Regional Vascular Effects of Serotonin and Ketanserin in Young, Healthy Subjects

GERARD J. BLAUW, PETER VAN BRUMMELEN, PETER C. CHANG, PIETER VERMEIJ, AND PIETER A. VAN ZWIETEN

SUMMARY The local hemodynamic effects of serotonin (5-hydroxytryptamine; 5-HT) and the selective 5-HT₂ antagonist ketanserin were investigated in the forearm of 20 healthy volunteers. Single doses of 5-HT (0.1–80 ng/kg/min) and ketanserin (5–125 ng/kg/min) were administered intra-arterially. The relative α₁-adrenergic receptor and 5-HT₂ blocking potencies of ketanserin were investigated using intra-arterial infusions of cumulative doses of methoxamine (0.1, 0.3, and 0.5 μg/kg/min), tyramine (0.25, 0.50, and 1.25 μg/kg/min), and 5-HT (10, 30, and 80 ng/kg/min) together with a low dose (5 ng/kg/min) and a high dose (50 ng/kg/min) of ketanserin. Forearm blood flow was measured by venous occlusion plethysmography. Heart rate and intra-arterial blood pressure were recorded semi-continuously. Intra-arterial infusion of 5-HT induced an initial transient vasodilatation, followed by a steady vasodilatation for the low doses of 5-HT (0.1–10 ng/kg/min; p < 0.05). A steady vasoconstriction was only obtained at the highest dose of 5-HT. Ketanserin induced a dose-dependent increase in forearm blood flow from 15 ng/kg/min (p < 0.05) onward. The vasodilatation induced by 5-HT (1 ng/kg/min) was significantly enhanced by ketanserin (125 ng/kg/min; p < 0.05), whereas the vasoconstriction elicited by 5-HT (80 ng/kg/min) was reversed by ketanserin (50 ng/kg/min; p < 0.05), thus confirming that 5-HT₂ receptors were stimulated by 5-HT. In this model ketanserin proved to be a more potent antagonist of α₁-adrenergic receptors than of 5-HT₂ receptors, since the vasoconstriction induced by methoxamine and tyramine was reduced by a lower dose of ketanserin than was the vasoconstriction induced by 5-HT. It is concluded that 5-HT acts predominantly as a vasodilator in healthy subjects, probably by 5-HT₂-like receptor stimulation. Only at high doses of 5-HT did vasoconstriction mediated by 5-HT₂ receptor stimulation occur. The vasodilatation induced by ketanserin was due most likely to its α₁-adrenergic blocking properties. (Hypertension 11: 256–263, 1988)

Key Words • serotonin • ketanserin • vasodilatation • vasoconstriction • 5-hydroxytryptamine receptors • α-adrenergic receptors

SEROTONIN (5-hydroxytryptamine; 5-HT) influences the vascular system in a complex manner, causing vasodilatation as well as vasoconstriction depending on the type of blood vessel involved and on the presence or absence of several physiological and pathological factors.1-6 A better understanding of the vascular effects of 5-HT has been facilitated by the recent introduction of a subdivision of vascular 5-HT receptors.7,8 According to this subdivision, at least two types of 5-HT receptors are assumed to be located in the vascular wall: 5-HT₁-like receptors, which mediate vascular relaxation in several species, and 5-HT₂ receptors, which trigger vasoconstriction on stimulation with 5-HT.7-11 This concept has been enhanced and extended by the development of selective agonists and antagonists for various 5-HT receptors.12-19 The selective 5-HT₂ antagonist ketanserin is currently the prototype of a 5-HT₂ blocking agent,12,13,15,20,21 although it has an affinity for α₁-adrenergic receptors as well. The antihypertensive properties of ketanserin have been well established, but the exact mechanism by which it lowers elevated blood pressure in humans remains to be elucidated.22-25 Most investigations of the vascular effect of 5-HT and ketanserin have been performed in vitro or in laboratory animals (for reviews see References 9, 10, 26, 27), whereas relatively few experimental data in humans are available. For this reason we explored the hemodynamic effects of 5-HT and ketanserin in the vascular bed of the human forearm.

From the Departments of Nephrology (G.J. Blauw, P. van Brummeelen, P.C. Chang) and Hospital Pharmacy (P. Vermeij), University Hospital, Leiden, and the Division of Pharmacotherapy (P.A. van Zwieten), University of Amsterdam, The Netherlands.

