Serotonin (5-hydroxytryptamine (5-HT)) is a mitogen of pulmonary artery smooth muscle cells (PASMC) and plays an important role in the development of pulmonary hypertension. Signal transduction initiated by 5-HT involves serotonin transporter-dependent generation of reactive oxygen species and activation of the MEK-ERK pathway. However, the downstream transcriptional regulatory components have not been identified. In systemic smooth muscle cells, GATA-6 has been shown to regulate mitogenesis by driving cells into a quiescent state, and the down-regulation of GATA-6 induces mitogenesis. Thus, the present study tested the hypothesis that 5-HT induces mitogenesis of PASMC by down-regulating GATA-6. Quiescent bovine PASMC were treated with 5-HT, and the binding activity of nuclear extracts toward GATA DNA sequence was monitored. Surprisingly, PASMC express GATA-4, and 5-HT up-regulates the GATA DNA binding activity. Pretreatment of cells with inhibitors of serotonin transporter, reactive oxygen species, and MEK blocks GATA-4 activation by 5-HT. GATA-4 is not activated when the ERK phosphorylation site is mutated, indicating that 5-HT phosphorylates GATA-4 via the MEK/ERK pathway. GATA up-regulation is also induced by other mitogens of PASMC such as endothelin-1 and platelet-derived growth factor. Dominant negative mutants of GATA-4 suppress cyclin D2 expression and cell growth, indicating that GATA-4 activation regulates PASMC proliferation. Thus, GATA-4 mediates 5-HT-induced growth of PASMC and may be an important therapeutic target for the prevention of pulmonary hypertension.

Exposure to chronic hypoxia leads to the development of pulmonary hypertension through persistent vasoconstriction

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Yuichiro J. Suzuki‡§§, Regina M. Day‡», Chia Chi Tan‡§, Tor H. Sandven‡, Qiangrong Liang**, Jeffery D. Molkentin***, and Barry L. Fanburg‡

From the ‡Pulmonary, Critical Care, and Sleep Division, Tufts-New England Medical Center, Tupper Research Institute, Department of Medicine and §Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts 02111 and the **Department of Pediatrics, Children’s Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio 45229

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The abbreviations used are: 5-HT, 5-hydroxytryptamine; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; ERK, extracellular signal-regulated kinase; SERT, serotonin transporter; PASMC, pulmonary artery smooth muscle cells; ROS, reactive oxygen species; ET-1, endothelin-1; PDGF, platelet-derived growth factor; EMSA, Electrophoretic mobility shift assay.
as superoxide (16) and H$_2$O$_2$ (17), presumably via the activation of NADPH oxidase. These signaling events appear to activate the MEK-ERK pathway as PD98059 blocked the 5-HT-induced PASMC growth (18). However, downstream signaling components, which are activated by ERK for the 5-HT-mediated induction of cell growth, have not yet been identified.

The GATA family of transcription factors includes six genes with a highly conserved zinc finger DNA binding domain that interacts with DNA regulatory elements containing consensus (A/T)GATA(A/G) sequences. The GATA-1/2/3 genes are essential for hematopoietic cell development (19), whereas the GATA-4/GATA-5/GATA-6 genes are involved in cell differentiation and endoderm-derived tissues (20). In aortic smooth muscle cells, GATA-6 has been shown to play a role in maintaining cells in a quiescent state, and mitogens down-regulate GATA-6 to induce proliferation of cells (21). The mechanism appears to involve p21(Cip1), because the adenovirus-mediated overexpression of GATA-6 was found to inhibit cellular entry into S-phase by inducing this cyclin-dependent kinase inhibitor (22). Furthermore, reversal of GATA-6 down-regulation in rats inhibited intimal hyperplasia in the balloon-injured carotid artery (23).

