenot F, Herve P, Petitpretz P, Parent F, Duroux P & Simonneau G (1993) Primary pulmonary hypertension and fenfluramine use. *Br Heart J* 70, 537-541.
- Breuer J, Georgarakis A, Sieverding L, Baden W & Apitz J (1996) Increased turnover of serotonin in children with pulmonary hypertension secondary to congenital heart disease. *Pediatr Cardiol* 17, 214-219.
- Bush E, Fielitz J, Melvin L, Martinez-Arnold M, McKinsey TA, Plichta R & Olson EN (2004) A small molecular activator of cardiac hypertrophy uncovered in a chemical screen for modifiers of the calcineurin signaling pathway. *Proc Natl Acad Sci U S A* 101, 2870-2875.
- Callebert J, Esteve JM, Herve P, Peoc'h K, Tournois C, Drouet L, Launay JM & Maroteaux L (2006) Evidence for a control of plasma serotonin levels by 5-hydroxytryptamine(2B) receptors in mice. *J Pharmacol Exp Ther* 317, 724-731.
- Chapman ME, Taylor RL & Wideman RF, Jr. (2008) Analysis of plasma serotonin levels and hemodynamic responses following chronic serotonin infusion in broilers challenged with bacterial lipopolysaccharide and microparticles. *Poult Sci* 87, 116-124.
- Cogolludo A, Moreno L, Bosca L, Tamargo J & Perez-Vizcaino F (2003) Thromboxane A₂-induced inhibition of voltage-gated K⁺ channels and pulmonary vasoconstriction: role of protein kinase C ζ . *Circ Res* 93, 656-663.
- Cogolludo A, Moreno L, Lodi F, Frazziano G, Cobeno L, Tamargo J & Perez-Vizcaino F (2006) Serotonin inhibits voltage-gated K⁺ currents in pulmonary artery smooth muscle cells: role of 5-HT_{2A} receptors, caveolin-1, and KV1.5 channel internalization. *Circ Res* 98, 931-938.
- Coppock EA, Martens JR & Tamkun MM (2001) Molecular basis of hypoxia-induced pulmonary vasoconstriction: role of voltage-gated K⁺ channels. *Am J Physiol Lung Cell Mol Physiol* 281, L1-12.
- Coppock EA & Tamkun MM (2001) Differential expression of K(V) channel α - and β -subunits in the bovine pulmonary arterial circulation. *Am J Physiol Lung Cell Mol Physiol* 281, L1350-1360.
- Courboulin A, Paulin R, Giguere NJ, Saksouk N, Perreault T, Meloche J, Paquet ER, Biardel S, Provencher S, Cote J, Simard MJ & Bonnet S Role for miR-204 in human pulmonary arterial hypertension. *J Exp Med* 208, 535-548.
- Douglas JG, Munro JF, Kitchin AH, Muir AL & Proudfoot AT (1981) Pulmonary hypertension and fenfluramine. *Br Med J (Clin Res Ed)* 283, 881-883.