Address for reprints: G. J. Blauw, Department of Nephrology C-3-P, University Hospital, Rijksnburgweg 10, 2333 AA Leiden, The Netherlands.

Received May 28, 1987; accepted October 21, 1987.
Subjects and Methods

Twenty healthy male volunteers (mean age, 23 years; age range, 19–28 years) participated in this study. Their medical history, physical examination findings, and routine laboratory test results did not show evidence of any relevant disease. None of the subjects was receiving any medication at the time of the study or in the 2 weeks before the study. On the day of the study and 12 hours before, all subjects refrained from smoking and from drinking caffeine-containing beverages. Informed consent was obtained from all subjects, and the protocol was approved by the Ethics Committee of the Leiden University Hospital.

Procedures

The studies were performed in a quiet room with a temperature between 21.5 and 23.5°C. During the experiments the subjects were in the supine position with the nondominant arm stabilized slightly above the level of the heart. After local anesthesia of the skin, the brachial artery of the nondominant arm was cannulated in the cubital fossa. This cannula (Autocath 1453.13, Plastimed, Saint-Leu-la Forêt, France) was used for infusion of drugs with a constant-rate infusion pump (Model 351, Sage Instruments, Cambridge, MA, USA) and for intra-arterial blood pressure (BP) recording with a Statham P231d pressure transducer (Gould, Oxnard, CA, USA). Heart rate (HR) was derived from a continuously recorded one-lead electrocardiogram (ECG). Forearm blood flow (FBF) was measured three to five times per minute by venous occlusion plethysmography (Hokanson EC-2 plethysmograph, Issaquah, WA, USA), using mercury-in-Silastic strain gauges and a rapid cuff inflator (Hokanson E-10). Tracings of ECG, BP, and FBF were directly recorded on a polygraph (Mingograph 803, Siemens-Elema, Stockholm, Sweden). A personal computer (Model AT III, IBM, Armonk, NY, USA) extended with an analog-digital convor (Model DT 2801, Data Translation, Marlborough, MA, USA) was used for R-wave–triggered control of the rapid cuff inflator and for on-line analysis of FBF, BP, and HR recordings.

During the measurements of FBF, the blood flow in the hand was excluded from the circulation using a small wrist cuff, inflated to 40 mm Hg above the systolic blood pressure. The experiments started at least 45 minutes after cannulation of the brachial artery. Between the various infusions, the wrist cuff was deflated and sufficient time (30–60 minutes) was allowed for FBF to return to basal levels. Skin temperature was recorded continuously at the ventral surface of the forearm by an electronic thermometer (Model MC 9200, Exacon Scientific Instruments, Roskilde, Denmark).

Drugs and Solutions

The following drugs were infused into the brachial artery: 5-HT HCl (Janssen Chimica), methoxamine (Vasoxin, Wellcome), tyramine HCl (Merck), ketanserin (Janssen Pharmaceutica), propranolol (Inderal, ICI), and sodium nitroprusside (Merck). The drugs were dissolved in saline except for sodium nitroprusside, which was dissolved in 5% glucose. All solutions were prepared from sterile stock solutions and ampules on the day of the study and kept at 4°C until used.

Study Protocol

Infusions of Serotonin and Ketanserin

In seven healthy volunteers 5-HT was infused intra-arterially in single sequential doses of 1, 3, 10, 30, and 80 ng/kg/min. Subsequently, ketanserin was infused in doses of 5, 15, and 50 ng/kg/min, respectively. Each infusion lasted 10 minutes. The infusions of 5-HT were always given before the ketanserin infusions to avoid possible carryover effects of ketanserin. Finally, 5-HT (80 ng/kg/min) was infused together with ketanserin (50 ng/kg/min). The hemodynamic variables FBF, BP, and HR were recorded semicontinuously during the infusions. Basal values were obtained during the 2 minutes preceding each infusion. The averages of FBF, BP, and HR during the last 2 minutes of each infusion were used for further analysis.

Infusions of Serotonin, Ketanserin, and Propranolol

The preceding experiments were extended in six other healthy volunteers: 5-HT was infused intra-arterially in doses of 0.1, 0.3, and 1.0 ng/kg/min in the presence of saline (0.4 ml/min i.a.). Each dose was given for 8 minutes. Subsequently, the 1.0 ng/kg/min dose of 5-HT was repeated in the presence of increasing doses of ketanserin (5, 50, and 125 ng/kg/min) and one dose of propranolol (1 μg/kg/min), in that order. A control experiment with the vehicle of ketanserin was performed in between the 5-HT infusions and the combined infusions. The infusions of saline, ketanserin, and propranolol were started 5 minutes before 5-HT was added. The hemodynamic variables FBF, BP, and HR were recorded semicontinuously, starting 2 minutes before each infusion. The average values corresponding to the last 2 minutes of each single or combined infusion were used for analysis.

