Mitogenic Effect of Serotonin on Vascular Endothelial Cells

Rajabu Pakala, PhD; James T. Willerson, MD; Claude R. Benedict, MD, DPhil

Background Recent studies indicate that serotonin (5-HT) has a growth-promoting effect on several different cell types, including smooth muscle cells. After percutaneous transluminal coronary angioplasty, there is damage and denudation of vascular endothelial cells, which promotes platelet aggregation at the site of injury. Aggregating platelets release 5-HT; thus, a high concentration of the amine may be present at sites of endothelial damage, which may act as a mitogen to endothelial cells.

Methods and Results The mitogenic effect of 5-HT was examined on canine and bovine aortic endothelial cells by (1) assessing the increase in \(^{3}H\)thymidine incorporation into DNA and (2) assessing the increase in the absolute number of cells after stimulation with 5-HT. 5-HT at an added concentration of 200 to 1000 \(\mu\)mol/L in the media induced a significant increase in \(^{3}H\)thymidine incorporation into endothelial cells and an increase in cell number. This effect was not observed with fibroblasts. As the concentrations of added 5-HT were decreased, the endothelial cells had to be stimulated with 5-HT for longer periods to induce the same degree of cellular proliferation. The precursors and metabolic breakdown products of 5-HT were inactive. The 5-HT-induced endothelial proliferation was reversed by 5-HT\(_2\) receptor antagonists and pertussis toxin. These data suggest that the mitogenic effect of 5-HT on endothelial cells is mediated by the 5-HT\(_2\) receptor, which is coupled to a G protein.

Conclusions 5-HT is a mitogen for endothelial cells at concentrations likely to be present at sites of vascular injury. This effect is probably mediated via the 5-HT\(_2\) receptor. The growth-promoting effects of 5-HT on endothelial cells may facilitate the healing of intima after vascular damage. (Circulation. 1994;90:1919-1926.)

Key Words • endothelium • serotonin • platelets

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humidified atmosphere of 5% CO2/95% air (vol/vol) in DMEM containing 10% FBS. The cells were passaged by treatment with 3 mL trypsin/EDTA in HBSS. The action of trypsin was stopped after 2 to 4 minutes by the addition of 9 mL of medium containing 10% FBS. The cells were harvested by centrifugation at 500g and suspended in fresh DMEM containing 10% FBS. The endothelial cells were characterized by staining for the presence of von Willebrand factor and the absence of α-actin.

[3H]Thymidine Incorporation

Canine aortic endothelial cells from passages 2 and 3 were seeded into 35-mm-diameter plates at a density of 65,000 to 75,000 cells per plate in DMEM containing 10% FBS and allowed to proliferate for approximately 72 hours. After 72 hours, the growth medium was replaced with 2 mL DMEM containing 0.1% FBS and incubated for approximately 72 hours for arresting cell growth and synchronization. After growth arrest, the medium was replaced with 2 mL DMEM supplemented with 1 mg/mL BSA, 10 μg/mL bovine insulin, 20 μg/mL human transferrin, and 100 μmol/L pargyline. Where indicated, 5-HT with pargyline or the precursors or metabolic breakdown products of 5-HT were added to this medium.

After 20 hours of incubation, 1 μCi [3H]thymidine was added to each plate and then incubated for an additional 4 hours. The medium was removed, and the plates were washed three times with ice-cold PBS. Then, 6% trichloroacetic acid was added to the cells, and the acid-insoluble thymidine was collected on a glass-fiber filter. The filters were washed with 100% ethanol and air-dried, and [3H]thymidine was quantified with a liquid scintillation counter. The counts were determined (Coulter counter) on the day of seeding and before changing to 0.1% serum medium to ensure that they were growing and, finally, on day 6 to determine that the cells were growth-released. All experiments were performed in quadruplicate.

Determination of Endothelial Cell Number

Washed endothelial cells were seeded at a density of 3 x 10⁴ to 5 x 10⁵ cells per 35-mm-diameter dish containing 3 mL serum-free medium (DMEM supplemented with 10 μg/mL insulin, 20 μg/mL human transferrin, 1 mg/mL BSA, and 100 μmol/L pargyline) and specified amounts of 5-HT. The serum-free medium containing 5-HT was changed every day. On specified days, 0.3 mL pancreatic trypsin in PBS (wt/vol) was added to each dish. The contents of each dish were diluted to 10 mL with Isoton II, and the cells were counted with a Coulter counter. Triplicate counts were taken for each plate, and quadruplicate plates were used for each determination.

