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COMMENTARY

THE ELUSORY ROLE OF SEROTONIN IN VASCULAR FUNCTION AND DISEASE

PAUL M. VANHOUTTE,* and RICHARD A. COHEN
Department of Physiology and Biophysics, Mayo Clinic and Foundation, Rochester, MN 55905, U.S.A.

Human blood contains 0.1 to 0.3 μg/ml of 5-hydroxytryptamine (serotonin), most of it stored in platelets. Although serotonin obviously reaches all parts of the body, it has no recognized physiological role on blood vessel walls, except as a modulator of platelet function and a contributor to the vascular phase of hemostasis [1–3]. However, attempts have been made to link cardiovascular diseases such as hypertension and vasospasm to the exaggerated liberation of serotonin from aggregating platelets [4–10]. This brief overview focuses on some of the reasons which make establishing such a link a difficult task to the basic scientist and seemingly an impossible one to the clinical researcher.

Complexity of turn-over

Part of the serotonin released by central or peripheral nerves and by chromaffin cells overflows to the capillaries and the plasma. Most of it is removed by the liver, or actively taken up and deaminated by endothelial cells, in particular in the pulmonary circulation. The serotonin escaping hepatic and endothelial metabolism is avidly taken up by the platelets and stored in the dense granules. During platelet aggregation, serotonin is liberated; it accelerates further aggregation by augmenting (potentiating, amplifying, enabling) the effect of most other stimuli which can trigger aggregation [2, 3].

The amounts of serotonin released from aggregating platelets are sufficient to contract the blood vessel wall *in vitro* [11–14]. However, the efficiency of the removal of serotonin from the plasma by non-aggregating platelets and endothelial cells implies that sufficiently high levels of free amine probably are reached only at sites of endothelial lesions where platelet aggregation occurs. Thus, determination of the circulating plasma level of serotonin probably will provide little useful information as long as the sampling cannot be performed at the interface between the aggregating platelets and the immediately surrounding structures, and as long as the normal mechanisms of removal remain opera-

* Author to whom all correspondence should be addressed.

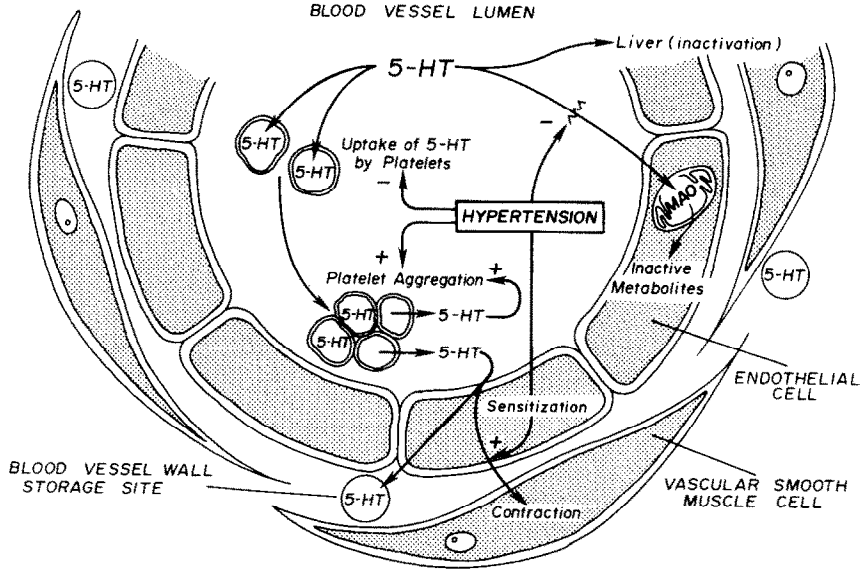

Fig. 1. Effects of high blood pressure on the handling of 5-hydroxytryptamine (5-HT) by platelets and the blood vessel wall. Key: MAO = monoamine oxidase; + = activation; and − = inhibitory effect. (From Ref. 8.)

tive. However, if the platelets take up less serotonin (premature aging?, hypertension?), if the protective enzymatic role of the endothelium is less efficient (abnormal desquamation?, atherosclerosis?, hypertension?), or if the rate of platelet aggregation is accelerated (stress?, endothelial lesions?, hypertension?), one would then predict that serotonin may affect the blood vessel wall *in vivo* (Fig. 1; [8, 10, 11].

