Platelet-derived growth factor (PDGF) and PDGF receptors in rat corpus cavernosum: changes in expression after transient in vivo hypoxia

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Abstract

Platelet-derived growth factor (PDGF) overactivity has been implicated in atherosclerosis and several fibrotic conditions including lung and kidney fibrosis, liver cirrhosis and myelofibrosis. Low oxygen tension (hypoxia) is a known stimulus for transcriptional induction of PDGF ligand and receptor genes in different tissues. We studied the expression and localization of PDGF-A, PDGF-B, and PDGF receptor (PDGFR)-α and -β subunits in adult rat isolated corpus cavernosum (CC) under generalized transient hypoxia (pO₂ 10%) in comparison with normoxic conditions. Semi-quantitative RT-PCR analysis of mRNA extracted from rat penis showed higher amounts of PDGF-A, PDGF-B and PDGFR-β mRNA transcripts in hypoxic versus normoxic animals. The immunohistochemical analysis showed that the localization of PDGF subunits and PDGFR-β was confined to the cytoplasm of the perivascular smooth muscle cells, endothelium and trabecular fibroblasts. Our findings indicate that transient low oxygen tension induces PDGF overexpression in rat CC, which in the long term may lead to an increase of connective tissue production. We suggest that a local impairment of the PDGF/PDGFR system may contribute to CC fibrosis, which is an established cause of erectile dysfunction in man.


Introduction

Platelet-derived growth factor (PDGF) is a major mitogen for cells of mesenchymal origin, such as fibroblasts and smooth muscle cells. PDGF is widely expressed in normal and transformed cells and is produced by monocytes and macrophages, vascular endothelial and smooth muscle cells (Antoniades 1991, Heldin 1992). There are three PDGF isoforms (AA, AB and BB) that exert their biological actions via binding to cell surface receptors (α and β) that belong to the protein tyrosine-kinase family of receptors (Williams 1989). PDGF-mediated events, which include chemotaxis, activation of inflammatory cells, vasoconstriction and influence on the synthesis or degradation of matrix constituents (Heldin 1992), are most likely exerted locally in an autocrine or paracrine manner and are involved in natural as well as pathological processes, such as neoplasia, atherosclerosis and fibrosis (Heldin 1992, Gnessi et al. 1993). Recently, immunohistochemical and electron microscopy studies showed that PDGF is highly expressed in penile tunica albuginea obtained from patients with veno-occlusive dysfunction and Peyronie’s disease (Gentile et al. 1996), suggesting that it could be involved in the pathogenesis of these two conditions that are frequently associated with erectile dysfunction (ED) in men.

In vivo, the reduction in the environmental oxygen tension to which cells are exposed leads to physiological and, eventually, pathological consequences associated with differential expression of specific genes which encode for cytokines and growth factors thought to play key roles in the regulation of synthesis and assembly of connective tissue proteins (Gerritsen & Bloor 1993, Bunn & Poyton 1996). For example, in rat corpus cavernosum smooth muscle cells in culture hypoxia stimulates the expression of transforming growth factor β₁ (TGF-β₁), a pleiotropic cytokine that is known to induce extracellular matrix expression and inhibit growth and proliferation of vascular smooth muscle cells (Faller 1999). Indeed, in human corpus cavernosum smooth muscle cells, TGF-β₁ is a
mitogen and induces a two- to fourfold increase in collagen synthesis (Moreland et al. 1995); also, it has been found to be overexpressed in tunica albuginea from men suffering veno-occlusive dysfunction (Nehra et al. 1996) and in plaques obtained from Peyronie’s disease (El-Sakka et al. 1997).

In this study, we compared for the first time the expression of PDGF subunits and PDGF receptor mRNAs in corpora cavernosa (CC) isolated from adult rats both in normal conditions and after acute hypoxia (pO₂ = 10 mmHg). The immunohistochemical localization of PDGF-A, PDGF-B and PDGF receptor (PDGFR)-α and -β subunits was also evaluated in comparison with that of the TGF-β₁.