Angioplasty of Iliac Arteries in Rabbits

To determine the concentration of 5-HT at a site of vascular injury, we performed angioplasty of the iliac arteries in rabbits by using a standard percutaneous carotid approach. Briefly, the USCI angioplasty catheter system with a 3F angioplasty catheter was used. The catheter was positioned in the right iliac artery and inflated at 3 atm six times and held for 30 seconds each time. The animals were killed either immediately after angioplasty (n=3) or 6 hours (n=3) or 72 hours after angioplasty (n=4). The dilated segments of the right iliac artery as well as the undisturbed left iliac artery were removed and rinsed rapidly in ice-cold saline to remove any visible thrombi or cellular debris. The tissue was blotted dry gently, weighed, and homogenized in 1 mL PBS, pH 7.4, with 20 mmol/L pargyline. After homogenization and centrifugation, 20 μL of the supernatant was assayed for 5-HT concentration.

Measurement of 5-HT Concentrations in Cell Culture Media and Tissues

The 5-HT concentration in the medium was measured by a radioenzymatic assay as previously described. Briefly, 20 μL of the medium was first acetylated with acetic anhydride and then methylated by using [3H]-S-adenosyl methionine (1 μCi) and hydroxyindole-O-methyl transferase prepared from bovine pineal glands. The [3H]-labeled melatonin was extracted with toluene and isooamyl alcohol and then dried. The residue was reconstituted in 95% ethanol containing unlabeled melatonin as a carrier and spotted on indicator silica gel plates by use of a multispotter. The plates were developed for 60 minutes in chloroform:methanol:ethylamine (12:2:1). The melatonin spot (Rf, 0.61) was located by inspection under ultraviolet light, scraped, and counted.

Statistical Analyses

Data were analyzed by one-way ANOVA. For each figure and table, values are mean±SD.

Results

Effect of 5-HT on [3H]Thymidine Incorporation by Endothelial Cells

The effect of increasing concentrations of 5-HT on [3H]thymidine incorporation into the DNA is shown in Fig 1. 5-HT at an added concentration of >100 μmol/L in the media induced a significant increase in [3H]thymidine incorporation into endothelial cells. However, as the concentration of 5-HT increased beyond 1000
μmol/L in the media, there was a reduction in the [3H]thymidine incorporation. Similarly, 5-HT increased the [3H]thymidine incorporation into the bovine pulmonary artery endothelial cells and NIH 3T3 cells but failed to have a proliferative effect on human fibroblasts (Fig 1). Next, we examined the time required for 5-HT to induce DNA synthesis in canine endothelial cells (Fig 2). When the cells were incubated with 5-HT for different time periods, there was no difference between the control (untreated) cells and the 5-HT-treated cells up to 4 hours. However, after 6 hours, there was a significant increase in [3H]thymidine incorporation, which peaked at 8 hours. This effect of 5-HT on [3H]thymidine incorporation persisted up to 24 hours (Fig 2).

Effect of 5-HT on Endothelial Cell Number

To determine whether the effect of serotonin on DNA synthesis resulted in an increase in cell number (hyperplasia), the endothelial cells were grown in serum-free medium in the absence (control) and presence of various concentrations of 5-HT, and the number of surviving cells was counted (Fig 3). The data show that 5-HT-induced DNA synthesis results in an increase in cell numbers when compared with no treatment. The cellular proliferation response appears to be a function of the 5-HT concentration in the medium and the duration of stimulation (exposure). At an added concentration of 200 μmol/L 5-HT, the cell number increased only after 96 hours of stimulation; with 600 μmol/L 5-HT, proliferation was seen within 24 to 48 hours; and at 1000 μmol/L, the mitogenic effect peaked within 24 hours, followed by a decrease in cell number. The latter finding suggests that very high concentrations of 5-HT may be cytotoxic to endothelial cells, particularly with prolonged exposure.