Infusions of Serotonin, Methoxamine, Tyramine, and Ketanserin

The 5-HT2 and α1-adrenergic receptor blocking properties of ketanserin were investigated in seven healthy volunteers. 5-HT, the selective α1-adrenergic receptor agonist methoxamine, and the indirect sympathomimetic drug tyramine were infused in a random order, in the presence of a continuous infusion of sodium nitroprusside (SNP, 3 ng/kg/min) to elevate the basal FBF up to the same level as expected during the infusion of ketanserin (50 ng/kg/min). Also given were cumulative dose infusions of 5-HT (10, 30, and 80 ng/kg/min), methoxamine (0.1, 0.3, and 0.5 μg/kg/min), and tyramine (0.25, 0.5, and 1.25 μg/kg/min). Each dose step was infused for 5 minutes. Subsequently, the infusions of 5-HT, methoxamine, and tyramine
were repeated in the presence of a low dose of ketanserin (5 ng/kg/min) together with SNP (3 ng/kg/min) and finally with a high dose of ketanserin alone (50 ng/kg/min). The infusions of SNP and ketanserin were started 5 minutes before the infusions of 5-HT, methoxamine, and tyramine, respectively. FBF, BP, and HR values recorded during the last 2 minutes of each dose step of the single and combined infusions were used for analysis.

Statistical Analysis

Results are given as means ± SEM. FBF values are expressed as percent changes from baseline. Wilcoxon's signed rank test for matched pairs and three-way analysis of variance were used to evaluate the statistical significance of the data. All p values lower than 0.05 were regarded as significant.

Results

In all experiments, changes in intra-arterial BP and HR were small and inconsistent, excluding important systemic hemodynamic effects of the doses used (Table 1). Infusion of saline (0.4 ml/min) or the vehicle of ketanserin did not significantly alter FBF. Baseline levels of FBF established in the various experiments are listed in Table 1.

Infusions of Serotonin Alone

All doses of 5-HT studied in the two groups induced a transient increase in FBF within the first few minutes of the infusion (Figure 1). Dose dependency of this phenomenon could not be established, although at the lowest dose of 0.1 ng/kg/min only a minor effect was observed. The maximum transient increase of FBF recorded was 360% at the dose of 1 ng/kg/min (see Figure 1B). After this transient vasodilatation, FBF was increased relative to baseline by the lower doses of 5-HT (0.1–10 ng/kg/min; p < 0.05) and decreased relative to baseline by the highest dose of 5-HT (80 ng/kg/min; p < 0.05; see Figure 1). Based on the averaged effect of the last 2 minutes of each infusion, a dose-response curve for the vascular effect of 5-HT was constructed (Figure 2). This curve is clearly biphasic with a maximal vasodilatation of approximately 60 to 70% at the dose of 1 ng/kg/min and a significant vasoconstriction of approximately 34% at the dose of 80 ng/kg/min (p < 0.05; see Figure 2).

---

**TABLE 1.** Baseline Levels of Forearm Blood Flow and Mean Arterial Pressure and Heart Rate Values Before and After the Various Infusions