The present study, therefore, tested the hypothesis that 5-HT may down-regulate GATA-6 in PASMC. Surprisingly, however, our results show that PASMC express GATA-4 that is activated by 5-HT and enhances PASMC growth.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Reagents**—Bovine PASMC were isolated and cultured in RPMI 1640 medium containing 10% fetal bovine serum, 1% penicillin/streptomycin, and 0.5% amphotericin B as previously described (1). Cells (passages 0–6) were grown-arrested for 72 h in medium containing 0.1% fetal bovine serum and treated with 5-HT (Sigma-Aldrich). In some experiments, cells were treated with imipramine, N-acetylcytistene, H$_2$O$_2$, endothelin-1 (ET-1), or PDGF purchased from Sigma-Aldrich. Ebselen was a kind gift from Dr. Helmut Sies (University of Dusseldorf). RPMI 1640 medium, penicillin/streptomycin, and amphotericin B were purchased from Invitrogen.

**Adenoassociated Infection**—The adenoassociated virus was implemented by adding the gene-carrying replication-deficient adenovirus to cells grown in 6-well plates. Cells were incubated with adenovirus in 0.75 ml of 0.1% fetal bovine serum-containing RPMI medium for 72 h. Adenovirus constructs expressing wild-type mouse GATA-4, dominant negative GATA-4, and adenovirus expressing wild-type mouse GATA-4, dominant negative MEK1 have been previously described (24, 25). The adenovirus-directed gene transfer was mediated overexpression of GATA-6 was found to inhibit cellular overexpression of GATA-6 was found to inhibit cellular

**RESULTS**

**5-HT Activates GATA DNA Binding Activity**—To test the hypothesis that 5-HT may down-regulate GATA-6 activity, nuclear extracts from 5-HT-treated PASMC were subjected to EMSA using 32P-labeled oligonucleotide probe containing the consensus GATA sequence. Surprisingly, 5-HT was found to enhance GATA DNA binding activity (Fig. 1A). The activation of GATA DNA binding activity by 5-HT was observed as early as 3 h and was sustained for at least 20 h. The densitometry analysis revealed that treatment of cells with 5-HT (1 μM) for 20 h caused a 5-fold increase in GATA DNA binding activity. Experiments using cold competitor oligonucleotides containing wild-type and mutated GATA elements showed that the GATA-4-regulated GATA proteins specifically interacted with the consensus GATA sequence (Fig. 1B). Fig. 1C shows that this 5-HT-induced GATA activation is blocked by pretreating cells with imipramine, an inhibitor of SERT (14). Imipramine alone did not alter the GATA DNA binding activity (data not shown).

**Identification of GATA Transcription Factors Expressed in PASMC**—To determine the identity of the GATA-binding protein(s) in PASMC, supershift experiments were performed using antibodies against GATA-4, -5, and -6. As shown in Fig. 2A, the antibody against GATA-4 reduced the intensity of the GATA-binding complex and caused a supershift as shown by the arrow, indicating that GATA-4 is expressed in PASMC. Surprisingly, the third and fourth lanes of Fig. 2A show that two distinct GATA-4 antibodies from goat (C-20) and rabbit (H-112) affected the GATA binding complex. The C-20 antibody caused a supershift of the GATA band, indicating that the antibody interacted with the DNA-GATA-4 complex, resulting in a band with reduced mobility. Although the H-112 antibody did not cause a supershift, it reduced the intensity of the GATA band, indicating that the antibody interacted with the GATA-4 molecule but also interfered with the DNA-protein interactions. On the other hand, the effect of the GATA-5 antibody was minimal. These results indicate that GATA-4 and -6 contribute to the formation of the GATA-binding protein complex. To confirm that GATA-4 is expressed in PASMC, nuclear extracts were immunoprecipitated with rabbit anti-GATA-4 IgG (H-112) and blotted with goat anti-GATA-4 IgG (C-20) in Western blot experiments. As shown in Fig. 2B, a band was detected at ~50 kDa, the same position as the control GATA-4 protein from adenosynically overexpressing cells. This band was not observed when the samples were

