Evidence that Serotonin Receptors Mediate the Cutaneous Vasoconstriction Produced by 5-Hydroxytryptamine in Canine Forelimbs

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SUMMARY. The effects of local intra-arterial infusions of serotonin (5 or 25 \( \mu \)g base/min) or norepinephrine (1 or 5 \( \mu \)g base/min) on cutaneous (skin) and skeletal muscle vasculatures were investigated in canine forelimbs perfused at constant flow in dogs anesthetized with pentobarbital. Norepinephrine produced dose-related constriction of the skin and skeletal muscle vasculatures. In the cutaneous vascular circuit, norepinephrine produced large artery, small vessel, and large vein constriction. The increase in cutaneous vascular resistance was primarily due to an increase in small vessel resistance. Serotonin did not increase skeletal muscle vascular resistance but produced marked cutaneous vasoconstriction subsequent to large artery and large vein constriction. The small vessels, if anything, tended to dilate. The skin and skeletal muscle vascular responses to serotonin and norepinephrine were similar in innervated and acutely denervated forelimbs. Phentolamine pretreatment completely blocked all vascular actions of norepinephrine, and largely inhibited the cutaneous vasoconstriction produced by the infusion of the low dose of serotonin. However, the cutaneous large artery and large vein constriction produced by the infusion of the high dose of serotonin was not affected by phentolamine pretreatment. Cyproheptadine pretreatment blocked or largely inhibited the cutaneous vasoconstriction produced by serotonin only in doses which also inhibited norepinephrine and vasopressin cutaneous vasoconstriction. Pretreatment with methysergide blocked or largely inhibited the cutaneous large artery and large vein constriction produced by infusions of serotonin. Norepinephrine and vasopressin produced significant vasoconstriction in the presence of methysergide. These data suggest that the cutaneous large artery and large vein constriction produced by serotonin is not due to the activation of postjunctional \( \alpha \)-adrenergic receptors. Instead, serotonin stimulates a cutaneous 5-hydroxytryptamine vascular receptor which is selectively inhibited by methysergide but not by cyproheptadine. Phentolamine is a weak antagonist of the cutaneous vascular 5-hydroxytryptamine receptor.


THE actions of serotonin on canine forelimb total and segmental (large artery, small vessel, and large vein) vascular resistances in skin (cutaneous) and skeletal muscle were originally characterized by Haddy et al., 1957, and these findings have been repeatedly confirmed and extended by other investigators (Abboud, 1968; Daugherty et al., 1968; Merrill et al., 1974). In naturally perfused canine forelimbs, local intra-arterial infusions of serotonin produce only small increases in total resistance to blood flow, except at high infusion rates. Total vascular resistance in the skin vasculature is, however, markedly increased. The large arteries and large veins are preferentially constricted by serotonin (Abboud, 1968; Daugherty et al., 1968; Haddy et al., 1957; Merrill et al., 1974) in this vascular circuit. Small vessel resistance is either not affected, or slightly increased, subsequent to a decrease in transmural pressure. In the skeletal muscle circuit, serotonin may either constrict or dilate the vasculature subsequent to actions on the small vessels (Daugherty et al., 1968; Emerson et al., 1973; Haddy et al., 1959). Serotonin consistently produces large artery and large vein constriction in the cutaneous vascular bed irrespective of the level of initial vascular tone. Both \( \alpha \)-adrenergic and serotonergic mechanisms have been implicated in the vasoconstriction produced by serotonin (Apperley et al., 1980; Curro et al., 1978). However, in the canine forelimb, pharmacological blocking agents have not been utilized previously to determine the mechanism(s) of serotonin's vasoconstrictor action in the cutaneous vasculature.

In this study, the actions of serotonin on total and segmental vascular resistances in the cutaneous circuit were compared and contrasted to those produced by norepinephrine in the canine forelimb. Constant controlled flow conditions, denervation, \( \alpha \)-adrenergic and serotoninergic blocking agents were utilized to characterize more completely the cutaneous vascular constrictor actions of serotonin in the canine forelimb.

