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SEROTONIN AND VASCULAR RESPONSES

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INTRODUCTION:

The vasoconstrictor properties of defibrinated blood and serum were first described over a century ago (1) and periodically thereafter (2, 3). Indeed, platelets were considered to be a likely source for this vasoactive, "adrenaline-like" material over 70 years ago (3). The responsible agent, serotonin, was crystalized and its structure ultimately identified by Irvine Page and his coworkers in their early attempts to identify a vasoconstrictor in blood that might contribute to the pathogenesis of hypertension (4). That agent was angiotensin. In a recent essay, with the piquant title "The Neonatology of Serotonin," Dr. Page reviewed that early history (5), pointing out that "plasma carefully prepared had no vasoconstrictor properties, but serum had. This clearly posed a problem for me. Any vasoconstrictor I isolated from the blood of hypertensives would always be suspect, because one could never be sure some unseen coagulation had not occurred. Platelets and their secretions are not easily controllable." His interest primarily resided in serotonin's "nuisance value in the search of vasoactive angiotensin," but as he pointed out, there has been a recent resurgence of interest in serotonin, and "substances in the body that are nuisances to one person give tenure to others."

Not that early interest in the cardiovascular effects of serotonin was lacking. In Page's review in 1954, he cited 153 references (6), and only 4 years later, his update cited 530 more (7). During the following two decades, interest in the cardiovascular actions of serotonin continued but at a substantially lower level. This was not because serotonin's role had been delineated. Indeed, a bewildering multiplicity of actions exerted by serotonin on blood vessels had been identified (summarized recently by Vanhoutte, 8).

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These actions include a direct vasoconstrictor effect by way of a specific receptor, amplification of the vasoconstrictor actions of other neurohumoral mediators, actions at the post-junctional alpha adrenergic receptor, an indirect sympathomimetic action by displacement of norepinephrine from adrenergic nerve terminals, and release of platelet vasoactive mediators such as thromboxane A_2. Vasodilation also occurs, further complicating the matter, perhaps reflecting an influence on endothelial-dependent relaxation factor release (9–11). Alternative possibilities include inhibition of adrenergic neurotransmission, activation of inhibitory autonomic nerves, vasodilator prostaglandin release and stimulation of beta adrenergic receptors. Given the myriad of actions, many of which were not blocked by serotonin antagonists, it is not surprising that serotonin's role in normal circulatory physiology and in disease has remained obscure. Regional differences are also important: cyclooxygenase inhibition, as one example, does not influence serotonin-induced limb arteriolar vasodilation (12), but blunts strikingly the dilator response to serotonin of the renal blood supply (13).

A sequence in which the discovery of a novel antagonist leads to clarification of physiological mechanisms, insights into the pathogenesis of disease, and the identification of subtypes of receptors for an endogenous agent is now a paradigm. This familiar story, played out first for acetylcholine and obviously applicable to catecholamines and histamine, now clearly applies to serotonin as well (14–16). The systematic delineation of the 5-HT_2 receptor and the development of an antagonist for that receptor, ketanserin, led to recognition that the 5-HT_2 receptor mediates contraction in vascular smooth muscle. That sequence, in turn, played a major role in the resurgence of interest in serotonin.

Another line of investigation was immediately relevant. Recognition that the interaction of platelets with the vessel wall could result in a process far more complex and interesting than the mere creation of a mechanical hemostatic plug—through the release of a host of agents with actions on vascular function—provided an opportunity to apply the potential of the 5-HT_2 antagonist, ketanserin, to some of the more important problems in modern medicine.

In this essay, no attempt is made to provide a detailed review of all of these subjects; indeed, such an attempt would be doomed to failure given the extraordinary scope of the subject. Rather, the goal is to delineate what new insights and promising leads have come from these recent advances, with special reference to the pathogenesis of cardiovascular disease involving large arteries. Because a series of excellent recent review articles (8, 17) has described the extraordinary number of in vitro studies, these are presented only briefly, to establish certain principles; emphasis is given to the more limited number of vascular studies performed in vivo. The problem of sero-

tonin's role in hypertension, involving the blood supply at the arteriolar level, has also been reviewed recently (17) and lies beyond the scope of this essay.

Because serotonin is delivered from its site of synthesis in the gut by platelets, it is appropriate to open this essay with a discussion of the platelet and vessel wall, with specific emphasis on 5-HT and thromboxane.

PARTICIPATION OF SEROTONIN AND THROMBOXANE A_2 IN PLATELET–VESSEL-WALL INTERACTIONS

Even minimal injury to the endothelium results in platelet aggregation at the site of injury (18). In their brief preface to the recent American Physiological Society Monograph on this subject, *Interaction of Platelets With the Vessel Wall,* the editors pointed out that ". . . the physiological integrity of the circulation depends on continuous surveying of the vessel wall by circulating platelets. During each minute of transit . . . 10^{12} platelets survey a $1000M^2$ of capillary surface area carpeted with 7×10^{11} endothelial cells. Any break in the continuity of the vessel wall is met with an instant response from platelets, which contact the zone of injury, spread and clump" (19). Among the 13 chapters in that monograph, published in 1985, 5 dealt directly with thromboxane, prostacyclin, and other metabolites of arachidonic acid—and none dealt with serotonin. Indeed, serotonin does not appear in the index at the end of the monograph. Perhaps it is not surprising, then, that only recently have we come to recognize the interactions among the vasoactive agents that bathe the vessel wall during the platelet release action and that we know so little of their actions and interactions in vivo.