**Activation of GATA-4 by Serotonin**

**Electrophoretic Mobility Shift Assays (EMSA)**—Cells were washed in phosphate-buffered saline and solubilized with 50 mM Hepes solution (pH 7.4) containing 1% (v/v) Triton X-100, 4 mM EDTA, 1 mM sodium fluoride, 0.1 mM sodium orthovanadate, 1 mM tetrasodium pyrophosphate, 2 mM phenylmethanesulfonyl fluoride, 10 μg/ml leupeptin, and 10 μg/ml aprotinin. Cell lysates (10 μg of protein) were electrophoresed through a reducing SDS-polyacrylamide gel and electroblotted onto a membrane. The membrane was blocked and incubated with polyclonal IgG for phospho-specific MEK1/2 (Cell Signaling Technology, Beverly, MA). Anti-MEK1/2, cyclin D2, or GATA-4 (Santa Cruz Biotechnology). The levels of bands and phospho-proteins were detected with horseradish peroxide-linked secondary antibodies and the ECL System (Amersham Biosciences).

Immunoprecipitation experiments were performed by incubating nuclear extracts with 1 μg of rabbit anti-GATA-4 or GATA-6 IgG and 10 μl of GammaBind G-Sepharose (Amersham Biosciences) overnight at 4 °C while gently shaking. After washing twice, the pellet was boiled in Laemmli buffer and centrifuged, and the supernatant was electrophoresed. A Western blot was performed using goat anti-GATA-4 or GATA-6 IgG.

**Statistical Analysis**—Means ± S.E. were calculated and statistically significant differences between two groups were determined by the Student’s t test at p < 0.05.
Nuclear extracts were isolated, and the GATA DNA binding activity value at \( p \) asterisk GATA band determined by densitometry in arbitrary units (a.u.). The bar graph prepared, and the GATA DNA binding activity was monitored by \( 5\text{-HT} \). As shown in the immunoprecipitation using rabbit anti-GATA-4 and GATA-6 the nuclear extracts of cells with or without 5-HT treatment via (i) increased synthesis of GATA factors or (ii) post-translational modifications. To determine whether the gene transcription of GATA factors may be enhanced in response to 5-HT, 5-HT-induced GATA activation could be via (i) increased synthesis of GATA factors or (ii) post-translational modifications. To determine whether the gene transcription of GATA factors may be enhanced in response to 5-HT, protein expressions of GATA-4 and GATA-6 were determined. GATA-4- and GATA-6-enriched samples were prepared from the nuclear extracts of cells with or without 5-HT treatment via immunoprecipitation using rabbit anti-GATA-4 and GATA-6 IgG. As shown in the top panel of Fig. 4A, samples from 5-HT-treated cells exhibited higher GATA DNA binding activity. However, Western blotting of these samples with goat anti-GATA-4 or GATA-6 IgG showed that 5-HT did not increase the expression of GATA-4 or GATA-6 (Fig. 4A). Furthermore, in cells pretreated with 15 \( \mu \text{g} \)/ml actinomycin D (a general inhibitor of gene transcription), 5-HT still enhanced the GATA DNA binding activity (data not shown). 5-HT also enhanced the activity of exogenously expressed GATA-4 via adenosine-mediated gene transfer (Fig. 4B). The 5-HT-induced activation of exogenous GATA-4 was detectable as early as 10 min. In contrast, the activity of exogenously expressed GATA-6 was not enhanced by 5-HT (Fig. 4B, lower panel). These results suggest that 5-HT exerts post-translational modifications of GATA-4 to enhance its activity.