Methods

Mongrel male dogs with an average weight of 22 kg (range 17-27 kg) were anesthetized with sodium pento-
barbital (30 mg/kg) and ventilated with room air, using a Harvard respirator.

**Hemodynamic Measurements**

The skin of the right forelimb was circumferentially sectioned 3–4 cm above the elbow. The right brachial artery, forelimb nerves, brachial and cephalic veins were isolated, and the muscles and remaining connective tissues were sectioned by electrocautery. The humerus was cut and the ends of the marrow cavity packed with bone wax to prevent blood loss. Blood entered the limb only through the brachial artery and exited only through the brachial and cephalic veins. The forelimb nerves (median, ulnar, radial, and musculocutaneous) were left intact and coated with an inert silicone spray to prevent drying. Heparin (300 U/kg) was administered intravenously to prevent clotting.

Intravascular pressures were measured with small-bore polyethylene tubing inserted into the following sites: (1) skin small artery from the third superficial volar metacarpal artery on the ventral surface of the paw, (2) skin small vein from the second superficial dorsal metacarpal vein on the dorsal surface of the paw, (3) skin large vein from the cephalic vein via a side branch, and (4) muscle large vein from the brachial vein via a side branch. The small artery catheters were inserted in a downstream direction, whereas the small vein catheters were directed upstream from the site of insertion. The cannulated small vessel acts as an extension of the catheter and thus a pressure is measured in the immediate vessel or vessels to which the cannulated vessel connects. This pressure is a true lateral pressure as long as the cannulated vessel is patent and without valves (verified by the ability to freely withdraw blood from and to flush saline into the cannulated vessel). The presence of the catheter does not measurably alter the pressure in the arterial or venous system because, in the canine forelimb, the cannulated vessel is a negligible fraction of the total cross-sectional area of the arterial or venous bed, and there are abundant artery-to-artery and vein-to-vein anastomoses. Pressures were measured with low volume displacement Statham transducers and recorded on a Hewlett-Packard direct-writing oscillograph.

The brachial and cephalic veins were partially transected 3–5 cm downstream from the tip of large vein pressure catheters, and the end of each vessel was cannulated with a short section of polyethylene tubing (P.E. 320). Outflow from both veins was directed into a reservoir maintained at constant volume with a variable speed pump which continuously returned blood to the animal via a cannulated jugular vein. In this preparation, the median cubital vein represents the major anastomotic channel between the brachial and cephalic vein. This vessel was ligated in all experiments to ensure that brachial venous flow was predominantly from muscle and that cephalic venous flow was primarily from skin.

A Masterflex roller pump was used to pump-perfuse the brachial artery at a constant flow rate with femoral arterial blood. Blood flow was maintained throughout the experiment at a constant rate achieved by perfusing the forelimb at a pressure just slightly less than mean aortic pressure. Perfusion pressure was measured by cannulating the brachial artery via a side branch with small bore polyethylene tubing downstream from the tip of the catheter used to perfuse the brachial artery. Mean aortic pressure was measured from a catheter inserted into the brachial or carotid arteries.

**Results**

**Hemodynamics**

**Innerveated Forelimbs**

Norepinephrine (Table 1; Figs. 1–6). Local intraarterial infusions of norepinephrine (1 or 5 µg base/min) produced marked dose-dependent increases in perfusion pressure, small vein pressure, skin vascular resistance, and skeletal muscle vascular resistance in forelimbs perfused at constant flow. The skin (cutaneous) vasculature constricted proportionately...
more than the skeletal muscle vaculature, resulting in small dose-related shifts in blood flow from skin to skeletal muscle. The increase in total skin vascular resistance was due to large artery, large vein, and especially small vessel constriction.

Serotonin (Table 2; Figs. 1–6). Local intra-arterial infusions of serotonin (5 or 25 μg base/min) produced marked dose-dependent increases in perfusion pressure, small vein pressure, and cutaneous vascular resistance. Skeletal muscle vascular resistance was little affected by these infusion rates of serotonin. The increase in total vascular resistance in the cutaneous circuit was exclusively due to large artery and large vein constriction. The small vessels, if anything, tended to dilate. The differential action of serotonin on the skin and skeletal muscle vaculatures resulted in marked dose related shifts in blood flow from skin to skeletal muscle.