Materials and Methods

Hypoxic exposure and CC preparation

Male Sprague–Dawley rats (55–60 days) purchased from Charles River Italia (Calco, Italy), were continuously gassed for 6 h with a mixture of 10% O₂ and 90% N₂ (ten rats) or normal air (ten rats) in a 70 l gas-tight box (Bucher et al. 1996); animals were conscious and had free access to food and water. At the end of the procedure decapitation was performed, blood was collected from the left ventricle for pO₂, sO₂ and pCO₂ determination by hemogasanalysis (Franchini et al. 1994), and CC were rapidly prepared according to Broderick et al. (1994) with minor modifications. Briefly, rat penises were surgically removed and the corpus spongiosum and the urethra were excised. The CC tissues were carefully dissected free from the surrounding tunica albuginea and made available for RT-PCR and immunohistochemical studies. The Animal Care Committee of the University of Rome Medical School approved this protocol.

RNA extraction and RT-PCR analysis

Tissues mRNA were extracted by using a commercial kit (Micro–Fast–Track Kit, Invitrogen, San Diego, CA, USA). Reverse transcription was performed using an annealing temperature of 70 °C in a final volume of 25 µl containing 250 mM Tris–HCl, 375 mM KCl, 15 mM MgCl₂, 50 mM dithiothreitol (DTT), 0.5 mM dNTPs, 0.5 µg random hexamer oligonucleotide, 200 U M-MLV-RT, 26 U ribonuclease inhibitor (Promega, Madison, WI, USA). β-actin was used as a constitutively expressed gene product for comparison of PDGFs and PDGFRs mRNA abundance between samples. A 0.5 µl volume of the RT products was amplified with 2.5 units of Taq DNA polymerase (Promega) and 20 µM specific rat β-actin primer (Table 1) in 50 µl of reaction mixture containing 500 mM KCl, 200 mM Tris–HCl, and 1.5 mM MgCl₂ as follows: 94 °C, 1 min; 58 °C, 1 min; 72 °C, 1 min. To ensure amplification in the exponential phase of PCR, reactions were temporarily halted at 20, 25, 30, 35 and 40 cycles, and 10 µl of PCR products were removed from each tube (see Fig. 1). All products were analyzed by 1% agarose gel electrophoresis and 30 cycles were chosen for further analysis. Quantitation of the signals was performed by densitometric analysis, using densitometry computer software (Kodak Digital Science ID Image Analysis Software, Eastman Kodak Company, Rochester, NY, USA). Dilution of RT products was made where necessary and the amplification procedure was repeated until all samples were standardized for β-actin content. After standardization, PCR was performed using appropriately diluted RT products in 50 µl of the reaction mix by utilizing 20 µM of each rat PDGFs and PDGFRs primers (Table 1). For each gene examined, all primers were derived from separate exons and spanned at least one intron of genomic sequence, thus excluding the possibility of genomic DNA contamination. No PCR product was obtained with any of the set of primers in the absence of cDNA template (negative control) (Caprio et al. 1999). Thermocycling conditions were: initial denaturation for 3 min at 94 °C, 30 cycles of amplification (since levels of PCR products increased in a linear fashion for up to 35 cycles for PDGFs and PDGFRs, Fig. 1) with 1 min of denaturation at 94 °C, different annealing temperature for each pair of primers (Table 1), 1 min extension at 72 °C, followed by a final elongation of 5 min at 72 °C.

Immunohistochemistry and light microscopy

After decapitation, the skin overlying the penis was incised, and the whole penis body, including the CC crura and the bulbospongiosum covered by the ischiocavernous and bulbospongiosus skeletal muscles, was excised in one piece, fixed in Bouin's solution for 12 h, and prepared for immunostaining (Gnassi et al. 1993, 2000). Immunostaining was carried out by incubating tissue sections (3 µm) with TGF-β₁, PDGFs and PDGFRs antisera (1:100) overnight at 4 °C (Gnassi et al. 1993, Caprio