Because 5-HT-induced mitogenesis has been shown to be blocked by PD98059 (18) and GATA-4 can be phosphorylated via the MEK-ERK pathway in cardiac muscle cells (25, 27, 28), 5-HT may activate GATA-4 through ERK-dependent phosphorylation. Thus, the role of the MEK-ERK pathway in the 5-HT-induced GATA-4 activation was tested. As shown in Fig. 4C, 5-HT caused the activation of MEK as determined using a phospho-specific antibody. The 5-HT-induced GATA activation was blocked by pretreatment of cells with PD98059 (a MEK inhibitor) (Fig. 4D) or with a dominant negative mutant of MEK (Fig. 4E), suggesting that the signaling is dependent on MEK and perhaps ERK. PD98059 (data not shown) and adenosine expressing a dominant negative mutant MEK (Fig. 4E) by themselves did not alter the GATA DNA binding activity.

To determine the role of ERK-dependent phosphorylation in the 5-HT-induced GATA-4 activation, cells were infected with adenovirus expressing mutant mouse GATA-4 in which serine 105 is replaced with alanine (S105A). This serine is the preferential ERK phosphorylation site and has been shown to play a major role in the phosphorylation and activation of GATA-4 in cardiac myocytes (25). The EMSA results showed that, although 5-HT enhanced the DNA binding activity of wild-type GATA-4, the S105A mutant of GATA-4 was not activated (Fig. 4F). Thus, the MEK/ERK-dependent phosphorylation of the
serine 105 residue of GATA-4 appears to be involved in the 5-HT-induced GATA-4 activation in PASMC.

Role of GATA-4 in PASMC Growth—To characterize the

Fig. 3. Role of reactive oxygen species in 5-HT signaling for GATA activation. A, PASMC were pretreated with N-acetylcysteine (1 mM) or ebselen (20 μM) and then treated with 5-HT (1 μM) for 20 h. Nuclear extracts were isolated, and the GATA DNA binding activity was monitored. B, PASMC were treated with hydrogen peroxide (H₂O₂) for 20 h. Nuclear extracts were isolated, and the GATA DNA binding activity was monitored.

Fig. 4. Role of MEK/ERK-dependent phosphorylation in the mechanism of 5-HT signaling for GATA activation. A, nuclear extracts from PASMC with or without treatment with 5-HT (1 μM) for 20 h were immunoprecipitated with rabbit anti-GATA-4 or GATA-6 IgG. Samples were subjected to EMSA to monitor GATA DNA binding activity. Samples were boiled, loaded on a 10% SDS-PAGE gel, and blotted with goat anti-GATA-4 or GATA-6 IgG in Western blot (WB) experiments. The bar graphs indicate means ± S.E. of the intensities of GATA-4 and GATA-6 bands in Western blot gels as determined by densitometry (n = 4), a.u., arbitrary units. B, PASMC were infected with adenovirus expressing GATA-4 (AdGATA4) or GATA-6 (AdGATA6) and treated with 5-HT for 10 min. Nuclear extracts were isolated, and the GATA DNA binding activity was monitored by EMSA, and protein expression levels were determined by Western blot. C, PASMC were treated with 5-HT (1 μM) for 5 min. Cell lysates were prepared, and the activation of MEK was monitored by Western blot using phospho-specific MEK antibody. D, PASMC were pretreated with PD98059 (PD, 30 μM) and then treated with 5-HT for 20 h. Nuclear extracts were isolated, and the GATA DNA binding activity was monitored. E, PASMC were infected with 50 plaque-forming units of adenovirus expressing dominant negative MEK1 (AdDN-MEK) or control adenovirus (AdCont) and then treated with 5-HT for 20 h. Nuclear extracts were isolated, and the GATA DNA binding activity was monitored. F, PASMC were infected with wild type GATA-4 (WT) or mutant GATA-4 with serine 105 substituted with alanine (S105A) for 48 h and then treated with 5-HT (1 μM) for 10 min. Nuclear extracts were prepared, GATA DNA binding activity was monitored by EMSA, and GATA-4 expression was determined by Western blot (WB). The bar graph indicates means ± S.E. of fold-increase in GATA DNA binding activity in response to 5-HT treatment as determined by densitometry. The asterisk denotes significant difference at p < 0.05 (n = 3).
functions of 5-HT-induced activation of GATA-4 in PASMC, the potential role in cell mitogenesis was addressed. We first asked whether other mitogens of PASMC also activate GATA-4. An important mitogen of PASMC and a mediator of pulmonary hypertension, ET-1, was found to activate the GATA DNA binding activity. As shown in Fig. 5A, the EMSA show that the nuclear binding activity toward the GATA sequence was enhanced by ET-1. The densitometric analysis revealed that a 20-h treatment with 30 nM ET-1 caused a 5-fold increase in the GATA activity.