Denervated Forelimbs

Norepinephrine (Table 1; Figs. 1–6). Local intra-arterial infusions of norepinephrine (1 or 5 μg base/min) into denervated canine forelimbs perfused at constant flow produced effects similar to that in innervated forelimbs. The skeletal muscle vasoconstriction was more intense, whereas the cutaneous vasoconstriction was slightly less intense in the denervated forelimbs, resulting in smaller shifts in blood flow from skin to skeletal muscle. The low dose of norepinephrine failed to constrict the large veins in the denervated forelimbs though the high dose of this agent produced marked large vein constriction under these conditions.

Serotonin (Table 2; Figs. 1–6). Local intra-arterial infusions of serotonin (5 or 25 μg base/min) into denervated forelimbs perfused at constant flow pro-
duced effects very similar to those in innervated forelimbs. The cutaneous and skeletal muscle vasoconstriction was slightly greater in denervated than in innervated forelimbs. In the denervated cutaneous vasculature, the large artery constriction was slightly enhanced and the large vein constriction was slightly reduced, compared with responses in the innervated forelimb.

Phentolamine Treatment

Norepinephrine (Table 1; Figs 1–6). Phentolamine treatment completely inhibited all arterial and venous vascular actions produced by local intra-arterial infusions of norepinephrine (1 or 5 μg base/min, ia) into innervated canine forelimbs perfused at constant flow.

Serotonin (Table 2; Figs. 1–6). The vascular responses produced by local intra-arterial infusions of the low dose of serotonin (5 μg base/min) into innervated canine forelimbs perfused at constant flow were largely inhibited by phentolamine treatment. However, phentolamine treatment failed to alter the cutaneous vasoconstriction produced by local intra-arterial infusions of high doses of serotonin (25 μg base/min). Phentolamine treatment decreased forelimb cutaneous vascular resistance but increased skeletal muscle vascular resistance. Under these conditions, the local intra-arterial infusion of the high dose of serotonin produced marked vasodilation of the skeletal muscle vasculature. This active skeletal muscle vasodilation resulted in smaller increases in forelimb perfusion pressure during the local infusion of serotonin than in innervated or denervated forelimb.

Cyproheptadine Treatment (Tables 1 and 2; Figs. 1–6)

Cyproheptadine (400 μg/min) treatment largely or partially inhibited the canine forelimb vasoconstriction produced by local intra-arterial infusions of norepinephrine (1 or 5 μg base/min) or serotonin (5 or 25 μg base/min) into innervated forelimbs perfused at constant flow. Cyproheptadine inhibited or reduced both the large artery and large vein constriction produced by serotonin. Vasopressin (0.8 P.U./min) significantly increased perfusion pressure from 125 ± 6 to 199 ± 11 mm Hg in innervated forelimbs, but not in animals treated with cyproheptadine (n = 6). The lower infusion rates of cypro-
heptadine (100 or 200 µg/min) failed to prevent the vascular changes produced by either norepinephrine, serotonin, or vasopressin.

**Methysergide Treatment (Tables 1 and 2; Figs. 1–6)**

Pretreatment with methysergide largely prevented the increase in cutaneous large artery and large vein resistance produced by local intra-arterial infusions of serotonin (5 or 25 µg base/min). In contrast, norepinephrine (1 or 5 µg base/min) and vasopressin (0.8 P.U./min) produced cutaneous vasoconstriction in the presence of methysergide. Vasopressin (0.8 P.U./min) significantly increased perfusion pressure from 127 ± 6 to 197 ± 10 mm Hg in innervated forelimbs, and from 195 ± 5 mm Hg to 280 ± 12 mm Hg in animals treated with methysergide (n = 6).

Brachial and cephalic large vein pressures averaged less than 5 mm Hg in all studies reported in this manuscript. These pressures were only slightly changed (<5 mm Hg) when flow shifted between skin and muscle. Large vein pressure fell when flow was reduced and increased when flow increased. In contrast, small vein pressures were markedly increased by serotonin and norepinephrine (Tables 1 and 2). In the interest of economy, large vein pressures were not included in the tables, but were utilized in the calculations of total and segmental vascular resistances.