Rather more is known from studies of in vitro systems, where isolated vessels often demonstrate a striking contraction in response to aggregating platelets and their products (9, 10, 20–25). Very shortly after the development of ketanserin, De Clerck & Van Nueten demonstrated that ketanserin would abolish a substantial portion of the response of the isolated rat caudal artery to products released by aggregating platelets (21). Serotonin, thromboxane AII, and thromboxane mimetics induce contraction of the canine and porcine coronary artery (9, 24, 26), the rat caudal artery (20, 21), and human digital arteries (27, 28). In all three systems, serotonin potentiated thromboxane-induced contractions, and a thromboxane mimetic amplified responses to serotonin, which raised the intriguing possibility that their mutual amplification plays a role in the vasospasm that may accompany the platelet release reaction (20, 24, 28).

This possibility was evaluated in detail recently in the isolated digital artery obtained from humans post mortem (28), where a thromboxane mimetic enhanced substantially the responses to serotonin. Serotonin appeared to amplify the responses to thromboxane rather less but did enhance the re-

sponse. The response of the arteries to aggregating platelets, moreover, was substantially larger than the sum of the anticipated response to thromboxane A_2 release and serotonin release. This observation, of course, raises two possibilities: first, that some factor other than serotonin or thromboxane was responsible for the contraction; second, that their action was enhanced by amplification. Several lines of evidence favored the latter interpretation, including the time dependency of the response and the actions of ketanserin and thromboxane synthetase inhibitors.

De Clerck et al (29) have recently extended these observations to the platelet. They found that the combination of ketanserin and a thromboxane antagonist induced significantly more pronounced inhibition in the extent of the irreversible platelet aggregation elicited by ADP, than when the individual blockers were used alone. The possibility of synergism in the interaction between serotonin and thromboxane in this process—which is a primary event in the interaction of platelets with a damaged vessel wall—led them to explore the interaction in vivo. They employed tail bleeding time in rats as an in vivo model of the platelet–vessel-wall interaction, and again they documented that the simultaneous administration of both classes of antagonist resulted in a much more marked prolongation of bleeding time than when either agent was employed alone.

There are occasional but quantitatively important regional differences, perhaps species related (30), in vascular responsiveness to serotonin and thromboxane A_2. For example, the canine pulmonary artery shows little or no response to thromboxane AII, whereas serotonin induces a striking response (23). The coronary artery (24, 26) and the basilar artery of the dog, on the other hand, are sensitive to both thromboxane AII and to serotonin (31, 32).

Pharmacological antagonists have provided an index of the relative contribution to the in vitro response of various mediators released by platelets. In the case of human digital arteries, serotonin was responsible for about 50% of the response (27); in the case of the rat caudal artery, about 60% of the response was serotonin mediated (20). In canine pulmonary arteries, by contrast, serotonin accounted for virtually all of the response (23), reflecting the insensitivity of this vascular bed to thromboxane A_2. A constrictor response to aggregating platelets in each system assessed to date seems to have been accounted for by serotonin and thromboxane, but dilator responses may be explained by other platelet factors, such as adrenine nucleotides (33).

THE ROLE OF ENDOTHELIUM

Endothelial integrity plays several roles in platelet–vessel-wall interactions. An intact endothelium separates the platelets from the subendothelial ele-

ments that engage them and lead to platelet aggregation and the release reaction (18, 19).

Another major role of endothelium reflects the fact that arteries relax in response to some vasodilators only if the endothelium is present. Since Furchgott & Zawadski (34) first reported that endothelium was required for acetylcholine to relax the rabbit aorta, the obligatory role of a diffusible factor from endothelium (EDRF) for vasodilation has been demonstrated for many additional agents, including bradykinin, substance P, ATP, and other adenine nucleotides and bradykinin. Other vasodilator agents, however, such as nitrates, papaverine, isoproterenol, and prostaglandins do not require endothelium. Recent reviews in the *Annual Review of Pharmacology and Toxicology* (35) and elsewhere (36, 37) on EDRF make a detailed review here unnecessary. The nature of the factor or factors remains obscure.

What is immediately germane to this review is the observation that aggregating platelets induce relaxation of pre-contracted rings of canine coronary arteries only if endothelial cells are present, but produce only contraction if these cells have been removed (10). This observation was quickly followed by reports that serotonin induced endothelium-dependent relaxation of coronary arteries when the endothelium was intact, but contraction when the endothelium was absent (9, 11). The contractile response of coronary arteries to a thromboxane mimetic, on the other hand, was not endothelial dependent (11). Endothelium-dependent relaxation was demonstrated in pre-contracted pig renal and mesenteric artery rings, suggesting a very widespread distribution (11, 37).

The serotonin receptors responsible for the release of EDRF and for the contractile response of smooth muscle differ, since ketanserin does not interfere with release of the vasodilator factor from endothelium but does block the smooth muscle response (11).

Serotonin, however, may play little role in the endothelial-dependent relaxation in response to aggregating platelets (33). The relaxation was sharply attenuated by the enzyme, aprase, which hydrolyzes adenosine tri- and diphosphate but has no action on serotonin. Thus, it appears that adenine nucleotides from platelets play a key role in mediating endothelium-dependent relaxation of canine coronary arteries during aggregation.

The potential relevance of these observations on endothelium to disease was highlighted recently by the observation that acetylcholine infused directly into the coronary arteries of patients with atherosclerotic coronary artery disease induced paradoxical vasoconstriction, documented by angiography (38). Indeed, in patients with apparently minimal disease, acetylcholine also induced vasoconstriction. In the normal coronary arterial tree in humans, acetylcholine caused a modest but unequivocal dose-dependent dilatation. All

of the vessels dilated in response to nitroglycerin, an agent which induces vasodilatation that is not endothelial-dependent. These observations suggest strongly the presence of a defect in endothelial vasodilator function during the course of coronary atherosclerosis (38), making a review of atherosclerosis appropriate.