- Dumitrascu R, Kulcke C, Konigshoff M, Kouri F, Yang X, Morrell N, Ghofrani HA, Weissmann N, Reiter R, Seeger W, Grimminger F, Eickelberg O, Schermuly RT & Pullamsetti SS (2006) Terbufenadine ameliorates monocrotaline induced pulmonary hypertension in rats. *Eur Respir J*.
- Eddahibi S, Guignabert C, Barlier-Mur AM, Dewachter L, Fadel E, Darteville P, Humbert M, Simonneau G, Hanoun N, Saurini F, Hamon M & Adnot S (2006) Cross talk between endothelial and smooth muscle cells in pulmonary hypertension: critical role for serotonin-induced smooth muscle hyperplasia. *Circulation* 113, 1857-1864.
- Eddahibi S, Hanoun N, Lanfumey L, Lesch KP, Raffestin B, Hamon M & Adnot S (2000a) Attenuated hypoxic pulmonary hypertension in mice lacking the 5-hydroxytryptamine transporter gene. *J Clin Invest* 105, 1555-1562.
- Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, Simonneau G, Darteville P, Hamon M & Adnot S (2001) Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. *J Clin Invest* 108, 1141-1150.
- Eddahibi S, Humbert M, Fadel E, Raffestin B, Darmon M, Capron F, Simonneau G, Darteville P, Hamon M & Adnot S (2002) Hyperplasia of pulmonary artery smooth muscle cells is causally related to overexpression of the serotonin transporter in primary pulmonary hypertension. *Chest* 121, 97S-98S.
- Eddahibi S, Humbert M, Sediame S, Chouaid C, Partovian C, Maitre B, Teiger E, Rideau D, Simonneau G, Sitbon O & Adnot S (2000b) Imbalance between platelet vascular endothelial growth factor and platelet-derived growth factor in pulmonary hypertension. Effect of prostacyclin therapy. *Am J Respir Crit Care Med* 162, 1493-1499.
- Eddahibi S, Raffestin B, Launay JM, Sitbon M & Adnot S (1998) Effect of dexfenfluramine treatment in rats exposed to acute and chronic hypoxia. *Am J Respir Crit Care Med* 157, 1111-1119.
- Eddahibi S, Raffestin B, Pham I, Launay JM, Aegerter P, Sitbon M & Adnot S (1997) Treatment with 5-HT potentiates development of pulmonary hypertension in chronically hypoxic rats. *Am J Physiol* 272, H1173-1181.
- Evans AM, Osipenko ON & Gurney AM (1996) Properties of a novel K⁺ current that is active at resting potential in rabbit pulmonary artery smooth muscle cells. *J Physiol* 496 (Pt 2), 407-420.
- Fedida D, Wible B, Wang Z, Fermini B, Faust F, Nattel S & Brown AM (1993) Identity of a novel delayed rectifier current from human heart with a cloned K⁺ channel current. *Circ Res* 73, 210-216.
- Frishman WH, Huberfeld S, Okin S, Wang YH, Kumar A & Shareef B (1995) Serotonin and serotonin antagonism in cardiovascular and non-cardiovascular disease. *J Clin Pharmacol* 35, 541-572.
- Gaborit N, Le Bouter S, Szuts V, Varro A, Escande D, Nattel S & Demolombe S (2007) Regional and tissue specific transcript signatures of ion channel genes in the non-diseased human heart. *J Physiol* 582, 675-693.

- Guignabert C, Izikki M, Tu LI, Li Z, Zadigue P, Barlier-Mur AM, Hanoun N, Rodman D, Hamon M, Adnot S & Eddahibi S (2006) Transgenic mice overexpressing the 5-hydroxytryptamine transporter gene in smooth muscle develop pulmonary hypertension. *Circ Res* 98, 1323-1330.
- Guignabert C, Raffestin B, Benferhat R, Raoul W, Zadigue P, Rideau D, Hamon M, Adnot S & Eddahibi S (2005) Serotonin transporter inhibition prevents and reverses monocrotaline-induced pulmonary hypertension in rats. *Circulation* 111, 2812-2819.
- Guignabert C, Tu L, Izikki M, Dewachter L, Zadigue P, Humbert M, Adnot S, Fadel E & Eddahibi S (2009) Dichloroacetate treatment partially regresses established pulmonary hypertension in mice with SM22alpha-targeted overexpression of the serotonin transporter. *Faseb J* 23, 4135-4147.
- Guilluy C, Eddahibi S, Agard C, Guignabert C, Izikki M, Tu L, Savale L, Humbert M, Fadel E, Adnot S, Loirand G & Pacaud P (2009) RhoA and Rho kinase activation in human pulmonary hypertension: role of 5-HT signaling. *Am J Respir Crit Care Med* 179, 1151-1158.
- Gurtner HP (1985) Aminorex and pulmonary hypertension. A review. *Cor Vasa* 27, 160-171.
- Hassoun PM, Mouthon L, Barbera JA, Eddahibi S, Flores SC, Grimminger F, Jones PL, Maitland ML, Michelakis ED, Morrell NW, Newman JH, Rabinovitch M, Schermuly R, Stenmark KR, Voelkel NF, Yuan JX & Humbert M (2009) Inflammation, growth factors, and pulmonary vascular remodeling. *J Am Coll Cardiol* 54, S10-19.
- Herve P, Drouet L, Dosquet C, Launay JM, Rain B, Simonneau G, Caen J & Duroux P (1990) Primary pulmonary hypertension in a patient with a familial platelet storage pool disease: role of serotonin. *Am J Med* 89, 117-120.
- Herve P, Launay JM, Scrobohaci ML, Brenot F, Simonneau G, Petitpretz P, Poubeau P, Cerrina J, Duroux P & Drouet L (1995) Increased plasma serotonin in primary pulmonary hypertension. *Am J Med* 99, 249-254.
- Hironaka E, Hongo M, Sakai A, Mawatari E, Terasawa F, Okumura N, Yamazaki A, Ushiyama Y, Yazaki Y & Kinoshita O (2003) Serotonin receptor antagonist inhibits monocrotaline-induced pulmonary hypertension and prolongs survival in rats. *Cardiovasc Res* 60, 692-699.
- Humbert M, Morrell NW, Archer SL, Stenmark KR, MacLean MR, Lang IM, Christman BW, Weir EK, Eickelberg O, Voelkel NF & Rabinovitch M (2004) Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol* 43, 13S-24S.
- Izikki M, Hanoun N, Marcos E, Savale L, Barlier-Mur AM, Saurini F, Eddahibi S, Hamon M & Adnot S (2007) Tryptophan hydroxylase 1 knockout and tryptophan hydroxylase 2 polymorphism: effects on hypoxic pulmonary hypertension in mice. *Am J Physiol Lung Cell Mol Physiol* 293, L1045-1052.
- Keegan A, Morecroft I, Smillie D, Hicks MN & MacLean MR (2001) Contribution of the 5-HT(1B) receptor to hypoxia-induced pulmonary hypertension: converging