**Discussion**

It is now well documented that a variety of agonists, including serotonin, may modulate norepi-
nephrine release from adrenergic nerve terminals via actions on presynaptic receptors (Langer, 1980). The presynaptic action of serotonin is usually reported to suppress adrenergic neurotransmitter release elicited during sympathetic nerve stimulation (McGrath, 1977; Watts et al., 1981; Feniuk et al., 1979; Martinez and Lokhandwala, 1980). However, in certain tissues and in certain species, serotonin facilitates adrenergic neurotransmitter release (Fozard and Leach, 1968; Fozard and Mwaluko, 1976). Moreover, high concentrations of serotonin will displace norepinephrine from neuronal storage vesicles, and the displaced transmitter may then interact with adrenoceptors located pre- or postjunctionally (Trendelenburg, 1972). In this study, acute denervation and phentolamine were used to determine whether a release of norepinephrine contributed to the cutaneous large artery and large vein constriction produced by serotonin. The presynaptic modulation of norepinephrine release from adrenergic neurons is dependent on a tonic sympathetic discharge. Therefore, if serotonin produced cutaneous vasoconstriction, in part, via a presynaptic release of norepinephrine, acute denervation would be predicted to significantly reduce serotonin-induced cutaneous vasoconstriction. Since the cutaneous vasoconstriction produced by serotonin was not significantly different in innervated and denervated forelimbs, the data suggest that this amine does not elicit a presynaptic release of norepinephrine. This conclusion is supported by the phentolamine data. The failure of phentolamine treatment to significantly reduce the cutaneous vasoconstriction produced by the high dose of serotonin indicates that serotonin does not elicit a release of norepinephrine in amounts sufficient to contribute to the cutaneous vasoconstriction. The unique pattern of vasoconstriction produced by serotonin also supports this conclusion. Serotonin primarily increases cutaneous large artery resistance and, if anything, usually dilates the skeletal muscle vasculature. Norepinephrine produces primarily small vessel constriction in both the cutaneous and skeletal muscle vasculatures. This conclusion is in agreement with that of other investigators. Feniuk et al. (1981) demonstrated that serotonin produces a marked presynaptic inhibition of adrenergic neurotransmitter release in the femoral arterial vascular bed of the dog via stimulation of specific presynaptic serotonin receptors. It has also been shown that serotonin produces a presynaptic inhibition of norepinephrine release in isolated femoral artery and saphenous vein preparations (Watts et al., 1981; Apperley et al., 1980). Thus, it is concluded that serotonin produces cutaneous vasoconstriction in the canine forelimb subsequent to the stimulation of postsynaptic large artery and large vein vascular receptors.

In numerous other studies and in this study, it has been demonstrated that phentolamine antagonizes serotonin-induced contractions of arterial and venous smooth muscle (Humphrey, 1978; Apperley et al., 1976; Curro et al., 1978). This observation may be explained in two ways. One, serotonin may directly stimulate postjunctional \( \alpha \)-adrenergic receptors. Two, the postjunctional cutaneous vascular \( \alpha \)-adrenergic and serotonin receptors may be distinct, yet structurally similar, and phentolamine may block both of these vascular receptors. The findings from the present study strongly suggest that serotonin's cutaneous vasoconstrictor action is not mediated by the stimulation of postjunctional \( \alpha \)-adrenergic receptors, since the pattern of responses elicited during \( \alpha \)-adrenergic stimulation was different from that produced by serotonin. Norepinephrine produces marked increases in blood flow resistance in the cutaneous vascular circuit primarily by producing...
TABLE 2
Effects of Local Intra-arterial Infusions of Saline or Serotonin on Mean ±SE Vascular Pressures and Blood Flows in Canine Forelimbs Perfused at a Constant Pump-Controlled Flow Rate