ATHEROSCLEROSIS

Prompted by evidence that coronary artery spasm participates in the pathophysiology of ischemic heart disease, and that some patients show a potentiated coronary vascular response to the vasoconstrictor actions of the ergot alkaloid ergonovine, Henry & Yokoyama (39) examined the responses of the rabbit aorta after about 10 weeks on a high cholesterol diet, a time sufficient to increase substantially both serum cholesterol and the cholesterol content of the vascular tissue. They documented supersensitivity of the isolated arterial strips to ergonovine and to serotonin, but not to norepinephrine. Supersensitivity expressed itself in both a reduction in the serotonin dose required to induce a threshold response and an increase in the maximum response. They speculated that the functional changes in the atherosclerotic arteries were unlikely to be attributable to alterations in their structure, since responses to alpha receptor agonists were unaltered, and a structural change was unlikely to alter the threshold concentration of serotonin required to induce a response.

Yokoyama et al went on to document supersensitivity to ergonovine and to serotonin not only in the aorta but also in the coronary arteries of 8 to 12 month old rabbits of the Watanabe strain, which develop hyperlipidemia and atherosclerosis as a result of inbreeding (40). Again, the supersensitivity was specific; responses to phenylephrine were not altered. This study suggested regional arterial differences, since neither the carotid nor the femoral artery in this strain of rabbit showed a potentiated response to serotonin or ergonovine.

An increase in the number of receptors for serotonin was described in the aorta from rabbits on a high cholesterol diet; this could account for an increase in the response to serotonin. An apparent increase in the number of receptors for alpha adrenergic agonists was also documented (41). Although an increase in serotonin receptor number would provide an attractive explanation for the increase in the vascular responsiveness to serotonin, and especially the reduction in threshold serotonin concentration required for a response, the apparent increase in alpha adrenergic receptors is somewhat puzzling. Responses of atherosclerotic aortas to alpha agonists were not enhanced in the earlier studies (39). Unfortunately, only an abstract has been published, so details are not available.

The first evidence that a potentiated response to serotonin occurred in atherosclerotic vessels in vivo was found by Heistad et al (42) in hypercholesterolemic and atherosclerotic monkeys treated for three to five years with an atherogenic diet. They studied the hindlimb, perfused at constant flow, so that changes in perfusion pressure indicated changes in vascular resistance, and segmental pressure and resistance could be assessed. Specifically, they measured the pressure gradient from the iliac to the dorsal pedal artery to assess the responses of the large artery segment. Serotonin decreased total hindlimb vascular resistance in normal and hypocholesterolemic monkeys, but increased total limb vascular resistance in the atherosclerotic monkeys. The constrictor response of large arteries to serotonin in the atherosclerotic monkeys was increased tenfold and was largely responsible for the increase in total vascular resistance. Vasoconstrictor responses to norepinephrine were more complex, since they were increased in hypercholesterolemic monkeys prior to the development of atherosclerosis but were normal when atherosclerosis had supervened. Moreover, the enhanced response to norepinephrine was confined to the arteriolar level: Large artery responses to norepinephrine were unaltered by either hypercholesterolemia or atherosclerosis. Ketanserin reduced the vasoconstrictor responses to serotonin in the atherosclerotic monkeys but did not influence the response to norepinephrine. The results suggest that the enhanced large artery response to serotonin reflected an action on the 5-HT_2 receptor.

Hypercholesterolemia can clearly influence vascular responses (43–45). EDRF-dependent relaxation of the aorta can be lost within four weeks (43). Rosendorff et al (44) rendered dogs hypercholesterolemic by cholesterol feeding for a short time, 26–32 days, too short a time for atherosclerosis to occur. A low dose of norepinephrine reduced coronary vascular resistance, but higher doses increased vascular resistance. Wright & Angus (45) documented a small reduction in the vasodilator response to acetylcholine in rabbits made hypercholesterolemic with a 4-week high cholesterol diet, which deposited lipid in the aortic intima. Vasodilator responses of the limb resistance vessels to serotonin were unchanged by this regimen. No attempt was made to assess the large artery response in either study.

To the extent that vascular occlusion occurs as a consequence of atherosclerosis, collateral arterial vessels become critical in the delivery of blood flow. Here, also, a story is emerging concerning a role for serotonin.

ARTERIAL COLLATERAL BLOOD VESSELS

When a major artery is occluded, whether the tissue it normally supplies will be destroyed or will survive is largely dependent on the availability of a collateral arterial supply at the time of occlusion to maintain tissue perfusion

and integrity (46). Thereafter, the rapid but variable growth of collateral arteries occurs. A growing body of evidence indicates that, like the atherosclerotic process itself, collateral vessels and their responsiveness are complex: collateral arteries are not passive conduits but rather a reactive system.

Acute occlusion of the terminal aorta in the cat resulted in substantially more ischemia of the spinal cord and limb when the occlusion involved thrombus, leading to speculation that thrombus might release vasoactive factors that further reduced blood flow, through an action on the collateral arterial supply (47). The suggestion was prescient. Intrinsic vascular tone, reversible by vasodilators, had already been established in the collateral blood supply to the limb of the dog (48, 49).

However, no information on the anatomy was available. An alternative to release by the thrombus of vasoactive factors was thrombus extension beyond its initial size, or embolization, to occlude the potential collateral vessels mechanically. Vasodilators increased the outflow of blood from the limb (48, 49), but the increase in blood flow could have occurred in normal intact vascular pathways that bypassed the area of occlusion, rather than via collaterals.