- evidence using 5-HT(1B)-receptor knockout mice and the 5-HT(1B/1D)-receptor antagonist GR127935. *Circ Res* 89, 1231-1239.
- Kereveur A, Callebort J, Humbert M, Herve P, Simonneau G, Launay JM & Drouet L (2000) High plasma serotonin levels in primary pulmonary hypertension. Effect of long-term epoprostenol (prostacyclin) therapy. *Arterioscler Thromb Vasc Biol* 20, 2233-2239.
- Ko EA, Han J, Jung ID & Park WS (2008) Physiological roles of K⁺ channels in vascular smooth muscle cells. *J Smooth Muscle Res* 44, 65-81.
- Launay JM, Herve P, Peoc'h K, Tournois C, Callebort J, Nebigil CG, Etienne N, Drouet L, Humbert M, Simonneau G & Maroteaux L (2002) Function of the serotonin 5-hydroxytryptamine 2B receptor in pulmonary hypertension. *Nat Med* 8, 1129-1135.
- Launay JM, Schneider B, Loric S, Da Prada M & Kellermann O (2006) Serotonin transport and serotonin transporter-mediated antidepressant recognition are controlled by 5-HT_{2B} receptor signaling in serotonergic neuronal cells. *Faseb J* 20, 1843-1854.
- Lawrie A, Spiekerkoetter E, Martinez EC, Ambartsumian N, Sheward WJ, MacLean MR, Harmar AJ, Schmidt AM, Lukanidin E & Rabinovitch M (2005) Interdependent serotonin transporter and receptor pathways regulate S100A4/Mts1, a gene associated with pulmonary vascular disease. *Circ Res* 97, 227-235.
- Lee SD, Shroyer KR, Markham NE, Cool CD, Voelkel NF & Tudor RM (1998) Monoclonal endothelial cell proliferation is present in primary but not secondary pulmonary hypertension. *J Clin Invest* 101, 927-934.
- Lee SL, Simon AR, Wang WW & Fanburg BL (2001) H₂O₂ signals 5-HT-induced ERK MAP kinase activation and mitogenesis of smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 281, L646-652.
- Lee SL, Wang WW & Fanburg BL (1997) Association of Tyr phosphorylation of GTPase-activating protein with mitogenic action of serotonin. *Am J Physiol* 272, C223-230.
- Li XQ, Wang HM, Yang CG, Zhang XH, Han DD & Wang HL Fluoxetine inhibited extracellular matrix of pulmonary artery and inflammation of lungs in monocrotaline-treated rats. *Acta Pharmacol Sin* 32, 217-222.
- Liu Y & Fanburg BL (2006) Serotonin-induced growth of pulmonary artery smooth muscle requires activation of phosphatidylinositol 3-kinase/serine-threonine protein kinase B/mammalian target of rapamycin/p70 ribosomal S6 kinase 1. *Am J Respir Cell Mol Biol* 34, 182-191.
- Liu Y, Li M, Warburton RR, Hill NS & Fanburg BL (2007) The 5-HT transporter transactivates the PDGFβ receptor in pulmonary artery smooth muscle cells. *Faseb J* 21, 2725-2734.
- Liu Y, Suzuki YJ, Day RM & Fanburg BL (2004) Rho kinase-induced nuclear translocation of ERK1/ERK2 in smooth muscle cell mitogenesis caused by serotonin. *Circ Res* 95, 579-586.