<table>
<thead>
<tr>
<th>Infusion*</th>
<th>No. of subjects</th>
<th>Basal FBF (ml/dl/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Saline</td>
<td>6</td>
<td>2.3 ± 0.4</td>
<td>77 ± 3</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>5-HT</td>
<td></td>
<td>0.1</td>
<td>2.4 ± 0.6</td>
<td>79 ± 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3</td>
<td>2.4 ± 0.5</td>
<td>79 ± 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>3.0 ± 0.4</td>
<td>81 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>4.0 ± 0.4</td>
<td>82 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>3.8 ± 0.4</td>
<td>83 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>3.8 ± 0.4</td>
<td>85 ± 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td>4.0 ± 0.4</td>
<td>85 ± 1</td>
</tr>
<tr>
<td>KET</td>
<td></td>
<td>5</td>
<td>3.0 ± 0.5</td>
<td>84 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>3.9 ± 0.8</td>
<td>83 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
<td>3.4 ± 0.5</td>
<td>84 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125</td>
<td>2.2 ± 0.2</td>
<td>83 ± 4</td>
</tr>
<tr>
<td>KET, 5, +5-HT, 1</td>
<td>6</td>
<td>2.0 ± 0.3</td>
<td>82 ± 4</td>
<td>79 ± 4</td>
</tr>
<tr>
<td>KET, 50, +5-HT, 1</td>
<td>6</td>
<td>2.8 ± 0.2</td>
<td>78 ± 4</td>
<td>76 ± 4</td>
</tr>
<tr>
<td>KET, 125, +5-HT, 1</td>
<td>6</td>
<td>3.8 ± 0.4</td>
<td>82 ± 4</td>
<td>80 ± 4</td>
</tr>
<tr>
<td>KET, 50, +5-HT, 80</td>
<td>5</td>
<td>5.4 ± 0.9</td>
<td>85 ± 3</td>
<td>89 ± 3</td>
</tr>
<tr>
<td>PROP</td>
<td></td>
<td>6</td>
<td>3.1 ± 0.6</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>PROP +5-HT, 1</td>
<td>6</td>
<td>3.9 ± 0.6</td>
<td>83 ± 3</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>METH + SNP</td>
<td>7</td>
<td>2.9 ± 0.4</td>
<td>77 ± 2</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>TYR + SNP</td>
<td>7</td>
<td>3.0 ± 0.4</td>
<td>77 ± 3</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>5-HT + SNP</td>
<td>7</td>
<td>2.5 ± 0.3</td>
<td>77 ± 3</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>METH + SNP + KET, 5</td>
<td>7</td>
<td>3.1 ± 0.5</td>
<td>77 ± 2</td>
<td>80 ± 2</td>
</tr>
<tr>
<td>TYR + SNP + KET, 5</td>
<td>7</td>
<td>2.9 ± 0.5</td>
<td>79 ± 2</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>5-HT + SNP + KET, 5</td>
<td>7</td>
<td>2.8 ± 0.5</td>
<td>78 ± 2</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>METH + KET, 50</td>
<td>7</td>
<td>3.2 ± 0.5</td>
<td>80 ± 3</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>TYR + KET, 50</td>
<td>7</td>
<td>3.5 ± 0.7</td>
<td>79 ± 2</td>
<td>82 ± 2</td>
</tr>
<tr>
<td>5-HT + KET, 50</td>
<td>7</td>
<td>2.8 ± 0.6</td>
<td>78 ± 2</td>
<td>82 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SEM. FBF = forearm blood flow; 5-HT = serotonin; KET = ketanserin; PROP = propranolol; METH = methoxamine; TYR = tyramine; SNP = sodium nitroprusside.

*Doses of 5-HT and KET are given in ng/kg/min.
VASCULAR EFFECTS OF 5-HT AND KETANSERIN/Blauw et al. 259

Simultaneous Infusions of Serotonin and Ketanserin

Percent changes of FBF during the combined infusions of 5-HT and ketanserin are shown in Figure 4. Ketanserin (5 and 50 ng/kg/min) did not significantly influence the increase of FBF induced by a low dose of 5-HT (1 ng/kg/min), whereas this effect was slightly enhanced by ketanserin (125 ng/kg/min; \( p < 0.05, n = 6 \)). However, ketanserin (50 ng/kg/min) reversed the vasoconstriction induced by 5-HT given in the vasoconstrictor dosage (80 ng/kg/min; \( p < 0.05, n = 5 \); see Figure 4).

Cumulative Dose Infusions of Serotonin, Methoxamine, and Tyramine Together with Sodium Nitroprusside and Ketanserin

Percent changes in FBF during these infusions are shown in Figures 5 and 6. In the presence of SNP (3 ng/kg/min) a dose-dependent decrease of FBF was induced by methoxamine (\( p < 0.001 \); see Figure 5), tyramine (\( p < 0.001 \); see Figure 5), and 5-HT (NS; see Figure 6), respectively. Ketanserin (5 ng/kg/min) together with SNP slightly but significantly attenuated the vasoconstriction induced by methoxamine and tyramine (\( p < 0.001 \) for both; see Figure 5) but had no effect on the 5-HT response (see Figure 6). Ketanserin (50 ng/kg/min) further attenuated the response of methoxamine and tyramine (\( p < 0.001 \) for both; see Figure 5) and reversed the vasoconstrictor response to 5-HT (\( p < 0.001 \); see Figure 6).