Effect of Pargyline on 5-HT–Induced Endothelial Cell Mitogenesis

Previous studies have shown that endothelial cells contain monoamine oxidase, which can metabolize 5-HT and may limit the mitogenic effect. Therefore, we examined the effect of pargyline, a monoamine oxidase inhibitor, added to 5-HT on [3H]thymidine incorporation (Fig 4). The data demonstrated that although pargyline by itself did not have an effect, it enhanced the 5-HT–induced [3H]thymidine incorporation into endothelial cells. The effect of pargyline on preventing metabolism of 5-HT is shown in Table 1, which shows that the amount of added 5-HT in the medium was higher when pargyline was also present.

Stability of 5-HT in the Culture Media

At neutral pH (as in culture media), 5-HT is highly labile and breaks down rapidly. Since it appeared that 6 or more hours was required for stimulation of [3H]thymidine incorporation, it seemed likely that the true 5-HT concentration present in the media might decrease with time. Measurements of 5-HT in the culture media showed that the amount of 5-HT in the media was higher when pargyline was also present.
medium indicated that indeed 30% to 35% of the added 5-HT was metabolized even in the presence of pargyline (Table 1). This suggests that the effective concentrations of 5-HT that induced endothelial proliferation were significantly less than the concentrations added to the medium.

**Effect of Precursors and Metabolic Breakdown Products of 5-HT on Endothelial Cell Proliferation**

To determine whether the mitogenic effect of 5-HT could be mimicked by its precursors, the effect of D-tryptophan, L-tryptophan, and 5-hydroxy-L-tryptophan on endothelial proliferation was examined at concentrations that were 1-, 10-, and 100-fold higher than the maximally effective concentration of 5-HT. None of these compounds had an effect on the \[^3H\]thymidine incorporation (Table 2). Similarly, 5-hydroxyindole acetic acid, 5-hydroxytryptophol, and melatonin, the metabolic breakdown products of 5-HT, did not have a significant effect on \[^3H\]thymidine incorporation into canine and bovine vascular endothelial cells (Table 2).

**Mechanism of Stimulatory Effect of 5-HT on Endothelial Cells**

We determined the mechanisms responsible for the mitogenic effect of 5-HT on endothelial cells. When cells were preincubated for 2 hours with various concentrations of ketanserin (5-HT\(_1\) receptor antagonist) (Fig 5A) or LY281067 (5-HT\(_2\) receptor antagonist) (Fig 5B), the mitogenic effect of 5-HT on endothelial cells was reversed in a dose-dependent manner by both 5-HT\(_1\) receptor antagonists. In contrast, when the cells were preincubated with MDL 73147EF (5-HT\(_2\) receptor antagonist) (Fig 5C), methiothepin (5-HT\(_1\)/5-HT\(_2\) receptor antagonist) (Fig 5D), or NAN-190 (5-HT\(_{1A}/5\)-HT\(_{1D}\) receptor antagonist; data not shown), they did not reverse the effect of 5-HT on \[^3H\]thymidine incorporation. Similarly, when bovine pulmonary artery endothelial cells were preincubated with 0, 1.85, and 18.5 \(\mu\)mol/L LY281067, this completely inhibited the mitogenic effect of 5-HT (data not shown). It is also important to note that none of these 5-HT receptor antagonists were cytotoxic to the cells at the concentrations tested (data not shown).

Although in some types of cells, the mitogenic effect of 5-HT is dependent on the G protein–coupled intracellular signal transduction pathway,\(^{11,13}\) it is not known whether the same mechanism is operative in vascular endothelial cells. Therefore, we examined whether pertussis toxin could inhibit the 5-HT–induced \[^3H\]thymidine incorporation into endothelial cells. When the cells

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**TABLE 1. Stability of Serotonin in the Culture Medium**

<table>
<thead>
<tr>
<th>Concentration of 5-HT Added to the Medium</th>
<th>Measured Concentration of 5-HT in Medium, (\mu)g/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 h 8 h 24 h</td>
</tr>
<tr>
<td>800 (\mu)mol/L 5-HT</td>
<td>85±5 67±3* 68±4* 46±6</td>
</tr>
<tr>
<td>800 (\mu)mol/L 5-HT with pargyline</td>
<td>89±7 72±5 70±3* 62±2</td>
</tr>
<tr>
<td>1000 (\mu)mol/L 5-HT</td>
<td>133±8 113±7* 77±5* 48±3</td>
</tr>
<tr>
<td>1000 (\mu)mol/L 5-HT with pargyline</td>
<td>131±14 113±10* 119±12* 89±6</td>
</tr>
</tbody>
</table>

5-HT indicates serotonin. Values are mean±SD.