- Long L, MacLean MR, Jeffery TK, Morecroft I, Yang X, Rudarakanchana N, Southwood M, James V, Trembath RC & Morrell NW (2006) Serotonin increases susceptibility to pulmonary hypertension in BMPR2-deficient mice. *Circ Res* 98, 818-827.
- Loogen F, Worth H, Schwan G, Goeckenjan G, Losse B & Horstkotte D (1985) Long-term follow-up of pulmonary hypertension in patients with and without anorectic drug intake. *Cor Vasa* 27, 111-124.
- Macian F (2005) NFAT proteins: key regulators of T-cell development and function. *Nat Rev Immunol* 5, 472-484.
- MacLean MR, Deuchar GA, Hicks MN, Morecroft I, Shen S, Sheward J, Colston J, Loughlin L, Nilsen M, Dempsie Y & Harmar A (2004) Overexpression of the 5-hydroxytryptamine transporter gene: effect on pulmonary hemodynamics and hypoxia-induced pulmonary hypertension. *Circulation* 109, 2150-2155.
- Mandegar M, Fung YC, Huang W, Remillard CV, Rubin LJ & Yuan JX (2004) Cellular and molecular mechanisms of pulmonary vascular remodeling: role in the development of pulmonary hypertension. *Microvasc Res* 68, 75-103.
- Marcos E, Adnot S, Pham MH, Nosjean A, Raffestin B, Hamon M & Eddahibi S (2003) Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. *Am J Respir Crit Care Med* 168, 487-493.
- Marcos E, Fadel E, Sanchez O, Humbert M, Darteville P, Simonneau G, Hamon M, Adnot S & Eddahibi S (2004) Serotonin-induced smooth muscle hyperplasia in various forms of human pulmonary hypertension. *Circ Res* 94, 1263-1270.
- Marcos E, Fadel E, Sanchez O, Humbert M, Darteville P, Simonneau G, Hamon M, Adnot S & Eddahibi S (2005) Serotonin transporter and receptors in various forms of human pulmonary hypertension. *Chest* 128, 552S-553S.
- Mays DJ, Foose JM, Philipson LH & Tamkun MM (1995) Localization of the Kv1.5 K⁺ channel protein in explanted cardiac tissue. *J Clin Invest* 96, 282-292.
- McMurtry MS, Archer SL, Altieri DC, Bonnet S, Haromy A, Harry G, Bonnet S, Puttagunta L & Michelakis ED (2005) Gene therapy targeting survivin selectively induces pulmonary vascular apoptosis and reverses pulmonary arterial hypertension. *J Clin Invest* 115, 1479-1491.
- McMurtry MS, Bonnet S, Wu X, Dyck JR, Haromy A, Hashimoto K & Michelakis ED (2004) Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis. *Circ Res* 95, 830-840.
- Michelakis ED, Webster L & Mackey JR (2008) Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer. *Br J Cancer* 99, 989-994.
- Morecroft I, Heeley RP, Prentice HM, Kirk A & MacLean MR (1999) 5-hydroxytryptamine receptors mediating contraction in human small muscular pulmonary arteries: importance of the 5-HT1B receptor. *Br J Pharmacol* 128, 730-734.
- Morecroft I, Loughlin L, Nilsen M, Colston J, Dempsie Y, Sheward J, Harmar A & MacLean MR (2005) Functional interactions between 5-hydroxytryptamine receptors and the serotonin transporter in pulmonary arteries. *J Pharmacol Exp Ther* 313, 539-548.
- Morrell NW, Adnot S, Archer SL, Dupuis J, Jones PL, MacLean MR, McMurtry IF, Stenmark KR, Thistlethwaite PA, Weissmann N, Yuan JX & Weir EK (2009)