Simultaneous Infusions of Serotonin and Propranolol

The vasodilatation induced by 5-HT (1 ng/kg/min) was not influenced by propranolol administration (change in FBF, 70 ± 16% before and 67 ± 10% after propranolol administration; \( n = 6, \text{ NS} \)). Furthermore, the initial transient increase of FBF caused by 5-HT was not influenced by \( \beta \)-blockade.

Effects on the Forearm and Skin Temperature

In all subjects the infusions of methoxamine induced local piloerection of the skin, which was not statistically significant changes from the dose of 15 ng/kg/min onward, as shown in Figure 3.

Simultaneous Infusions of Serotonin and Ketanserin

Percent changes of FBF during the combined infusions of 5-HT and ketanserin are shown in Figure 4. Ketanserin (5 and 50 ng/kg/min) did not significantly influence the increase of FBF induced by a low dose of 5-HT (1 ng/kg/min), whereas this effect was slightly enhanced by ketanserin (125 ng/kg/min; \( p < 0.05, n = 6 \)). However, ketanserin (50 ng/kg/min) reversed the vasoconstriction induced by 5-HT given in the vasoconstrictor dosage (80 ng/kg/min; \( p < 0.05, n = 5 \); see Figure 4).

Cumulative Dose Infusions of Serotonin, Methoxamine, and Tyramine Together with Sodium Nitroprusside and Ketanserin

Percent changes in FBF during these infusions are shown in Figures 5 and 6. In the presence of SNP (3 ng/kg/min) a dose-dependent decrease of FBF was induced by methoxamine (\( p < 0.001 \); see Figure 5), tyramine (\( p < 0.001 \); see Figure 5), and 5-HT (NS; see Figure 6), respectively. Ketanserin (5 ng/kg/min) together with SNP slightly but significantly attenuated the vasoconstriction induced by methoxamine and tyramine (\( p < 0.001 \) for both; see Figure 5) but had no effect on the 5-HT response (see Figure 6). Ketanserin (50 ng/kg/min) further attenuated the response of methoxamine and tyramine (\( p < 0.001 \) for both; see Figure 5) and reversed the vasoconstrictor response to 5-HT (\( p < 0.001 \); see Figure 6).

Simultaneous Infusions of Serotonin and Propranolol

The vasodilatation induced by 5-HT (1 ng/kg/min) was not influenced by propranolol administration (change in FBF, 70 ± 16% before and 67 ± 10% after propranolol administration; \( n = 6, \text{ NS} \)). Furthermore, the initial transient increase of FBF caused by 5-HT was not influenced by \( \beta \)-blockade.

Effects on the Forearm and Skin Temperature

In all subjects the infusions of methoxamine induced local piloerection of the skin, which was not
influenced by the infusions of ketanserin. Piloerection was also seen in five subjects during the infusions of tyramine. The highest dose of 5-HT caused erythema of the skin of the forearm in all subjects and a burning sensation and itching in three subjects. These effects completely disappeared within 10 to 15 minutes after discontinuation of the infusion. Erythema was markedly less when 5-HT was infused together with ketan-
serin (50 ng/kg/min). No significant changes in skin temperature were observed.

Discussion

5-HT induced a complex vascular response in the forearm, in which two phases could be distinguished: a transient, rapid vascular relaxation within the first few minutes after the start of the infusion, followed by a gradual vasodilatation for the lower doses of 5-HT and a vasoconstriction for the highest dose of 5-HT. These vascular responses were mediated by local effects of 5-HT in the forearm vasculature, since relevant changes in intra-arterial BP or HR were not observed.

The initial rapid and transient vasodilator response was evoked by all doses of 5-HT, without a clear dose dependency (see Figure 1). Similar effects of intra-arterially infused 5-HT were shown by Roddie et al., but the explanation is still open to speculation. From the present study it can be concluded only that β-adrenergic receptors and 5-HT_2 receptors were not involved, since this initial response was influenced neither by propranolol nor by ketanserin. A possible explanation for this phenomenon is a 5-HT-triggered release of endothelium-derived relaxing factor (EDRF) although in that case a dose-dependent phenomenon would have been expected. Involvement of the cholinergic nervous system should also be considered, since there is convincing evidence that 5-HT can increase cholinergic activity and that stimulation of cholinergic nerves can induce vasodilatation in this vascular bed. In this respect, acetylcholine is an important mediator for the release of EDRF.