Treatment of PASMC with PDGF also induced a 4-fold increase in the GATA DNA binding activity (Fig. 5B). Furthermore, PDGF plus 5-HT exerted synergistic enhancement (11-fold) of GATA DNA binding activity (Fig. 5B), consistent with the synergistic ability of these agents to induce PASMC proliferation (1).

To determine the role of GATA-4 in mitogenesis of PASMC, we studied the regulation of cyclin D2 expression because the promoter region of cyclin D2 gene contains GATA elements (29, 30). In PASMC, both 5-HT and ET-1 enhanced the protein expression of cyclin D2, suggesting that this cell cycle regulator may play a role in the PASMC mitogenesis (Fig. 6A). Further-

![Image](https://example.com/image.jpg)
more, forced expression of GATA-4 caused an increase in cyclin D2 expression (Fig. 6B), suggesting that gene regulation of this protein may be GATA-4-dependent. An increase in cyclin D2 expression alone, however, is not sufficient to elicit mitogenesis because forced expression of GATA-4 did not significantly increase the cell number (data not shown). To directly test the role of GATA-4 in 5-HT-induced PASMC growth, cells were infected with adenovirus expressing GATA-4-engrailed fusion protein (AdG4-Engr) with dominant negative GATA-4 activity (24). After 48 h of infection, the expression of the dominant negative mutant of GATA-4 alone caused a reduction of the cell number (Fig. 6C). Because this effect could be due to suppressed cell growth or increased cell death, the effects of the dominant negative GATA-4 on cyclin D2 expression was tested. The results show that the expression of the dominant negative mutant GATA-4 alone down-regulated the expression of cyclin D2 without influencing ERK expression (Fig. 6D). Furthermore, 5-HT did not enhance the cyclin D2 expression in dominant negative GATA-4-expressing cells (Fig. 6E). These results suggest that GATA-4 regulates the expression of cyclin D2, and suppression of this transcription factor affects the growth of PASMC.

To further explore the role of ERK-dependent phosphorylation of GATA-4 in PASMC growth, adenovirus expressing mutant GATA-4 with serine 105 replaced with alanine (S105A) was used. We found that this mutant also suppressed the constitutive cell number (Fig. 6F) as well as cyclin D2 expression (Fig. 6G). These results suggest that the S105A GATA-4 mutant may serve as a dominant negative mutant and that the phosphorylation of this site within the GATA-4 molecule plays a role for cell growth and/or survival.

**DISCUSSION**

5-HT plays an important role in the development of pulmonary hypertension, in part due to its ability to induce PASMC growth (1). The 5-HT signaling has been identified to involve 5-HT transport through SERT, tyrosine phosphorylation of GTPase-activating protein, which may in turn activate Ras-NADPH oxidase and result in production of ROS and the activation of MEK and ERK (14–18). There is little known about transcription factor activation by 5-HT. In skeletal muscle myoblasts, 5-HT has been shown to activate 5-HT2A receptor to stimulate the Jak-STAT pathway (signal transducers and activators of transcription) pathway (31), and 5-HT-dependent collagenase transcription in myometrial cells requires an AP-1 site (32). Similarly, 5-HT-inducible interleukin-1 transcription in uterine smooth muscle utilizes an AP-1 site (33). In the present study, we considered the mechanism identified by Walsh and coworkers for aortic smooth muscle cell proliferation, which involves the down-regulation of GATA-6 (21, 22). Thus, we initially hypothesized that 5-HT down-regulates GATA-6 in PASMC. Surprisingly, we found that 5-HT increased the GATA DNA binding activity in PASMC and that these cells also express GATA-4 transcription factor that is regulated by 5-HT signal transduction. Thus, GATA factors may respond differentially in systemic and pulmonary smooth muscle cell regulation.