Endothelial cells were incubated with medium alone (n=5) or with 800 \(\mu\)mol/L (103 \(\mu\)g/mL) (n=5) or 1000 \(\mu\)mol/L (129 \(\mu\)g/mL) (n=5) 5-HT with or without pargyline (100 \(\mu\)mol/L). The medium was collected 0 (baseline), 6, 8, and 24 hours after the addition of 5-HT, and its concentration was measured as described in "Methods." The concentration of 5-HT in the baseline medium was 150±15 pg/mL.

*\(P<.05\), †\(P<.01\), and ‡\(P<.001\) compared with corresponding baseline values (ANOVA).

**TABLE 2. Effect of Precursors and Breakdown Products of Serotonin on \[^3H\]Thymidine Incorporation in Endothelial Cells**

<table>
<thead>
<tr>
<th>Compounds Added</th>
<th>Concentration of the Compound 1 mmol/L 10 mmol/L 100 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Tryptophan</td>
<td>615±16 567±22 516±9</td>
</tr>
<tr>
<td>D-Tryptophan</td>
<td>598±66 598±69 523±33</td>
</tr>
<tr>
<td>5-Hydroxy-L-tryptophan</td>
<td>620±30 606±15 586±15</td>
</tr>
<tr>
<td>5-Hydroxyindole acetic acid</td>
<td>640±47 697±121 719±108</td>
</tr>
<tr>
<td>5-Hydroxytryptophol</td>
<td>589±42 823±113 746±9</td>
</tr>
<tr>
<td>Melatonin</td>
<td>564±29 640±48 646±38</td>
</tr>
</tbody>
</table>

Values are mean±SD (n=5 for each experiment).

Cells were grown in the presence of 10% fetal bovine serum (FBS) for 72 hours and then synchronized by growing in 0.1% FBS for 72 hours. Then, specified concentrations of the compounds were added in serum-free medium. After 20 hours, 1 \(\mu\)Ci per plate of \[^3H\]thymidine was added, and \[^3H\]thymidine incorporation was measured 4 hours later as described in "Methods." There was no statistically significant difference between the baseline and the treated groups for any of the compounds tested (ANOVA).
were preincubated for 2 hours with 5 ng/mL pertussis toxin and then stimulated with different concentrations of 5-HT, the pertussis toxin completely inhibited the 5-HT–induced DNA synthesis (Fig 6A). The half-maximal inhibition of 5-HT–induced endothelial cell proliferation by pertussis toxin was observed at approximately 10 pg/mL (Fig 6B).

Effect of Angioplasty on Accumulation of 5-HT at Sites of Vascular Injury

To determine the relevance of the in vitro observations for 5-HT–induced endothelial proliferation in vivo, we measured 5-HT concentrations at sites of vascular injury after angioplasty. 5-HT concentrations were measured immediately after angioplasty or at 6 or 72 hours after angioplasty. Previous histopathologic studies in this model indicate that after angioplasty of iliac arteries, neointimal proliferation develops in these vessels 6 to 8 weeks after injury (authors’ unpublished observations). We found significant increases in 5-HT accumulation at sites of vascular injury at 6 and 72 hours after angioplasty (Table 3).

Discussion

The data indicate that 5-HT at selected concentrations exerts a mitogenic effect on endothelial (canine aortic and bovine pulmonary artery) and NIH 3T3 cells, whereas it does not have a similar effect on human fibroblasts. The mitogenic effect was demonstrable by [3H]thymidine incorporation and by an increase in cell numbers. The mitogenic effect on endothelial cells was observed at lower concentrations of 5-HT, when the cells were exposed to the amine for a longer period. Despite the lower concentrations, the endothelial cells were stimulated to proliferate to the same degree. 5-HT is unstable under conditions of neutral pH and breaks down rapidly. In fact, in the present study, we found more than a third of the added 5-HT to be metabolized

**Table 3.** Serotonin Concentrations at the Site of Vascular Damage After Angioplasty

<table>
<thead>
<tr>
<th>Tissue</th>
<th>5-HT Concentration, pmol/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=3)</td>
<td>6 h (n=3)</td>
</tr>
<tr>
<td>Undisturbed left iliac artery</td>
<td>&lt;6.0</td>
</tr>
<tr>
<td>Dilated right iliac artery</td>
<td>96.6±25*</td>
</tr>
</tbody>
</table>

5-HT indicates serotonin. Values are mean±SD. Rabbits underwent right iliac artery angioplasty as described in the text. The dilated and the undisturbed contralateral arteries were removed immediately after angioplasty (baseline) or 6 or 72 hours after the procedure. The tissue was rinsed free of blood or cell debris and homogenized with pargyline, and the 5-HT concentration was measured.