The lower doses of 5-HT produced a net increase in FBF, and FBF was reduced only at very high doses of 5-HT (see Figure 2). These findings suggest that more
than one 5-HT receptor subtype is present in the forearm vascular bed. From animal experiments it is known that ketanserin is a very potent and selective antagonist of 5-HT2 receptors. The reversal by ketanserin of the vasoconstriction evoked by a high dose of 5-HT (see Figures 3 and 6) strongly suggests that this constrictor response was mediated by 5-HT2 receptors. The 5-HT2-antagonistic potency of ketanserin in humans has been shown only for the inhibition of platelet aggregation, and to our knowledge the present experiments are the first demonstration of 5-HT2 receptor antagonism by ketanserin in a human vascular bed in vivo.

The resistance of the 5-HT-evoked vasodilatation to 5-HT2 blockade (see Figure 4) suggests the presence of a different 5-HT receptor subtype in the peripheral vascular bed of the forearm. Based on the literature it seems most likely that so-called 5-HT1-like receptors are involved in this vasodilator response to low doses of 5-HT. These 5-HT1-like receptors are thought to be located on endothelial cells, where they appear to trigger the release of EDRF upon stimulation. Another mechanism involved in the 5-HT-mediated vascular relaxation could be the inhibition of norepinephrine release from sympathetic nerve terminals by presynaptic 5-HT1A-like receptors. In the present study ketanserin enhanced the 5-HT-induced vasodilatation (see Figure 4). This finding suggests that low doses of 5-HT stimulate 5-HT2 receptors, but this effect is masked by the prevailing vasodilatation. This 5-HT2 receptor stimulation by low doses of 5-HT could have pathophysiological relevance. Since propranolol had no effect on the 5-HT-induced vasodilatation, the involvement of β-adrenergic receptors was excluded.

It had previously been calculated that during the infusions of the vasodilator doses of 5-HT (0.1–10 ng/kg/min) the 5-HT plasma concentrations in the forearm were in the range of 2 to 20 nM. Recently, Anderson et al. have shown that under physiological circumstances the plasma concentration of free 5-HT is about 2 nM. Therefore, the main conclusion from the present experiments with 5-HT in healthy volunteers must be that this biogenic amine acts predominantly as a vasodilator, probably as a result of 5-HT2-like receptor stimulation, and that only at very high doses can a net vasoconstriction, mediated by 5-HT2 receptor stimulation, be expected.

Local infusion of ketanserin elicited a dose-dependent vasodilatation in the forearm (see Figure 3). Since ketanserin is known to have an affinity for 5-HT2 receptors as well as for α1-adrenergic receptors, blockade of either receptor population potentially can be held responsible for this vasodilatation. In the present study the α1-adrenergic blocking effect of ketanserin was confirmed by the finding that it significantly reduced the vasoconstrictor response to the selective α1-agonist methoxamine. Similar results were found for tyramine, which acts as an indirect agonist of α-adrenergic receptors by displacing norepinephrine from the sympathetic nerve endings, thus providing evidence that ketanserin also is able to counteract a vasoconstrictor response induced by endogenously released norepinephrine.

Although the α1-blocking effect of ketanserin has been regarded as weak by several investigators, the present study clearly showed that this effect of ketanserin in this particular vascular bed occurred at lower doses than are needed for 5-HT2 blockade (see Figures 5 and 6). Since it was demonstrated that 5-HT evokes mainly a vasodilator response in the forearm and that ketanserin is a more potent antagonist of α1-adrenergic receptors than of 5-HT2 receptors in this particular vascular bed, it seems very likely that α1-blockade is responsible for the observed vasodilatation.

This peripheral α1-antagonism of ketanserin can explain its antihypertensive effects in humans, which are still controversial. Our findings do not support an important role for 5-HT2 receptor blockade as an explanation of the antihypertensive effect of ketanserin in uncomplicated hypertension and favor the relevance of α1-blockade in this respect. This view is in accordance with the study of Hosie et al., who found that the selective 5-HT2 antagonist ritanserin, which is devoid of α1-adrenergic receptor blocking activity, does not lower blood pressure in humans. However, in elderly and hypertensive subjects the effect of ketanserin could be different.

This study showed that 5-HT acts mainly as a vasodilator in healthy volunteers, probably as a result of 5-HT2-like receptor stimulation. Only at very high doses of 5-HT was vasoconstriction observed, mediated by 5-HT2 receptor stimulation. β-Adrenergic receptors did not seem to be involved in the vascular response to 5-HT. The 5-HT2 antagonist ketanserin proved to be a more potent antagonist of α1-adrenergic receptors than of 5-HT2 receptors in the vascular bed of the forearm.