Important GATA-binding sites have been identified in multiple cardiac-specific transcriptional regulatory regions, and overexpression of GATA-4 has been shown to transactivate these elements. A number of proteins that have been shown to be up-regulated during cardiac hypertrophy such as angiotensin II type 1a receptor, α-myosin heavy chain, β-myosin heavy chain, myosin light chains, atrial natriuretic factor, and brain natriuretic factor contain GATA regulatory sites in their promoters (20). Thus, GATA-4 has been postulated to regulate cardiac muscle cell hypertrophy. GATA-4 can be activated by a signal transduction pathway involving calcineurin and NFAT3 (34). More recently, GATA-4 has shown also to be phosphorylated via the MEK/ERK pathway in response to ET-1 (27) or phenylephrine (28) in cardiac myocytes. Serine 105, the preferential ERK phosphorylation site, was identified to be phosphorylated in response to phenylephrine (25). Consistent with these findings, 5-HT-mediated activation of GATA-4 in PASMC requires MEK/ERK-dependent phosphorylation of serine 105 because MEK inhibitors blocked 5-HT-induced GATA activation, and the substitution of the ERK phosphorylation site serine 105 with alanine abolished the activation. This novel regulation for GATA-4 in PASMC, however, does not necessarily preclude a role of GATA-6 in mitogenesis as described in other vascular beds (21).

Functional roles of GATA-4 activation by 5-HT may include the regulation of PASMC proliferation. GATA elements have been found in promoter regions of cell growth-regulating proteins such as cyclin D2 (30) and cyclin D3 (35). Tanaka et al. (36) report that GATA-1 induced the sustained expression of cyclin D1 in a murine myeloid cell line M1. GATA-1 has also been shown to regulate the proliferation of definitive erythroid and megakaryocytic cells (37). Tsiad and Orkin (38) report that GATA-2 is required for the proliferation of hematopoietic cells. Results from the present study showing that the specific suppression of GATA-4 activity by a dominant negative mutant decreased the cell number and down-regulated the expression of cyclin D2 indicate that GATA-4 regulates mitogenesis of PASMC. Furthermore, other mitogens of PASMC such as ET-1 and PDGF also activate GATA DNA binding activity, suggesting that GATA-4 may be a universal mediator of PASMC proliferation.

Another possible role of GATA-4 activation is to regulate cell apoptosis and survival. In cardiac myocytes, GATA-4 was recently identified as a cell survival factor, and down-regulation of this transcription factor resulted in the induction of apoptosis (39, 40). Consistently, we found that 5-HT inhibited apoptosis of PASMC (41).

In summary, the present study demonstrates that PASMC express GATA-4 that is activated by 5-HT. From the data we have obtained, the 5-HT signal transduction for GATA-4 activation appears to involve the SERT, ROS, MEK/ERK pathway and the phosphorylation of serine 105, the preferential ERK phosphorylation site within the GATA-4 molecule (Fig. 7). Furthermore, adenovirus-mediated gene transfer of dominant neg-
ative GATA-4 mutants indicates that GATA-4 regulates the expression of cyclin D2 and PASMC growth. These results suggest that GATA-4 may play a role in 5-HT-induced PASMC growth and that this cascade of events may participate in the development of pulmonary hypertension. Thus, therapeutic strategies targeting GATA-4 may be useful against pulmonary hypertension.

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