*P<.0001 compared with the corresponding baseline values.
in 8 hours. Since endothelial cells contain monoamine oxidase, which can metabolize 5-HT, the addition of pargyline to the medium partially inhibited the metabolism of 5-HT and enhanced its mitogenic effect on endothelial cells. Similar potentiation of the effect of 5-HT on smooth muscle cells by the monoamine oxidase inhibitor, iproniazid, has been previously reported by other investigators. Since the metabolic product of 5-HT, 5-hydroxyindole-3-acetic acid, has the same indole structure as 5-HT, we examined whether the effect of 5-HT could be due to accumulation of 5-hydroxyindole-3-acetic acid in the media. 5-Hydroxyindole-3-acetic acid has been previously shown to promote growth of smooth muscle cells from the rat aorta but to be without any effect on bovine aortic or pulmonary artery smooth muscle cells. We found that the proliferative effect of 5-HT on endothelial cells was specific and not shared by its precursors or breakdown products even at concentrations 100-fold higher than used for 5-HT.

In agreement with the earlier reports in other cells, the stimulation of endothelial cell proliferation by 5-HT required prolonged incubation for at least 6 hours before inducing a mitogenic response. This suggests the activation of specific intracellular signaling pathways before an induction of cell proliferation. 5-HT appears to mediate its effect by different receptor subtypes. Serotonergic receptors have been characterized according to pharmacologic similarity and effector coupling into four different groups: (1) those negatively coupled to adenylate cyclase (5-HT1 class of receptors), (2) those coupled to phospholipase C (5-HT2 class of receptors), (3) a subtype coupled to Ca2+ influx by an unknown mechanism(s) (5-HT3), and (4) a new type (5-HT4). The growth-stimulating effects of 5-HT on nontransformed Chinese hamster lung fibroblasts and human pancreatic carcinoid cells are mediated by the 5-HT1B receptor, whereas in vascular smooth muscle cells, the contractile, chemotactic, and mitogenic responses are mediated by the 5-HT2 receptors. In bovine aortic smooth muscle cells, 5-HT stimulates [3H]thymidine incorporation and inhibits hydrolysis of inositol phosphate, increasing intracellular Ca2+ concentrations via the 5-HT1 receptor. Studies examining the effect of 5-HT on vascular endothelial cells have not been previously reported. As in vascular smooth muscle cells, we found the mitogenic effect of 5-HT on endothelial cells to be mediated by the 5-HT2 receptor because both LY281067 and ketanserin blocked the effect of 5-HT on these cells, whereas MDL 73147EF (5-HT2 receptor blocker), methiothepin (5-HT2, 5-HT3, receptor blocker), and NAN-190 (5-HT1a, 5-HT1p receptor blocker) were without effect. Whereas ketanserin may also have other α1-receptor blocking properties, LY281067 is devoid of such effects. It should be noted that the effect of 5-HT on endothelial cells was reversed by relatively high concentrations of ketanserin and LY281067. However, Cushing and Cohen and Houston and Vanhoutte have shown that high concentrations of 5-HT2 receptor agonists were required to block the 5-HT-mediated vasoconstrictor response in canine coronary arteries. It is also possible that at a lower concentration of 5-HT (approximately 10 μmol/L), which would induce a lower percentage (eg, 50%) of maximal thymidine incorporation, endothelial proliferation may be inhibited by lower concentrations of 5-HT2 receptor blockers. An alternate explanation could be that it may not be the classic 5-HT2 receptor that may mediate the mitogenic response but rather a 5-HT2p receptor. However, NAN-190 did not reverse the effect of 5-HT on endothelial cells. This suggests that 5-HT2 receptor-coupled phospholipase C activation could be a possible mechanism that may mediate 5-HT-induced canine and bovine endothelial cell proliferation. This indication for involvement of 5-HT2 receptors on endothelial cell proliferation must be interpreted with caution because the antagonists used have mixed 5-HT receptor inhibitor properties and endothelial cells may have other types of 5-HT receptor subtypes that are yet to be defined.