Angiography resolved the issue. Schaub et al (50) showed that extension of the thrombus, or embolism, could not account for the more substantial impact of thrombus, compared to that of mechanical occlusion, on hindlimb perfusion in the cat; they suggested that chemical factors of platelet origin might play a contributing role. They then evaluated serotonin as a determinant of blood flow following occlusion of the blood supply to the hindlimb (51). Blood flow, assessed with a hydrogen electrode, fell strikingly in response to serotonin three days after aortic ligation. Either the serotonin antagonist, cinanserin, or depletion of platelet serotonin stores with reserpine sustained collateral circulation to the limb. A reduction in platelet count induced by an antiserum directed against platelets, on the other hand, was not effective in restoring a limb's circulation, despite a striking fall in platelet count. A remarkably small number of activated platelets, it appears, are required to induce collateral arterial spasm.

Their observations were rapidly confirmed and extended. Serotonin induced striking ischemia in the rat limb from 5 days to 8 weeks after femoral artery ligation (52). Ketanserin, the 5-HT_2 receptor antagonist, prevented that response. Ketanserin also blunted the blood flow reduction and tissue damage induced by acute thrombotic obstruction of the aorta in the cat (53). An action of thromboxane A2 released by platelets was thought unlikely, since ketanserin was effective, and ketanserin does not inhibit the production, the release, or the actions of thromboxane A_2.

The application of quantitative arteriography answered a number of addi-

tional questions (54). In the normal dog, serotonin induced the anticipated, dose-related reduction in large artery caliber: At the same time, blood flow increased. The reduction in large artery caliber was prevented or reversed by ketanserin, but the blood flow increase was not (12). The larger the normal artery, the larger was the absolute and relative reduction in arterial lumen induced by serotonin (12).

The small collateral arteries were strikingly more sensitive to serotonin (54), and that response was also reversed by ketanserin. The increase in sensitivity expressed itself as a 10–30-fold reduction in the threshold serotonin dose required to induce vasoconstriction in the profunda femoris and the medial and lateral circumflex femoral arteries, the major stem vessels giving rise to the collateral tree. The slope relating serotonin dose to the degree of vasoconstriction, moreover, became much steeper. Calf blood flow, assessed with radioxenon, fell with serotonin infusion in the collateral-dependent limb and rose as anticipated in the normal limb. Responses of the collateral arterial supply were not potentiated to norepinephrine, and prazosin did not influence the response to serotonin. Taken in all, these data indicated that growing collateral arterial vessels display a specific increase in sensitivity to serotonin via the 5-HT_2 receptor and that the potentiated response was sufficient to limit blood flow.

The isolated, perfused hind quarters of rats studied either 5–9 days or two months after vascular occlusion showed a striking increase in sensitivity of the collateral bed to serotonin, but not for norepinephrine, a thromboxane A2 mimetic, or angiotensin II (55). Thus, the increase in sensitivity was confirmed as serotonin specific. Since no platelets were present in the perfusate, the increase in sensitivity did not reflect aggregation of platelets induced by serotonin. The fact that the responses to the thromboxane mimetic were not potentiated suggests that the serotonin-thromboxane AII interaction in in vivo, described below, may reflect serotonin-induced amplification of the response to thromboxane A2, as described earlier in vitro (20, 23, 27).

The duration of this special sensitivity of collateral vessels is prolonged. Studies performed 3 and 5 days after occlusion suggested that the response occurs early (52, 53). The longest study reported suggested that collateral vessel supersensitivity in the limb continues for at least 8 weeks in the rat (52). Our unpublished data on the rabbit suggests that supersensitivity to serotonin of limb collateral vessels continues for at least 8 months after femoral artery occlusion.

More circumstantial evidence for the cerebral collateral circulation indicates that serotonin supersensitivity occurs there as well (56). Within 2 weeks of occlusion of the left anterior descending coronary artery in the dog, there was a striking increase in the sensitivity of the collateral vessels to serotonin, a response that was reversed by ketanserin: In serial studies, that

enhanced response appears to last for at least 12 weeks (K. Huttl & N. K. Hollenberg, unpublished results).

Does serotonin released from platelets account for the entire collateral arterial response when thrombus complicates vascular occlusion? Helenski et al suggested that thromboxane A2 might play a role (57), but that is controversial (53). When platelet activation was induced in vivo by endothelial injury above the origin of the limb collateral arteries in the rabbit, spasm of the collateral vessels occurred routinely (N. K. Hollenberg & K. Monteiro, unpublished observations). Ketanserin in doses too low to influence the response to norepinephrine (30μg/kg) partially reversed the spasm. Thromboxane synthetase inhibition or an antagonist also induced a partial reversal, somewhat less in degree than that induced by ketanserin. When the two classes of agent were combined, a striking reversal of spasm occurred, substantially greater than when either was employed alone. The mechanism of the supersensitivity of collateral arterial arteries to serotonin is unclear. One possibility, again, involves the vasodilator influence of the endothelium (10). Endothelial cells of rapidly growing collateral arteries show marked changes, including hyperplasia demonstrated by radioautography with tritiated thymidine (58, 59). Perhaps dividing endothelial cells, and their daughter cells for some time after division, lose their ability to release the relaxant factor.

What are the therapeutic implications? There are no species-related exceptions: exquisite sensitivity of the limb collateral arterial tree to serotonin has been documented in the cat, the rat, the dog, and the rabbit (5, 52–54). Indeed, there appear to be no exceptions. The unpredictable but occasionally striking improvement in symptoms of intermittent claudication and limb perfusion in the patient with peripheral vascular disease treated with ketanserin (60) may reflect the fact that patients differ in the degree to which limb ischemia reflects an influence of activated platelets, and a release of vasoactive factors acts on the collateral-dependent limb.