Table 1 Primers utilized in PCR reactions

<table>
<thead>
<tr>
<th>Substance</th>
<th>5’-3’ sequence</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF-A₁</td>
<td>CCGTGGCCATCCGGACGAGAAGAGA</td>
<td>215–239</td>
</tr>
<tr>
<td>PDGF-A₂</td>
<td>CGATCCGGACTCTTGAGATGATC</td>
<td>1203–1223</td>
</tr>
<tr>
<td>PDGF-B₁</td>
<td>GCATCAGACTCTGATCAGGGCA</td>
<td>1617–1637</td>
</tr>
<tr>
<td>PDGF-B₂</td>
<td>ATCGACTCCAGTTGGAAGTTC</td>
<td>1881–1902</td>
</tr>
<tr>
<td>PDGF-α₂</td>
<td>TGACATCCACTICACAGGCA</td>
<td>2704–2724</td>
</tr>
<tr>
<td>PDGF-β₁</td>
<td>CAGACTTGCCGACAGCTTGT</td>
<td>28–49</td>
</tr>
<tr>
<td>PDGF-β₂</td>
<td>AGGGGACTCCTCAAGAGGTTAA</td>
<td>684–704</td>
</tr>
<tr>
<td>β-actin 1</td>
<td>ATTGGAATGACCGGTCTCCG</td>
<td>2413–2437</td>
</tr>
<tr>
<td>β-actin 2</td>
<td>CTCCTGCTTGCTGATCCACAT</td>
<td>2727–2349</td>
</tr>
</tbody>
</table>
PDGF-A (correlation coefficient revealed a strong linear relationship between cycles 20 and 35 for analysis of cycle-dependency for the generated PCR signals. Numbers of cycles were tested for each message. Quantitative for amplification in the exponential phase of PCR, different/p5

Values are given as means presented in the insets. OD, optical density.

determinations. A representative ethidium bromide-stained gel electrophoresis of the DNA products generated for each target is determined of hypoxic PDGFs and PDGFRs and a/p5

Figure 1 Optimization of RT-PCR conditions for semi-quantitative determination of hypoxic PDGFs and PDGFRs and β-actin mRNA. For amplification in the exponential phase of PCR, different numbers of cycles were tested for each message. Quantitative analysis of cycle-dependency for the generated PCR signals revealed a strong linear relationship between cycles 20 and 35 for PDGF-A (correlation coefficient $r^2=0.9889$) and between cycles 20 and 40 for other targets ($r^2=0.9778$ for PDGFR-α, $r^2=0.9840$ for PDGF-B, $r^2=0.9921$ for PDGFR-β, and $r^2=0.9442$ for β-actin). Values are given as means ± S.D. of three independent determinations. A representative ethidium bromide-stained gel electrophoresis of the DNA products generated for each target is presented in the insets. OD, optical density.

et al. 1999). The following antisera were used: rabbit anti-human TGF-β1 (Research Diagnostics, Inc., Flanders, NJ, USA), affinity purified polyclonal rabbit anti-PDGF-BB and anti-PDGF-AA antibodies (Genzyme, Cambridge, MA, USA); PDGFR-7 and PDGFR-3, rabbit polyclonal antisera to the PDGFR-α and β subunit respectively (provided by Dr Carl-Henrik Heldin, Ludwig Institute for Cancer Research, Uppsala, Sweden). PDGFR-7 was generated against a synthetic peptide covering amino acids 1066–1084 of the COOH-terminal region of human PDGFR-α subunit and does not cross-react with the PDGFR-β subunit. It recognizes both human and rat PDGFR-α subunit. PDGFR-3 was raised against a synthetic peptide corresponding to amino acids 981–994 of the mouse PDGFR-β. It recognizes rat PDGFR-β subunit. PDGFR-7 and PDGFR-3 were affinity purified on columns with immobilized synthetic peptides against which the antisera were raised (Hernanson et al. 1992, Gnessi et al. 1995). All the antibodies react specifically with the respective antigens in immunoprecipitation and Western blotting experiments (Hernanson et al. 1992, Eccleston et al. 1993). For better identification of smooth muscle cells lining the cavernosal spaces, adjacent sections were immunostained with a primary antisera and a secondary antibody (Alexa Fluor 488 goat-anti-mouse IgG) and counterstained with DAPI (1:1000; Vector Laboratories, Inc., Burlingame, CA, USA). The staining distribution and intensity were determined by two observers independently (P V and M A) with subsequent reconciliation of scored values. A score of zero was considered to be negative (−); mean scores between 0 and 1 were considered as weak staining intensity (+/−); mean scores between 1 and 2

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were considered as moderate staining intensity (+); and mean scores between 2-1 and 3 were considered as strong staining intensity (++) (see Table 2).

**Statistical analysis**

Student’s t-test for unpaired data was used for statistical analysis of the results. Data are presented as means ± s.e. unless otherwise specified; *P* values less than 0·05 were considered to be statistically significant.

**Results**

**Effects of generalized hypoxia on blood gas parameters**

After euthanization, hypoxic rats had higher pCO₂ and lower arterial pO₂ than control animals (80±1 ± 3·2 vs 50·7 ± 2·1 mmHg, *P*<0·001, and 20·2 ± 5·1 vs 48·3 ± 4·0 mmHg, *P*<0·001 respectively) as well as lower sO₂ (17% ± 7% vs 70% ± 5%, *P*<0·001).