Acknowledgments

We appreciate the technical assistance of Tobias A. Bruning and Jacques de Groot, the advice about statistical analysis from Jo Hermans, Ph.D., and the secretarial help of Annelies E.C. van der Geest. Ketanserin ampules were kindly supplied by Janssen Pharmaceuticals, Goirle, The Netherlands.

References

classification and nomenclature of functional receptors for 5-
receptors for 5-hydroxytryptamine. Trends Pharmacol Sci
1986;7:3-4
New York: Raven Press, 1985:95-112
10. Houston DS, Vanhoute PM. Serotonin and the vascular sys-
tem: role in health and disease, and implications for therapy.
Drugs 1986;31:149-163
11. Van Nueten JM, Leysen JE, De Clerck F, Vanhoute PM.
Serotonergic receptor subtypes and vascular reactivity. J Car-
diovasc Pharmacol 1984;6:5546-5574
12. Van Nueten JM, Janssen PAM, Van Beek J, Xhonneux R,
Verbeuren TJ, Vanhoute PM. Vascular effects of ketanserin
(R41 468B, a novel antagonist at 5-HT2 receptors). J Phar-
macol Exp Ther 1981;218:217-230
13. Leysen JE, Awouter SF, Kennis L, Laduron PM, Vandenberk
J, Janssen PAM. Receptor binding profile of R41 468B, a novel
antagonist at 5-HT2 receptors. Life Sci 1981;28:1015-
1022
14. Leysen JE, Gommeren W, Van Gongel P, Janssen PM,
Laduron PM. Receptor binding properties in vitro and in vivo
of ritalasin: a very potent and long acting serotonin-2 antago-
nist. Mol Pharmacol 1985;27:600-611
15. Cohen ML, Fuller RW, Kurz KD. Evidence that blood pres-
sure reduction by serotonin antagonists is related to alpha re-
ceptor blockade in spontaneously hypertensive rats. Hyperten-
sion 1983;5:676-681
16. Connor HE, Feniuk W, Humphrey PPA, Perren MJ. 5-Carbox-
amidotryptamine is a selective agonist at 5-hydroxytryptamine
receptors mediating vasodilation and tachycardia in anaes-
thetized cats. Br J Pharmacol 1986;87:417-426
17. Verduw PD, Jennewein HM, Mierau J, Saxena PR. N-(3-
Acetylaminopropyl) piperazine hydrochloride (BEA 1654), a
putative 5-HT2 agonist, causes constriction of arterovenous
anastomoses and dilatation of arterioles. Eur J Pharmacol
1985;107:337-346
18. Fozard JR, Mir AK, Middlemiss DN. Cardiovascular response
to 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in
the rat: site of action and pharmacological analysis. J Cardio-
vasc Pharmacol 1987;9:328-347
19. Fozard JR. MDL 72.222: a potent and highly selective antago-
nist of cardiovascular 5-hydroxytryptamine receptors.
Naunyn Schmiedebergs Arch Pharmacol 1984;326:36-44
20. Kalkman HO, Timmermans PBMWM, Van Zwieten PA.
Characterization of the antihypertensive properties of ketan-
serin (R41 468B) in rats. J Pharmacol Exp Ther 1982;222:
227-231
that vascular serotonin receptors are of the 5-HT2 type. Bio-
chem Pharmacol 1983;32:567-570
22. Vanhoute PM, Ball SG, Berdeaux A, et al. Mechanism of
action of ketanserin in hypertension. Trends Pharmacol Sci
1986;7:58-59
23. Wenting GJ, Willeitze AJJ, Man in’t Veld AJ, Schalekamp
MADH. 5-HT, alpha-adrenoceptors, and blood pressure: ef-
ects of ketanserin in essential hypertension and autonomic
insufficiency. Hypertension 1986;100-109
24. Reimann IW, Fröhlich JC. Mechanism of antihypertensive
25. Stokes GS, Menne BA, Marwood JF. Ketanserin and prazo-
sin: a comparison of antihypertensive and biochemical effects.
26. Mecca FE, Webb RC. Serotonin and vasodilatation. Bibl Car-
diol 1984;38:81-90
27. Göttler M. Serotonin receptors in the circulatory system. Prog
Pharmacol 1986;8:156-172
28. Chang PC, van Brummelen P. Calibration and variability of
forearm blood flow, measured by strain gauge plethysmogra-
phy. J Cardiovasc Pharmacol 1987;10(suppl 5):S123-
S125