THE CORONARY ARTERY TREE

It has been recognized that coronary artery vasospasm may be a significant contributor to disease in the occasional patient with atypical angina pectoris. The more recent evidence that spasm also contributes in the patient with more typical effort angina and unstable angina pectoris has focussed attention once more on the control of coronary artery responsiveness (61, 62). These abnormalities are likely to be multifactorial and hence have provided a complicated problem for dissection.

The simplest system for study is an isolated arterial strip, assessed in vitro. As pointed out in earlier sections, even in the simplest of systems, responses to serotonin and to the products of platelet aggregation have been complicated

by factors such as the presence or absence of an intact endothelium. When endothelium has been removed or injured, both aggregating platelets and serotonin contract the coronary artery in vitro. There are also potentially important species differences. One example involves vascular responses to ergonovine, as reviewed recently by Young & Vatner (62). In some systems and species an alpha adrenergic receptor is involved: in others, it is a serotonin receptor. In canine coronary arteries, perhaps the most widely studied coronary preparation, ergonovine-induced contraction was found to occur by way of serotonin receptors, with no evidence found for a role of alpha adrenergic receptors (63).

The branch level and size of the coronary artery segment under study is another important variable: Responsiveness to serotonin and to ergonovine was substantially less in smaller branch arteries than in the major epicardial branches, in studies of coronary artery strips from the dog in vitro (64). This pattern is similar to that identified in vivo for the dog limb, where larger arteries showed a substantially larger response and larger reduction in cross-sectional area than did smaller branches (12).

Shortly after ketanserin became available as a pharmacologic probe, Brazenor & Angus (65) reported a surprising finding. In canine coronary artery segments, ketanserin acted as a noncompetetive antagonist to vasoconstriction induced by serotonin. In very low concentrations ketanserin reduced the peak contractile response substantially, and increased ketanserin concentrations produced a progressive reduction in the peak response and a nonparallel shift in the dose-response curve. Indeed, four other serotonin antagonists showed similar kinetics. They speculated that, in the canine coronary artery preparation, events beyond the receptor interaction might be responsible for the loss of response. As an alternative explanation, apparently not tested, non-equilibrium kinetics could produce a similar phenomenon, by analogy with earlier studies on the beta haloalkylamines (66). In brief, competitive kinetics demand equal access of the agonists and the antagonists to the receptor site. If the antagonist has a very high binding affinity for the receptor, and once bound does not come off quickly, the result will be noncompetetive kinetics despite an action on the receptor.

Subsequent investigation has confirmed both the relative resistance to serotonin-induced contraction of canine coronary artery preparations and the noncompetetive nature of the response (33, 67). Both investigators found that methiothepin, which binds at both 5-HT_1 and 5-HT_2 receptors, was more effective than ketanserin in blocking serotonin-induced coronary artery responses. Both a 5-HT_1 and 5-HT_2 receptor may be involved in the canine coronary arterial tree. Too little is known of the coronary artery tree in other species to assess species specificity for this phenomenon.

There is substantially less information from studies in vivo. Bove & Dewey

(68) demonstrated with quantitative angiography that serotonin was substantially more effective than phenylephrine in inducing coronary artery vasoconstriction. Very large doses of serotonin, 100 μg/min infused into the left anterior descending coronary artery, were required to induce a rather limited response—about a 40% reduction in lumen cross-sectional area, perhaps reflecting the dominance of endothelial-dependent factors. Indeed, with endothelial damage induced by a balloon catheter, Brum et al (69) documented a clear increase in the sensitivity of the damaged area to serotonin.

In 1976 Folts et al (70) found that a cyclic flow reduction with a nadir near zero occurred in dogs in which a fixed 60–80% stenosis of an epicardial coronary artery had been induced. Evidence for a role of platelets included abolition of the response with aspirin, and histologic identification of platelet aggregates in the lumen of the coronary artery when taken at the time of reduced blood flow. The obvious potential relevance of this observation to ischemic syndromes in coronary artery disease has engendered a substantial series of investigations. A role for serotonin as a contributor was established by Bush et al, who documented that ketanserin abolished the reduction in blood flow, whereas prazosin and propranolol were ineffective in doing so (71). Yohimbine, a relatively selective alpha 2 adrenergic antagonist, produced a partial response. The role of serotonin was further confirmed by the observation that there was a striking increase in the concentration of serotonin at the site of the coronary arterial stenosis (72). The influence of ketanserin on the cyclic flow reduction was confirmed in this study. Serotonin administration restored cyclic flow variations.

Thromboxane also plays a role during platelet activation. The thromboxane synthetase inhibitor, dazoxiben, also abolished cycle flow reduction in this model (73), and thromboxane B2 levels were increased distal to the stenosis during the cyclic flow variations. A thromboxane antagonist was also effective in reducing the cyclic flow variations (74).

Findings in this series of studies are remarkably similar for those reported for collateral blood vessels, described above. Platelet activation induces a response that can be attenuated either by thromboxane synthetase inhibition or a thromboxane antagonist, on the one hand, or ketanserin on the other. In the collateral model, evidence of platelet aggregation and embolization disappeared with the use of either agent alone. The platelet response is more amenable to blockade with a single class of agent than is the vascular response.

Little information exists on the response of these systems in humans. DeCaterina (75) performed a double blind, placebo-controlled trial of ketanserin in patients with atypical angina pectoris: Ketanserin was ineffective. Whether this reflects the fact that serotonin is not involved, that one cannot

block serotonin without blocking thromboxane production or action, or whether the serotonin receptor involved is not a 5-HT_2 receptor, is unclear.