Multiplicity of serotonergic binding and/or receptor sites

Serotonergic receptors have received a number of labels which bear no relation to the elicited cellular responses [15–17]. Some of the subclassifications are mainly of historical importance. Thus, Gaddum and Picarelli [18] recognized that the different peripheral actions of 5-hydroxytryptamine are not necessarily antagonized by the same inhibitors, and proposed the subclassification in D- and M-serotonergic receptors, depending on whether the effects of 5-hydroxytryptamine were prevented by dibenamine or morphine respectively. This subdivision probably does not meet current criteria in pharmacology, in view of the many other effects, besides inhibition of serotonergic responses, of the antagonists used [17]. At the current stage of our knowledge, it seems desirable to limit formal identification of subtypes of receptors to those cases where serotonin induces "cellular responses" with pharmacological characteristics identical to those of pharmacologically well defined "binding sites" for the monoamine, rather than relying only on more or less selective pharmacological tools. To judge from experiments on brain tissue, there are at least two pharmacologically distinct and specific binding sites for 5-hydroxytryptamine, which have been labeled 5-HT_1 and 5-HT_2 (or S_1 and S_2), respectively [19–21]. Evidence has been presented which strongly suggests that the receptor mediating contraction of several types of vascular smooth muscle possesses the pharmacological characteristics of the 5-HT_2 binding site, and hence deserves to be subtyped as a 5-HT_2- (S_2) serotonergic receptor [17, 21, 22]. Whether the 5-HT_1 binding site has earned the status of receptor is still uncertain since no relationship between 5-HT_1 binding and the pharmacological effects of serotonergic agonists and antagonists seems obvious; one exception may be the receptor mediating the constriction of certain [23] but not all [24] cerebral blood vessels when exposed to serotonin. Since several vascular effects of 5-hydroxytryptamine (e.g. prejunctional inhibition of adrenergic neurotransmission) are not antagonized by the available "specific" or "selective" serotonergic antagonists [15, 22, 25, 26], one can predict the existence of more than two subtypes of peripheral serotonergic receptors in the blood vessel wall.

Heterogeneity in vascular smooth muscle responsiveness

If a cardiovascular pharmacologist were asked to describe the effect of serotonin, a very likely answer would be "unpredictable". Very early on, Dr. Page [4–6] and his colleagues already recognized the multiplicity of cardiovascular actions of serotonin and coined the term "amphibaric hormone". Later

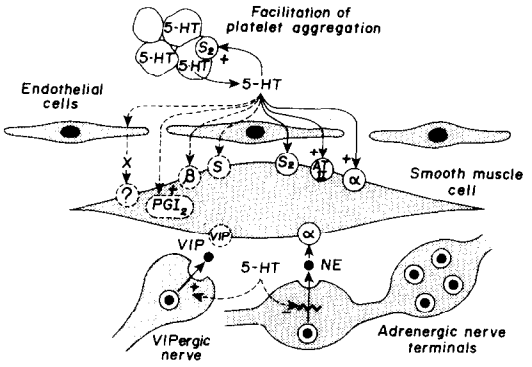

Fig. 2. Multiple effects of 5-HT on the blood vessel wall. Vasoconstriction could be caused by: (1) activation of 5-HT_2- (S_2) serotonergic receptors on the smooth muscle cells; (2) amplification of the vasoconstrictor responses of other neurohumoral mediators [e.g. norepinephrine (NE); angiotensin II]; (3) activation of post-junctional α-adrenergic receptors (α); or (4) an indirect sympathomimetic effect, by displacement of stored norepinephrine from adrenergic nerve terminals. Free 5-HT also activates S_2 receptors on platelets causing enhanced release of stored amine. Vasodilatation could be caused by: (1) inhibition of adrenergic neurotransmission; (2) activation of inhibitory autonomic nerves [presumably causing release of vasoactive intestinal polypeptide (VIP)]; (3) activation of inhibitory serotonergic receptors (S) on the smooth muscle cells; (4) activation of the production of prostacyclin (PGI_2); (5) stimulation of β-adrenoceptors (β); and (6) triggering of endothelium-dependent relaxation. Not all these effects have been demonstrated in all blood vessels. Key: + = excitatory effect, amplification (potentiation); and − = inhibitory effect. (modified from Ref. 9.)

accounts have utilized statements such as "serotonin can cause either constriction or dilatation" or "heterogeneity in vascular responsiveness to serotonin" [27]. There is at this time no satisfactory explanation for the diversity in responsiveness to serotonin of vascular smooth muscle of different anatomical origin. The "direct" effects of the monoamine on smooth muscle cells vary from relaxation to contraction (Fig. 2). Thus, both vasodilatation (blushing) and vasoconstriction (hypertension) observed in carcinoid syndrome may be explained by direct smooth muscle responses to augmented levels of serotonin. Not in every instance are true "serotonergic" mechanisms involved, as serotonin in certain tissues behaves as a beta-adrenergic (causing relaxation) or an alpha-adrenergic (causing contraction) agonist [26, 28, 29]. Serotonin also may accelerate the production by the smooth muscle cells of other vasoactive substances, such as prostacyclin [30]. However, in many instances, more or less specific serotonergic antagonists are able to prevent the effects of serotonin, whether inhibitory or excitatory. The differential responsiveness of vascular smooth muscle to serotonin may serve a physiological role. Thus, in the gut, a combination of arteriolar dilatation and post-capillary venular constriction, combined with an increased capillary permeability, would greatly favor the exudation of fluid during digestion, when the enterochromaffin cells discharge their content [1]. If exaggerated, a similar arterio-

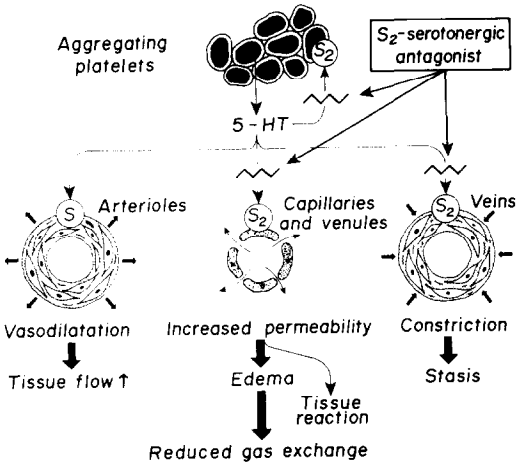

Fig. 3. Potential role of serotonin at the microcirculatory level. The release of serotonin from aggregating platelets would tend to *left:* cause vasodilatation at the arteriolar level; *middle:* increase capillary and venular permeability; and *right:* cause venoconstriction. The combination of these effects favors local edema and stasis. The increased permeability and venoconstriction are mediated by S_2-serotonergic receptors, at which selective antagonists could prevent the response.

venous difference in reactivity could lead to serious microcirculatory disturbances and help to explain certain types of stasis and ulceration (Fig. 3).

The assessment of serotonergic responsiveness is complicated further by the fact that the sensitivity of a given vascular smooth muscle, or a given vascular bed, to serotonin can be modulated both acutely and chronically. Thus, the constrictor responses to the monoamine are acutely exaggerated in cutaneous veins by cooling, and in coronary arteries, by hypoxia [31–33]; such augmentations could play a role in Raynaud's disease and coronary vasospasm respectively [8, 10, 11]. Chronic exposure to high blood pressure causes a remarkable augmentation of the vascular responsiveness to the vasoconstrictor effects of serotonin, presumably as a consequence of premature aging of the blood vessel wall [34–37]; this may play a role in the maintenance of the increased peripheral resistance seen in chronic essential hypertension (Fig. 1; [8, 10, 11]). This increased responsiveness with hypertension is seen also with partial agonists such as methysergide [37]. The effect of certain serotonergic antagonists on hemodynamics thus may depend considerably on variations in their partial agonistic properties depending on the status (age, arterial blood pressure) of the vascular smooth muscle cells of the precapillary wall [8, 10, 11, 16].

Interaction with other vasoactive substances

Besides the direct action it has on vascular smooth muscle, serotonin can augment (potentiate, amplify, enable) considerably the responses to other neurohumoral mediators [22, 38–40]. The augmentation occurs with low concentrations of serotonin and with a large number of other agonists used. In vascular smooth muscle the potentiation cannot be explained solely by an additive effect on serotonergic receptors; serotonin considerably augments the vasoconstrictor potential of substances such as norepinephrine or angiotensin II [22, 39]. This amplifying effect of serotonin appears to be mediated by S_2-serotonergic receptors [22, 39]. Hence, the amplifying effect of serotonin may help explain why the monoamine could contribute to the increase in peripheral resistance in chronic hypertension [8, 10, 11, 41]. Likewise, serotonin released from platelets aggregating at endothelial lesions could amplify the vasoconstrictor effects of arachidonic acid metabolites and could contribute to vasospasm, in particular of the coronary arteries [10, 11].

Multiplicity of target cells

Serotonin also affects the function of other cells of the blood vessel wall. This probably is a major factor in the heterogeneity of the responsiveness to serotonin, in particular in the intact organism.

Higher concentrations of the monoamine cause the displacement of norepinephrine from adrenergic nerves [26]; whereas in most blood vessels such an indirect sympathomimetic effect would cause alpha-adrenergically mediated constriction, the opposite effect can be expected in the coronaries or the facial veins, where the main effect of norepinephrine is to cause beta-adrenergically mediated relaxation [42, 43]. Lower concentrations of serotonin cause inhibition of the exocytotic release of norepinephrine (Fig. 2; [15, 25, 26]); in most blood vessels this would result in vasodilatation, but again in the coronaries or the facial veins a prejunctional inhibitory effect of serotonin can be expected to cause vasoconstriction [43]. In the gastrointestinal wall, serotonin probably releases vasoactive intestinal polypeptide, which contributes to the vasodilatation it causes (Fig. 2; [44]). The endothelial cells form an effective barrier against the vasoconstrictor action of serotonin, since the presence of endothelium reduces markedly the contractions evoked

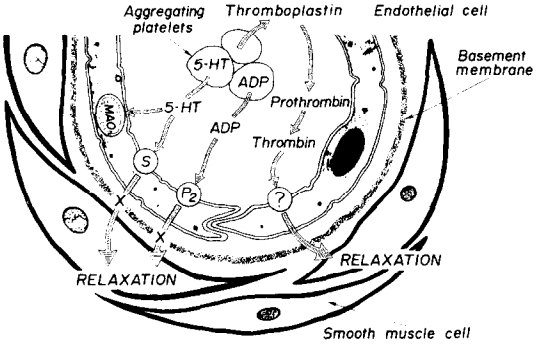

Fig. 4. Role of the endothelium in preventing vasoconstriction. The protective role of the endothelium depends not only on enzymatic destruction of serotonin (5-HT) by endothelial monoamine oxidase (MAO) but also on the fact that adenosine diphosphate (ADP) and serotonin, released from aggregating platelets, and thrombin can trigger endothelium-mediated relaxations of the smooth muscle cells of the arterial media. Key: S = serotonergic receptor; P_2 = P_2-purinergic receptors; and ?,X = unknown mechanism.

by aggregating platelets and exogenous serotonin [13, 45]. This protective role may result partially from enzymatic destruction of serotonin by endothelial monoamine oxidase (Fig. 1). In addition, the endothelium may mediate vascular relaxation when exposed to a number of substances [46–48]. Coronary vascular endothelial cells react to serotonin by triggering relaxation of the smooth muscle cells of the media (Fig. 2; [45, 49]. This endothelium-mediated response to serotonin, and other products released from aggregating platelets (e.g. adenosine diphosphate; [50]) or formed during blood clotting (e.g. thrombin; [51–53]), may imply that, if platelets were to aggregate, or coagulation were initiated in the vicinity of endothelial cells, this would trigger dilatation, favoring the removal of platelet aggregates and thrombus (Fig. 4; [13]). However, the absence of endothelium would permit full expression of the contractile responses to substances released from platelets aggregating at such a site. These mechanisms may be particularly relevant to the occurrence of episodes of vasospasm at sites of intimal damage [54].

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