<table>
<thead>
<tr>
<th>Condition</th>
<th>Perfusion pressure (mm Hg)</th>
<th>Skin small artery pressure (mm Hg)</th>
<th>Skin small vein pressure (mm Hg)</th>
<th>Brachial venous outflow (ml/min)</th>
<th>Cephalic venous outflow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Innervated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>126 ± 5</td>
<td>93 ± 5</td>
<td>17 ± 1</td>
<td>51 ± 4</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>5-HT, 5</td>
<td>176 ± 9*</td>
<td>92 ± 4</td>
<td>34 ± 2*</td>
<td>70 ± 3*</td>
<td>35 ± 2*</td>
</tr>
<tr>
<td>Control</td>
<td>133 ± 6</td>
<td>95 ± 6</td>
<td>15 ± 1</td>
<td>50 ± 4</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>5-HT, 25</td>
<td>210 ± 9*</td>
<td>55 ± 5*</td>
<td>49 ± 3*</td>
<td>83 ± 4*</td>
<td>27 ± 3*</td>
</tr>
<tr>
<td><strong>Acute denervation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>130 ± 4</td>
<td>72 ± 4</td>
<td>11 ± 1</td>
<td>54 ± 4</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>5-HT, 5</td>
<td>180 ± 7*</td>
<td>47 ± 4*</td>
<td>19 ± 1*</td>
<td>69 ± 7*</td>
<td>37 ± 3*</td>
</tr>
<tr>
<td>Control</td>
<td>128 ± 5</td>
<td>70 ± 4</td>
<td>12 ± 1</td>
<td>53 ± 4</td>
<td>60 ± 3</td>
</tr>
<tr>
<td>5-HT, 25</td>
<td>202 ± 9*</td>
<td>42 ± 3*</td>
<td>25 ± 2*</td>
<td>90 ± 5*</td>
<td>22 ± 2*</td>
</tr>
<tr>
<td><strong>Phentolamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>114 ± 6</td>
<td>55 ± 5</td>
<td>15 ± 1</td>
<td>45 ± 4</td>
<td>80 ± 6</td>
</tr>
<tr>
<td>5-HT, 5</td>
<td>123 ± 4</td>
<td>45 ± 6</td>
<td>16 ± 1</td>
<td>52 ± 5</td>
<td>72 ± 6</td>
</tr>
<tr>
<td>Control</td>
<td>121 ± 3</td>
<td>61 ± 4</td>
<td>15 ± 1</td>
<td>32 ± 3</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>5-HT, 25</td>
<td>152 ± 5*</td>
<td>45 ± 3*</td>
<td>32 ± 3*</td>
<td>72 ± 5*</td>
<td>16 ± 2*</td>
</tr>
<tr>
<td><strong>Cyproheptadine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>86 ± 3</td>
<td>46 ± 1</td>
<td>13 ± 1</td>
<td>70 ± 3</td>
<td>46 ± 1</td>
</tr>
<tr>
<td>5-HT, 5</td>
<td>98 ± 4*</td>
<td>58 ± 4*</td>
<td>18 ± 3*</td>
<td>76 ± 3*</td>
<td>39 ± 1*</td>
</tr>
<tr>
<td>Control</td>
<td>86 ± 3</td>
<td>44 ± 2</td>
<td>14 ± 1</td>
<td>66 ± 3</td>
<td>47 ± 1</td>
</tr>
<tr>
<td>5-HT, 25</td>
<td>102 ± 2*</td>
<td>57 ± 3*</td>
<td>25 ± 3*</td>
<td>87 ± 5*</td>
<td>28 ± 3*</td>
</tr>
<tr>
<td><strong>Methysergide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>195 ± 5</td>
<td>115 ± 4</td>
<td>13 ± 1</td>
<td>84 ± 4</td>
<td>55 ± 3</td>
</tr>
<tr>
<td>5-HT, 5</td>
<td>202 ± 3</td>
<td>123 ± 5</td>
<td>13 ± 1</td>
<td>86 ± 5</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>Control</td>
<td>190 ± 3</td>
<td>115 ± 4</td>
<td>12 ± 1</td>
<td>70 ± 3</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>5-HT, 25</td>
<td>197 ± 4</td>
<td>122 ± 4</td>
<td>15 ± 1</td>
<td>61 ± 4</td>
<td>36 ± 2</td>
</tr>
</tbody>
</table>

5-HT, 5 = serotonin creatinine sulfate, 5 μg base/min, i.a., for 3 minutes (n = 7). 5-HT, 25 = serotonin creatinine sulfate, 25 μg base/min, i.a., for 3 minutes (n = 7). Control = saline infused at the same volume rate as serotonin (n = 7).