**PDGF and PDGFRs mRNA expression in isolated rat CC**

Figure 1 shows the linearity of PCR response for each individual primer in hypoxic tissues. The linearity of PCR response in normoxic tissues was similar (data not shown). Semi-quantitative RT-PCR analysis of mRNA extracted from CC of the rat penis showed higher amounts of PDGF-A, PDGF-B and PDGFR-β mRNA transcripts in hypoxic versus control rats (*P*<0·001); no differences were found in PDGFR-α mRNA expression (Fig. 2, upper and lower panel). Hypoxia did not modify β-actin content.

**Immunohistochemical localization of TGF-β₁, PDGF and PDGFRs in rat CC**

Immunohistochemical localization of PDGF-A, PDGF-B, PDGFR-α, PDGFR-β and TGF-β₁ in CC both after acute hypoxia and in normal conditions is shown in Fig. 3. In normoxic rats staining for PDGF peptides and receptors and TGF-β₁ occurred in endothelial cells, perivascular smooth muscle cells and in the fibroblasts of the connective trabecular structures of the CC (Fig. 3B, D, F, H, J). For all peptides, cytoplasmic localization was focal in the endothelium, diffuse in the perivascular smooth muscle cells and perinuclear in the fibroblasts of the trabeculae of overall CC examined. The immunohistochemical localization in hypoxic animals was similar (Fig. 3A, C, E, G, J). The semi-quantitative comparison of staining intensities showed that in the endothelial cells PDGF peptides, PDGFR-β and TGF-β₁ immunoreactivity was more intense in hypoxic versus normoxic rat CC (Table 2). Perivascular smooth muscle cells, which also stained for α-actin (data not shown), showed a stronger signal in hypoxic versus normoxic rat for PDGF-A, PDGF-B and PDGFR-β; on the contrary, PDGFR-α staining intensity was not modified. The staining pattern in fibroblasts of the connective trabecular structures was similar to that described for the endothelium (Table 2). In hypoxic rat CC the TGF-β₁ immunostaining was more intense in all structures when compared with normoxic rats (Table 2 and Fig. 3J).

**Discussion**

The trabecular smooth muscle cells of the CC regulate penile vasoconstriction and vasodilation, and consist primarily of smooth muscle and extracellular connective tissue matrix delimitating vascular lacunae lined by the endothelium. The volumetric contribution of the corporal endothelium and autonomic nerves is considered to be negligible. The percent trabecular smooth muscle content in normal patients has been reported to range from 42 to 50% (Moreland et al. 1995). In vasculogenically impotent patients a decrease in the percentage of trabecular smooth muscle content has been described, with levels ranging...
from 28 to 35% out of normal content; also, it has been shown that in CC the relative amount of trabecular smooth muscle content is regulated by oxygen tension via activation of nitric oxide pathway (Kim et al. 1993, Kourembanas et al. 1997). Moreover, incubation under hypoxic conditions stimulates the release of PDGF from human macrophages and cultured endothelial cells (Kuwabara et al. 1995, Betsholtz & Raines 1997), as well as strongly up-regulates the PDGF-B chain gene expression (Kourembanas et al. 1990). In normal penile human tissues, vasal endothelial cells constitutively express PDGF; furthermore, fibroblasts from pathological tunica albuginea of impotent men with Peyronie’s disease and venocclusive dysfunction show intense immunostaining for PDGF-A and -B chains (Gentile et al. 1996). As a consequence, a higher expression of PDGF-A and -B proteins may determine an imbalance between trabecular smooth muscle and connective tissue ratio resulting in CC fibrosis and erectile dysfunction. In our study, we found that PDGF and PDGFR are constitutively expressed in the rat vascular endothelial cells as well as in penile nerves. More important, in the corpora of hypoxic rats there was a higher expression of PDGF-A and -B proteins than in normoxic rats. Immunohistochemistry showed that the expression was focal in the endothelium, diffuse in the perivascular smooth muscle cells and perinuclear in the fibroblasts of the trabeculae. After exposure to transient low oxygen tension, PDGFR-α expression was also increased in the same cell components of CC expressing PDGF peptides, suggesting that in this condition these cells become a more sensitive target for PDGF peptides. The absence of modifications in PDGFR-α expression may be explained with the concomitant overexpression of TGF-β which is known to down-regulate PDGFR-α in human fibroblasts (Bonner et al. 1995, Kuwabara et al. 1995). Thus, the PDGF overexpression in penile structures under transient hypoxia may well contribute to the cascade of events leading to tissue fibrosis under chronic hypoxic conditions. These events may occur in some patients with erectile dysfunction in which a chronic CC hypoxia has been reported (Tarhan et al. 1997).