THE CEREBRAL BLOOD SUPPLY

Substantial interest has arisen concerning the contribution of formed elements of the blood to cerebrovasospasm, in view of evidence that arterial spasm contributes to the late manifestations of subarachnoid hemorrhage (76, 77). The recent demonstration that calcium channel blocking agents can reduce the frequency of neurologic deficits in patients after subarachnoid hemorrhage reinforces earlier thoughts on the contribution of vasoactive spasm to the effects of this syndrome (78).

Because the cerebral blood supply is the subject of a specific chapter elsewhere in this volume, it is reviewed only briefly here.

In vitro studies indicate that the large, extracranial cerebral vessels respond to both serotonin (31) and to thromboxane (79). Intracarotid injection of serotonin in vivo promoted clear constriction of the internal carotid artery assessed by angiography (80), an observation that we have confirmed in the rabbit and extended to the basilar system. The spasm induced by serotonin was reversed by ketanserin in doses required for 5-HT_2 antagonism, about 30 μ/kg.

The smaller, pial microvasculature has generally been studied through implanted cranial windows. In this system, serotonin and platelet aggregate supernatant applied topically caused generalized cerebral small artery spasm, which again was blocked by ketanserin (81, 82).

THE DIGITAL CIRCULATION

Arteries to the hand isolated from humans post mortem are very sensitive to serotonin (27), raising the possibility that serotonin could contribute to vasospastic conditions involving the hand. Raynaud's phenomenon is a clinical syndrome in which episodic color changes, reflecting fluctuating blood flow, occur in the digits in response to cold and occasionally to emotional stress. The severity ranges from mild, without implications for well-being, to the destruction of the digits associated with gangrene. When serotonin is infused directly into the brachial artery in a human being, there is a rapid fall in digital temperature and the sequential changes in color characteristic of Raynaud's phenomenon occur (83). Vascular smooth muscle isolated from the subcutaneous blood vessels in patients with scleroderma (patients who were especially likely to develop Raynaud's phenomenon) shows enhanced responsiveness to serotonin (84). With exposure to cold as the provocative challenge, ketanserin improved digital artery blood flow in all forms of

Raynaud's phenomenon, and it was especially effective in patients with scleroderma (85, 86). In a clinical limb of the trial, which was carried out for only 4 weeks and was not double-blind or placebo controlled, there was at least moderate improvement in 83% of patients with scleroderma, but in only about one third of patients with Raynaud's phenomenon of other etiology.

In a double-blind study, ketanserin was compared with placebo in women with primary Raynaud's phenomenon (87). When ketanserin was administered prior to a cold challenge, there was little influence on the maintenance of digital blood flow. On the other hand, when ketanserin was administered at the time of cold-induced vasoconstriction, there was a prompt improvement in digital arterial flow. These observations suggest that different factors are involved in the initiation and the maintenance of the vasospasm: Perhaps local release of serotonin occurs primarily during the spasm and is provoked by cold (88).

As pointed out in a recent review (85), the precise role of serotonin in the pathogenesis of Raynaud's phenomenon and in the pathogenesis of the syndromes associated with Raynaud's phenomenon, such as scleroderma, remain obscure.

THE RENAL CIRCULATION

A host of conditions are characterized by renal failure—evidence of damage to the formed elements of the blood, including platelets; striking abnormalities of the major intrarenal arteries evident on arteriography—and there is no clear understanding of the pathogenesis of the renal vascular spasm and renal failure (89). In some of these syndromes, such as the hemolytic-uremic syndrome and scleroderma renal crisis, clear evidence exists of platelet activation, aggregation, and destruction. Non-steroidal anti-inflammatory agents are well documented to provoke renal functional deterioration (90, 91), and these agents potentiate strikingly the renal vasoconstrictor response to serotonin (13).

Although substantial interest in the renal action of serotonin has arisen since its discovery, no clear pattern emerges of its action in the kidney or of its role in pathogenesis. Indeed, reports show striking variation on both the direction and the magnitude of renal vascular responses: Some investigators reported a net increase in renal blood flow, whereas others reported vasoconstriction or no change, despite the use of substantial doses (13, 92–96).

The local renal release of vasodilator prostanoids in response to vasoconstrictor agents such as norepinephrine and angiotensin led to the examination of the effect of prostaglandin synthetase inhibitors on the renal vascular response to serotonin in the dog (13). Serotonin decreased blood flow acutely,

whether administered by bolus or by constant infusion, but the flow decrease was not sustained. Whatever the mode of delivery, a dose-related hyperemic response occurred after about 30 seconds. When prostaglandin synthetase inhibition was employed, the secondary vasodilator response disappeared, and sustained, striking vasoconstriction occurred. Ketanserin administration, which did little to influence renal blood flow prior to prostaglandin synthetase inhibition, now induced a dose-related reverse of the renal vasoconstriction. The pattern was identical whether renal blood flow measured by electromagnetic flowmeter or the renal arteriogram was used as the index. Similar patterns are documented in the rabbit kidney (97).

IMPLICATIONS FOR THERAPY

The discovery of a pharmacologic agent that blocks an endogenous pathway has often been the route both to an understanding of mechanisms and to new therapy. Indeed, it is interesting how often the therapeutic implications have gone well beyond what was imagined initially. In the case of the beta adrenergic blocking agents, who could have imagined the number of conditions for which they would find a use? The identification of a 5-HT_2 receptor and the development of antagonists with relative specificity for that receptor have provided us with a similar opportunity. Although the evidence of a role for serotonin released by platelets acting on a 5-HT_2 vascular receptor in disease remains circumstantial, the multiple lines of evidence that favor such a possibility and the wide variety of conditions to be considered make this a truly interesting time.