- Cellular and molecular basis of pulmonary arterial hypertension. *J Am Coll Cardiol* 54, S20-31.
- Olson TM, Alekseev AE, Liu XK, Park S, Zingman LV, Bienengraeber M, Sattiraju S, Ballew JD, Jahangir A & Terzic A (2006) Kv1.5 channelopathy due to KCNA5 loss-of-function mutation causes human atrial fibrillation. *Hum Mol Genet* 15, 2185-2191.
- Osipenko ON, Tate RJ & Gurney AM (2000) Potential role for kv3.1b channels as oxygen sensors. *Circ Res* 86, 534-540.
- Overturf KE, Russell SN, Carl A, Vogalis F, Hart PJ, Hume JR, Sanders KM & Horowitz B (1994) Cloning and characterization of a Kv1.5 delayed rectifier K⁺ channel from vascular and visceral smooth muscles. *Am J Physiol* 267, C1231-1238.
- Patel AJ, Lazdunski M & Honore E (1997) Kv2.1/Kv9.3, a novel ATP-dependent delayed-rectifier K⁺ channel in oxygen-sensitive pulmonary artery myocytes. *Embo J* 16, 6615-6625.
- Paulin R, Courboulin A, Meloche J, Mainguy V, Dumas de la Roque E, Saksouk N, Cote J, Provencher S, Sussman MA & Bonnet S Signal transducers and activators of transcription-3/pim1 axis plays a critical role in the pathogenesis of human pulmonary arterial hypertension. *Circulation* 123, 1205-1215.
- Post JM, Gelband CH & Hume JR (1995) [Ca²⁺]_i inhibition of K⁺ channels in canine pulmonary artery. Novel mechanism for hypoxia-induced membrane depolarization. *Circ Res* 77, 131-139.
- Pozeg ZI, Michelakis ED, McMurtry MS, Thebaud B, Wu XC, Dyck JR, Hashimoto K, Wang S, Moudgil R, Harry G, Sultanian R, Koshal A & Archer SL (2003) In vivo gene transfer of the O₂-sensitive potassium channel Kv1.5 reduces pulmonary hypertension and restores hypoxic pulmonary vasoconstriction in chronically hypoxic rats. *Circulation* 107, 2037-2044.
- Rabinovitch M (2008) Molecular pathogenesis of pulmonary arterial hypertension. *J Clin Invest* 118, 2372-2379.
- Reeve HL, Michelakis E, Nelson DP, Weir EK & Archer SL (2001) Alterations in a redox oxygen sensing mechanism in chronic hypoxia. *J Appl Physiol* 90, 2249-2256.
- Remillard CV, Tigno DD, Platoshyn O, Burg ED, Brevnova EE, Conger D, Nicholson A, Rana BK, Channick RN, Rubin LJ, O'Connor D T & Yuan JX (2007) Function of Kv1.5 channels and genetic variations of KCNA5 in patients with idiopathic pulmonary arterial hypertension. *Am J Physiol Cell Physiol* 292, C1837-1853.
- Ren W, Watts SW & Fanburg BL Serotonin transporter interacts with the PDGFβ receptor in PDGF-BB-induced signaling and mitogenesis in pulmonary artery smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 300, L486-497.
- Said SI (2008) The vasoactive intestinal peptide gene is a key modulator of pulmonary vascular remodeling and inflammation. *Ann N Y Acad Sci* 1144, 148-153.