29. Chang PC, Verlinde R, Bruning T, van Brummelen P. A
microcomputer based R-wave triggered system for hemody-
(in press)
30. Cohen RA, Shepherd J, Vanhoute PM. 5-Hydroxytryptamine
can mediate endothelium dependent relaxation of coronary
31. Angus JA, Cocks TM. Role of endothelium in vascular re-
sponses to norepinephrine, serotonin and acetylcholine. Bibl
Cardiol 1984;38:43-52
32. Cocks TM, Angus JA. Endothelium dependent relaxation of
coronary arteries by noradrenaline and serotonin. Nature
1983;305:627-630
33. Kalkman HO, Engel G, van Hoyder D. Three distinct subtypes
of serotonergic receptors mediate the triphasic blood pressure
response to serotonin in rats. J Hypertens 1984;2(suppl 3)::
143-145
34. Richardson BP, Engel G, Donatsh P, Stadler PA. Identification
of serotonin M-receptor subtypes and their specific block-
ade by a new class of drugs. Nature 1985;316:126-131
35. Fozard JR. Neutral 5-HT receptors in the periphery. Neurophar-
camology 1984;23(12B):1473-1486
Br J Pharmacol Chemother 1959;12:232-328
37. Blair DA, Glover WE, Greenfeld ADM, Roddie IC. Excita-
tion of cholinergic vasodilator nerves to human skeletal mus-
cles during emotional stress. J Physiol (Lond) 1959;154:633-
647
38. Goldstein DS, Keiser HR. Pressor and depressor responses after
endothelium blockage in humans. Am Heart J 1984;107:
974-979
relaxant factor: identification of the art lecture. Hypertension 1985;
31:94-100
40. Furcht RF, Jothianandan D, Cherry PD. Endothelium-de-
dependent responses: the last three years. Bibl Cardiol 1984;38:
1-15
41. Arnaut J, Van Russelt M, De Caille J, et al. Platelet hyper-
sensitivity to serotonin after prolonged ketanserin intake? J Car-
diovasc Pharmacol 1983;7(suppl 7):S302-322
42. Leysen JE, De Chaffoy de Courcelles D, De Clerck F, Nieme-
geers CJE, Van Nueten JM. Serotonin-S 2 receptor binding
sites and functional correlates. Neuropharmacology 1984;
23(12B):1493-1501
43. Vanhoute PM, Lüscher TF. Serotonin and the blood vessel
44. Kalkman HO, Timmermans PBMWM, Van Zwieten PA.
Characterization of the antihypertensive properties of ketan-
serin (R41 468B) in rats. J Pharmacol Exp Ther 1982;222:
227-231
45. Cohen ML, Mason N, Wiley KS, Fuller RW. Further evidence
that vascular serotonin receptors are of the 5-HT2 type. Bio-
chem Pharmacol 1983;32:567-570
46. Vanhoute PM, Bag SG, Berdeaux A, et al. Mechanism of
action of ketanserin in hypertension. Trends Pharmacol Sci
1986;7:58-59
47. Wenting GJ, Willeitze AJJ, Man in’t Veld AJ, Schalekamp
MADH. 5-HT, alpha-adrenoceptors, and blood pressure: ef-
ects of ketanserin in essential hypertension and autonomic
insufficiency. Hypertension 1986;100-109
48. Reimann IW, Fröhlich JC. Mechanism of antihypertensive
49. Stokes GS, Menne BA, Marwood JF. Ketanserin and prazo-
sin: a comparison of antihypertensive and biochemical effects.
50. Mecca FE, Webb RC. Serotonin and vasodilatation. Bibl Car-
diol 1984;38:81-90
51. Göttler M. Serotonin receptors in the circulatory system. Prog
Pharmacol 1986;8:156-172
52. Chang PC, van Brummelen P. Calibration and variability of
forearm blood flow, measured by strain gauge plethysmogra-
phy. J Cardiovasc Pharmacol 1987;10(suppl 5):S123-
S125
53. Chang PC, Verlinde R, Bruning T, van Brummelen P. A
microcomputer based R-wave triggered system for hemody-

Regional vascular effects of serotonin and ketanserin in young, healthy subjects.
G J Blauw, P van Brummelen, P C Chang, P Vermeij and P A van Zwieten

Hypertension. 1988;11:256-263
doi: 10.1161/01.HYP.11.3.256

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/11/3/256

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/