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Literature Cited

1. Ludwig, C., Schmidt, A. 1868. Das Verhalten der Gase, welche mit dem Blut durch den reissbaren Säugetiermuskel strömen. *Arb. Physiol. Anst. Leivie* 3:12
2. Freund, H. 1920. Über die pharmakologischen Wirkungen des defibrinierten Blutes. *Arch. Exp. Pathol. Pharmakol.* 86:266–80
3. O'Connor, J. M. 1912. Über den Adrenalingehalt des Blutes. *Arch. Exp. Pathol. Pharmakol.* 67:195–232
4. Page, I. H. 1952. The vascular action of natural serotonin, 5-and 7-hydroxytryptamine and tryptamine. *J. Pharmacol. Exp. Ther.* 105:58–73
5. Page, I. H. 1985. The neonatology of serotonin. In *Serotonin and the Cardiovascular System*, ed. P. M. Vanhoutte, pp. xiii–xv. New York: Raven. 288 pp.
6. Page, I. H. 1954. Serotonin (5-hydroxytryptamine). *Physiol. Rev.* 34:563–88

7. Page, I. H. 1958. Serotonin (5-hydroxytryptamine); the last four years. *Physiol. Rev.* 38:277–35
8. Vanhoutte, P. M. 1983. 5-Hydroxytryptamine and vascular disease. *Fed. Proc.* 42:233–37
9. Cohen, R. A., Shepherd, J. T., Vanhoutte, P. M. 1983. 5-Hydroxytryptamine can mediate endothelium-dependent relaxation of coronary arteries. *Am. J. Physiol.* 245:H1077–80
10. Cohen, R. A., Shepherd, J. T., Vanhoutte, P. M. 1983. Inhibitory role of the endothelium in the response of isolated coronary arteries to platelets. *Science* 221:273–74
11. Cocks, T. M., Angus, J. A. 1983. Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. *Nature* 305:627–30
12. Blackshear, J. L., Orlandi, C., Garnic, J. D., Hollenberg, N. K. 1985. Differential large and small vessel responses to serotonin in the dog hindlimb in vivo: Role of the 5HT-2 receptor. *J. Cardiovasc. Pharmacol.* 7:45–9
13. Blackshear, J. L., Orlandi, C., Hollenberg, N. K. 1986. Serotonin and the renal blood supply: role of prostaglandins and the $5HT_2$ receptor. *Kidney Int.* 30:304–10
14. Cohen, M. L., Fuller, R. W., Wiley, K. S. 1981. Evidence for $5HT_2$ receptors mediating contraction in vascular smooth muscle. *J. Pharmacol. Exp. Ther.* 218:421–25
15. Peroutka, S. J., Snyder, S. H. 1979. Multiple serotonin receptors: Differential binding of ^{3}H-5-hydroxytryptamine, ^{3}H-lysergic acid diethylamide and ^{3}H-spiroperidol. *Mol. Pharmacol.* 16:687–99
16. Van Nueten, J. M., Janssen, P. A. J., Van Beek, J., Xhonneux, R., Verbeuren, T. J., Vanhoutte, P. M. 1981. Vascular effects of ketanserin (R 41 468), a novel antagonist of $5\text{-}HT_2$ serotonergic receptors. *J. Pharmacol. Exp. Ther.* 218:217–30
17. Vanhoutte, P. M. 1982. 5-Hydroxytryptamine, vasospasm and hypertension. In *5-Hydroxytryptamine and Peripheral Reactions*, ed. F. De Clerck, P. M. Vanhoutte, pp. 163–74. New York: Raven
18. Ashford, T. 1968. Platelet aggregation at sites of minimal endothelial injury. *Am. J. Pathol.* 53:599–607
19. Oates, J. A., Hawiger, J., Ross, R. 1985. Preface to *Interaction of Platelets With the Vessel Wall*. Bethesda: Am. Physiol. Soc.
20. De Clerck, F., Van Nueten, J. M. 1982. Platelet-mediated vascular contractions: Inhibition of the serotonergic component by ketanserin. *Thromb. Res.* 27:713–27
21. De Clerck, F., Van Nueten, J. M. 1983. Platelet-mediated vascular contractions. Inhibition by flunarizine, a calcium-entry blocker. *Biochem. Pharmacol.* 32:765–71
22. Lindblad, L. E., Shepherd, J. T., Vanhoutte, P. M. 1984. Cooling augments platelet-induced contraction of peripheral arteries of the dog. *Proc. Soc. Exp. Biol. Med.* 176:119–22
23. McGoon, M. D., Vanhoutte, P. M. 1984. Aggregating platelets contract isolated canine pulmonary arteries by releasing 5-hydroxtryptamine. *J. Clin. Invest.* 74:828–33
24. Mullane, K. M., Bradley, G., Moncada, S. 1982. The interactions of platelet-derived mediators on isolated canine coronary arteries. *Eur. J. Pharmacol.* 84:115–18
25. Van Nueten, J. M. 1983. 5-Hydroxytryptamine and precapillary vessels. *Fed. Proc.* 42:223–27
26. Ellis, E. F., Oelz, O., Roberts, L. J., Payne, N. A., Sweetman, B. J., et al. 1976. Coronary arterial smooth muscle contraction by a substance released from platelets: Evidence that it is thromboxane A_2. *Science* 193:1135–37
27. Moulds, R. F. W., Iwanov, V., Medcalf, R. L. 1984. The effects of platelet-derived contractile agents on human digital arteries. *Clin. Sci.* 66:443–51
28. Young, M. S., Iwanov, V., Moulds, R. F. W. 1986. Interaction between platelet-released serotonin and thromboxane A_2 on human digital arteries. *Clin. Exp. Pharmacol. Physiol.* 13:143–52
29. De Clerck, F., Xhonneux, B., Van Gorp, L. J., Beetens, P. A. J. 1986. S_2-Serotonergic receptor inhibition (ketanserin), combined with thromboxane A_2/prostaglandin endoperoxide receptor blockade (BM 13.177): Enhanced anti-platelet effect. *Thromb. Haemostas.* 56:236
30. Somlyo, A. P., Somlyo, A. V. 1970. Vascular smooth muscle. II. Pharmacology of normal and hypertensive vessels. *Pharmacol. Rev.* 22:249–353
31. Muller-Schweinitzer, E., Engel, G. 1983. Evidence for mediation by $5\text{-}HT_2$ receptors of 5-hydroxytryptamine-induced contraction of canine basilar artery. *Naunyn Schmiedebergs Arch. Pharmacol.* 324:287–92
32. Van Nueten, J. M., Vanhoutte P. M. 1981. Selectivity of calcium antagonism and serotonin antagonism with respect to