* P < 0.05 relative to control value.

small vessel and, inferentially, arteriolar vasoconstriction (Abboud, 1968; Abboud and Eckstein, 1966). In contrast, serotonin fails to actively constrict the cutaneous small vessel segment, but produces intense large artery and large vein vasoconstriction. Activation of postjunctional α-adrenergic receptors by serotonin could not explain the preferential large artery and large vein constriction, and, if anything, the small vessel vasodilation produced by this agent in the cutaneous vascular circuit. Moreover, norepinephrine constricts both skin and skeletal muscle vascularatures, whereas serotonin only constricts the cutaneous vascular circuit under these conditions. It is more reasonable to assume that the cutaneous serotonin vascular receptor is structurally similar to, yet distinct from, the postjunctional vascular α-adrenergic receptor, and that phentolamine may block both serotonin receptors and α-adrenergic receptors in the cutaneous vasculature of the canine forelimb. Although phentolamine prevented the cutaneous large artery and large vein vascular constriction produced by local intra-arterial infusions of the low dose of serotonin, this postjunctional α-adrenergic blocking agent failed to reduce the cutaneous large artery and large vein constriction produced by the local intra-arterial infusion of the high dose of serotonin. This suggests that phentolamine is not a potent antagonist of the cutaneous vasoconstrictor serotonin receptor.

These conclusions are in agreement with that of others (Apperley et al., 1976; Curro et al., 1978). Additionally, it has also been demonstrated that the α-adrenergic receptor-blocking agent tolazoline not only fails to antagonize the contractions of vascular smooth muscle produced by serotonin, but, instead, augmented serotonin-induced contractions of the saphenous vein. The fact that phentolamine treatment did not reduce the cutaneous vasoconstriction produced by the high dose of serotonin, and the unique pattern of vasoconstriction produced by this
The saphenous vein contractions are only weakly antagonized by cyproheptadine and methysergide in vitro studies of canine cutaneous large artery and large vein responses to serotonin. Serotonin elicits contractions of femoral artery and saphenous vein strips in vitro. The femoral artery contractions are specifically antagonized by cyproheptadine and methysergide (Apperley et al., 1980). Curro et al. (1978) reported that methysergide failed to inhibit serotonin-induced contractions of canine saphenous veins. The reasons for the discrepancies are not clear, but in vivo and in vitro actions of vasoactive substances frequently differ. Other investigators have also suggested that classical serotonin receptors are absent in the saphenous vein of the dog (Clement et al., 1969), the cutaneous artery of the rabbit (Apperley et al., 1976), and in rat vasculature (Curro et al., 1978). Perhaps endothelial cells play a role in in vivo responses to serotonin, as with other agents. This possibility warrants further evaluation.

In summary, serotonin constricted large arteries and large veins in the cutaneous vasculature, but failed to constrict small vessels. The cutaneous vasoconstriction was largely inhibited by treatment with methysergide in doses which did not prevent vasoconstriction produced by norepinephrine or vasopressin. Cyproheptadine in high doses produced a nonselective inhibition of the cutaneous vasoconstriction produced by serotonin, norepinephrine, and vasopressin. The serotonin vascular receptors in canine forelimb cutaneous vessels may well be unique in that cyproheptadine, which blocks other actions of serotonin, does not selectively block cutaneous serotonin vascular constrictor receptors.

Methysergide is a more selective antagonist of the cutaneous serotonin vascular constrictor receptor. Phentolamine is also a weak antagonist of the cutaneous serotonin vascular constrictor receptor. Moreover, no blocking agent produced a preferential inhibition of serotonin’s action on cutaneous arteries and veins. Large artery and large vein responses to serotonin were about equally inhibited by the various blocking agents.

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References


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