- Sato K, Webb S, Tucker A, Rabinovitch M, O'Brien RF, McMurtry IF & Stelzner TJ (1992) Factors influencing the idiopathic development of pulmonary hypertension in the fawn hooded rat. *Am Rev Respir Dis* 145, 793-797.
- Souza R, Humbert M, Sztrymf B, Jais X, Yaici A, Le Pavec J, Parent F, Herve P, Soubrier F, Sitbon O & Simonneau G (2008) Pulmonary arterial hypertension associated with fenfluramine exposure: report of 109 cases. *Eur Respir J* 31, 343-348.
- Sullivan CC, Du L, Chu D, Cho AJ, Kido M, Wolf PL, Jamieson SW & Thistlethwaite PA (2003) Induction of pulmonary hypertension by an angiopoietin 1/TIE2/serotonin pathway. *Proc Natl Acad Sci U S A* 100, 12331-12336.
- Suzuki YJ, Day RM, Tan CC, Sandven TH, Liang Q, Molkentin JD & Fanburg BL (2003) Activation of GATA-4 by serotonin in pulmonary artery smooth muscle cells. *J Biol Chem* 278, 17525-17531.
- Walczak-Drzewiecka A, Ratajewski M, Wagner W & Dastyk J (2008) HIF-1 α is up-regulated in activated mast cells by a process that involves calcineurin and NFAT. *J Immunol* 181, 1665-1672.
- Wang Y, Han DD, Wang HM, Liu M, Zhang XH & Wang HL Downregulation of Osteopontin Is Associated with Fluoxetine Amelioration of Monocrotaline-Induced Pulmonary Inflammation and Vascular Remodelling. *Clin Exp Pharmacol Physiol*.
- Wang Z, Fermini B & Nattel S (1993) Sustained depolarization-induced outward current in human atrial myocytes. Evidence for a novel delayed rectifier K⁺ current similar to Kv1.5 cloned channel currents. *Circ Res* 73, 1061-1076.
- Weir EK, Reeve HL, Huang JM, Michelakis E, Nelson DP, Hampl V & Archer SL (1996) Anorexic agents aminorex, fenfluramine, and dexfenfluramine inhibit potassium current in rat pulmonary vascular smooth muscle and cause pulmonary vasoconstriction. *Circulation* 94, 2216-2220.
- Young KA, Ivester C, West J, Carr M & Rodman DM (2006) BMP signaling controls PASM KC channel expression in vitro and in vivo. *Am J Physiol Lung Cell Mol Physiol* 290, L841-848.
- Yu Y, Platoshyn O, Zhang J, Krick S, Zhao Y, Rubin LJ, Rothman A & Yuan JX (2001) c-Jun decreases voltage-gated K⁺ channel activity in pulmonary artery smooth muscle cells. *Circulation* 104, 1557-1563.
- Yuan JX, Aldinger AM, Juhaszova M, Wang J, Conte JV, Jr., Gaine SP, Orens JB & Rubin LJ (1998a) Dysfunctional voltage-gated K⁺ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. *Circulation* 98, 1400-1406.
- Yuan XJ (1995) Voltage-gated K⁺ currents regulate resting membrane potential and [Ca²⁺]_i in pulmonary arterial myocytes. *Circ Res* 77, 370-378.
- Yuan XJ, Wang J, Juhaszova M, Gaine SP & Rubin LJ (1998b) Attenuated K⁺ channel gene transcription in primary pulmonary hypertension. *Lancet* 351, 726-727.
- Zhai FG, Zhang XH & Wang HL (2009) Fluoxetine protects against monocrotaline-induced pulmonary arterial hypertension: potential roles of induction of apoptosis and upregulation of Kv1.5 channels in rats. *Clin Exp Pharmacol Physiol* 36, 850-856.

Zhu SP, Mao ZF, Huang J & Wang JY (2009) Continuous fluoxetine administration prevents recurrence of pulmonary arterial hypertension and prolongs survival in rats. *Clin Exp Pharmacol Physiol* 36, e1-5.

IntechOpen

IntechOpen

Pulmonary Hypertension - From Bench Research to Clinical Challenges

Edited by Dr. Roxana Sulica

ISBN 978-953-307-835-9

Hard cover, 326 pages

Publisher InTech

Published online 09, December, 2011

Published in print edition December, 2011

The textbook "Pulmonary Hypertension - From Bench Research to Clinical Challenges" addresses the following topics: structure and function of the normal pulmonary vasculature; disregulated cellular pathways seen in experimental and human pulmonary hypertension; clinical aspects of pulmonary hypertension in general; presentation of several specific forms of pulmonary hypertension, and management of pulmonary hypertension in special circumstances. The textbook is unique in that it combines pulmonary and cardiac physiology and pathophysiology with clinical aspects of the disease. First two sections are reserved for the basic knowledge and the recent discoveries related to structure and cellular function of the pulmonary vasculature. The chapters also describe disregulated pathways known to be affected in pulmonary hypertension. A special section deals with the effects of hypoxia on the pulmonary vasculature and the myocardium. Other three sections introduce the methods of evaluating pulmonary hypertension to the reader. The chapters present several forms of pulmonary hypertension which are particularly challenging in clinical practice (such as pulmonary arterial hypertension associated with systemic sclerosis), and lastly, they address special considerations regarding management of pulmonary hypertension in certain clinical scenarios such as pulmonary hypertension in the critically ill.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Christophe Guignabert (2011). Interplay Between Serotonin Transporter Signaling and Voltage-Gated Potassium Channel (Kv) 1.5 Expression, Pulmonary Hypertension - From Bench Research to Clinical Challenges, Dr. Roxana Sulica (Ed.), ISBN: 978-953-307-835-9, InTech, Available from: <http://www.intechopen.com/books/pulmonary-hypertension-from-bench-research-to-clinical-challenges/interplay-between-serotonin-transporter-signaling-and-voltage-gated-potassium-channel-kv-1-5-express>

INTeCH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820

www.intechopen.com

Fax: +385 (51) 686 166
www.intechopen.com

Fax: +86-21-62489821

IntechOpen

IntechOpen

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen