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

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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, serotoninergic 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).
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 (Ca2+) channels, Ca2+ influx, and intracellular Ca2+ levels. The increase in cytoplasmic free Ca2+ 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, IKur (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-1α (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 µm.
A recent study has provided the first evidence that 5-HT, via 5-HTT, decreases Kv1.5 expression by inhibiting nuclear NFATc2 translocation \textit{in vitro} & \textit{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) \textit{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.](image)

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, Ca\textsuperscript{2+}/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 \textit{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 \textsuperscript{3}H-thymidine incorporation that dichloroacetate (5 x 10\textsuperscript{-4} M), 11R-VIVIT (4 x 10\textsuperscript{-6} M), cycloporine A (10\textsuperscript{-6} M) and fluoxetine (10\textsuperscript{-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\textsuperscript{-6} M). All these \textit{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.
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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 \times 10^{-4} 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); 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).
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-1α 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 (Kvß2) 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-1α has been reported in the PA-SMCs of patients with idiopathic PAH and in those from fawn-hooded rats. Inhibition of HIF-1α 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-1α promoter at position 728 bp suggests that NFAT and HIF-1α, 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 (PPARγ), Pim1, vasoactive intestinal peptide (VIP) and miR-204 (Courboulin et al., 2008; Paulin et al., 2008; 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.

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7. References

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