In the rat, it has been demonstrated that growth factors may be involved in the autocrine/paracrine loop involved in tissue fibrosis (Battegay et al. 1990). TGF-β is overexpressed in tissues chronically exposed to experimental hypoxia and has a key role in determining lung and kidney fibrosis (Border & Noble 1994). In cultured human CC smooth muscle cells, TGF-β stimulates the synthesis of fibrillar collagen (Moreland 1998) and it has been involved in the increased collagen trabecular smooth muscle cell synthesis that occurs under hypoxic conditions (Moreland et al. 1995). Furthermore, intrapenile oxygen tensions consistent with faccid blood PO2 (30 mmHg) increase TGF-β mRNA expression by approximately twofold in 18 h and threefold in 24 h in men (Moreland 1998). Accordingly, we found that exposure of penile tissue to transient low blood PO2 (~20 mmHg) in vivo led to an

![Figure 2](https://example.com/figure2.png)

**Figure 2** Upper panel, RT-PCR expression analysis of PDGF peptides and PDGF receptors in corpus cavernosum of hypoxic and normoxic rats, in rat testis (positive control) and in the absence of cDNA template (negative control). All data were normalized for β-actin (internal control) and quantified by densitometry computer software. Lower panel, mean densitometric analysis of the results obtained from three consecutive experiments; the s.e. was less than 10% (*P<0.001). Solid bars indicate hypoxic and open bars indicate normoxic rats. OD, optical density.
Immunohistochemical staining pattern of PDGF-A (A, B), -B (C, D) and PDGFR-α (E, F) and -β (G, H) with affinity-purified antibody in cross-sections of hypoxic (A, C, E, G) by comparison with normoxic (B, D, F, H) rat corpus cavernosum, counterstained with hematoxylin. The expression was intense in the cytoplasm of trabecular fibroblasts (triangles) and endothelial cells (arrowheads), and more diffuse in smooth muscle cells (arrows). The scale bar in A represents 25 μm and applies to A-H. Sections of rat corpus cavernosum immunostained for TGF-β1 in hypoxic (I) and normoxic (J) conditions are also shown. The scale bar in I represents 50 μm and also applies to J. TF=fibroblasts of the trabeculae; E=endothelium; V=vessel; SM=smooth muscle cells.
increased TGF-β1 immunostaining in the rat penile CC, suggesting that multiple genes encoding matrix molecules leading to fibrotic alterations inside the penis may be activated even during transient hypoxia, similar to that described in the endothelium (Gerritsen & Bloor 1993).

Low-low priapism is a frequent complication of vasoactive intracavernous pharmacotherapy in men affected by erectile dysfunction, especially when combination drugs are used (Fabbri et al. 1997). Human CC undergo major ultrastructural changes, i.e. corporeal fibrosis during priapism, but pharmacological detumescence is not recommended until 12 h has passed (Hauri et al. 1983). However, it is known that in a rabbit model, hypoxia induced by prolonged erection and subsequent local acidosis impair contractility of trabecular smooth muscles. This phenomenon impedes the drainage of blood, perpetuates the ischemic state and may cause early ultrastructural changes (Kim et al. 1996, Saenz de Tejada et al. 1997, Moon et al. 1999). Taking into account our findings, the risk that fibrotic alterations may begin early after acute hypoxia has occurred inside the corpora is quite elevated. Thus, in the clinical outpatient setting prompt detumescence of erections that exceed a duration of 2 h should be recommended (Aversa et al. 2000).

In conclusion, transient in vivo hypoxia increases the expression of the PDGF system in the rat penis. It is conceivable that these changes may occur also in conditions of chronic hypoxia in men and may lead to alterations in penile structures similar to those already described in other organs (Wespes et al. 1998, Okabe et al. 1999). These phenomena might contribute to the pathogenesis of erectile dysfunction that frequently complicate atherosclerosis, diabetes mellitus, hypertension, obstructive pulmonary disease and intense cigarette smoking.

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