Generally, serotonergic receptors are found to be coupled to G proteins in most cell types, and the effects of 5-HT appear to be mediated through the G1 subtype. Pertussis toxin is known to reverse the G protein-mediated responses either by inactivating the inhibitory G protein for adenylate cyclase or by inhibiting phosphoinositide hydrolysis and the synthesis of second messenger. In the present study, pertussis toxin reversed the mitogenic effect of 5-HT on endothelial cells in a dose-dependent manner. However, this finding does not localize the precise intracellular mechanism or the specific G proteins that may mediate the mitogenic effect of 5-HT on endothelial cells. For example, although pertussis toxin reversed the mitogenic effect of 5-HT, this does not appear to involve phosphoinositide hydrolysis, phorbol ester-sensitive kinase C activity, or changes in peak intracellular Ca2+ or cAMP concentrations. Similarly, thrombin- and bombesin-induced mitogenesis on Swiss 3T3 cells and hamster fibroblasts is reversed by pertussis toxin without the hydrolysis of phosphoinositide, suggesting the presence of other intracellular signaling pathways that are coupled to G proteins.

Under normal conditions, the concentration of 5-HT in plasma and tissue is very low because the 5-HT entering the vasculature is taken up by platelets or metabolized by endothelial monoamine oxidase. Patients with the carcinoid syndrome have high levels of 5-HT and may develop endothelial thickening and fibrosis involving the right side of the heart. Since lungs are an active site for removal of 5-HT from plasma, no changes are usually observable in the left side of the heart unless there are pulmonary metastases. In contrast to the systemically elevated levels of 5-HT in patients with carcinoid syndrome, a local increase in 5-HT concentrations has been reported after endothelial injury to arteries. Thus, at the site of vascular injury, the surviving endothelial cells may be exposed to high concentrations of 5-HT. We found that after angioplasty of the iliac artery, there was a gradual increase in 5-HT concentrations over a period of 72 hours at the site of vascular dilatation and intimal-medial injury. Since we have previously demonstrated that 5-HT accumulation at sites of vascular injury directly correlates with In-labeled platelet disposition, the increase in 5-HT concentrations likely reflects the continuing platelet aggregation and release of granular contents at the site of damage. We performed angioplasty in histologically normal arteries. Previous studies in atherosclerotic vessels indicate that after injury there
is a significantly higher degree of platelet disposition when compared with similar injury in normal arteries.48,49 Further, in blood vessels with atherosclerosis, the relative lack of monoamine oxidase activity25 may amplify the effect of 5-HT by decreasing its breakdown.25 Clearly, the in vitro conditions in our cell culture study do not mimic the conditions that may be present in vivo; therefore, any extrapolation must be made with great caution. However, the concentrations of 5-HT measured at the site of angioplasty are probably within the range of concentrations found to induce endothelial cell proliferation in vitro. The results of the long-term in vitro stimulation studies indicate that the mitogenic effect of 5-HT was dependent on both the duration of exposure and the concentrations used. Thus, it is possible that the chronic platelet aggregation and accumulation of 5-HT at sites of vascular injury may contribute to proliferation of the surviving endothelial cells. Further, 5-HT present at sites of injury may also act synergistically with other growth factors known to induce endothelial cell mitogenesis.

The role of endothelial cell proliferation in remodeling of the blood vessel after angioplasty remains unclear. Some suggest that regrowth of endothelial cells after intimal injury may inhibit the growth of smooth muscle cells and limit the development of restenosis.50 Other findings do not support this conclusion. Minick et al.51 found that the greatest area of intimal thickening after balloon denudation was at the edge of the regenerated sheet of endothelium. Further, the injured/regenerating endothelium is known to release growth factors (PDGF or PDGF-like proteins) that promote proliferation of smooth muscle cells.40 Thus, the specific effect of endothelial proliferation after vascular injury remains unclear at present. However, it is possible that 5-HT-facilitated endothelial regeneration may play a role in the healing of the intimal layer after vascular injury.

Acknowledgments

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