venous and arterial tissues. *Angiology* 32:476–84
33. Houston, D. S., Shepherd, J. T., Vanhoutte, P. M. 1985. Adenine nucleotides, serotonin, and endothelium-dependent relaxations to platelets. *Am. J. Physiol.* 17:H389–H395
34. Furchgott, R. F., Zawadski, J. V. 1980. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 288:373–76
35. Furchgott, R. F. 1984. The role of endothelium in the responses of vascular smooth-muscle to drugs. *Ann. Rev. Pharmacol. Toxicol.* 24:175–97
36. Furchgott, R. F. 1983. Role of endothelium in responses of vascular smooth muscle. *Circ. Res.* 53:557–72
37. Cocks, T. M., Angus, J. A. 1984. Endothelium-dependent modulation of blood vessel reactivity. In *The Peripheral Circulation*, ed. S. Hunyor, J. Ludbrook, J. Shaw, M. McGrath, pp. 9–21. New York: Elsevier
38. Ludmer, P. L., Selwyn, A. P., Shook, T. L., Wayne, R. R., Mudge, G. H., et al. 1986. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N. Engl. J. Med.* 315:1046–51
39. Henry, P. D., Yokoyama, M. 1980. Supersensitivity of atherosclerotic rabbit aorta to ergonovine. Mediation by a serotonergic mechanism. *J. Clin. Invest.* 66:306–13
40. Yokoyama, M., Akita, H., Mizutani, T., Fukazaki, H., Watanabe, Y. 1983. Hyperreactivity of coronary arterial smooth muscles in response to ergonovine from rabbits with hereditary hyperlipidemia. *Circ. Res.* 53:63–71
41. Nanda, V., Henry, P. D. 1982. Increased serotonergic and alpha adrenergic receptors in aortas from rabbits fed a high cholesterol diet. *Clin. Res.* 30: 209A (Abstr.)
42. Heistad, D. D., Armstrong, M. L., Marcus, M. L., Piegors, D. J., Mark, A. L. 1984. Augmented responses to vasoconstrictor stimuli in hypercholesterolemic and atherosclerotic monkeys. *Circ. Res.* 54:711–18
43. Jayakody, L., Senarantne, M., Thomson, A., Kappagoda, T. 1987. Endothelium-dependent relaxation in experimental atherosclerosis in the rabbit. *Circ. Res.* 60:251–64
44. Rosendorff, C., Hoffman, J. I. E., Verrier, E. D., Rouleau, J., Boerboom, L. E. 1981. Cholesterol potentiates the coronary artery response to norepinephrine in anesthetized and conscious dogs. *Circ. Res.* 48:320–29
45. Wright, C. E., Angus, J. A. 1986. Effects of hypertension and hypercholesterolemia on vasodilatation in the rabbit. *Hypertension* 8:361–71
46. Liebow, A. A. 1963. Situations which lead to changes in vascular patterns. In *Handbook of Physiology, Circulation*, ed. W. F. Hamilton, P. Dow, 2:1251–76. Bethesda, MD: Am. Physiol. Soc.
47. Imhoff, R. K. 1962. Production of aortic occlusion resembling acute aortic embolism syndrome in cats. *Nature* 192:979–80
48. Coffman, J. D. 1966. Peripheral collateral blood flow and vascular reactivity in the dog. *J. Clin. Invest.* 45:923–31
49. Thulesius, O. 1962. Hemodynamic studies on experimental obstruction on the femoral artery of the cat with special references to the peripheral action of vasoactive substances. *Acta Physiol. Scand.* 199:1–95
50. Schaub, R. G., Meyers, K. M., Sande, R., Hamilton, G. 1976. Inhibition of feline collateral vessel development following thrombotic occlusion. *Circ. Res.* 39:736–43
51. Schaub, R. G., Meyers, K. M., Sande, R. 1977. Serotonin as a factor in depression of collateral blood flow following experimental arterial thrombosis. *J. Lab. Clin. Med.* 90:645–53
52. Verheyen, A., Vlaminckx, E., Lauwers, F., Van Den Broeck, C., Wouters, L. 1984. Serotonin-induced blood flow changes in the rat hindlegs after unilateral ligation of the femoral artery. Inhibition by the S2 receptor antagonist ketanserin. *Arch. Int. Pharmacodyn. Ther.* 270:280–98
53. Nevelsteen, A., De Clerck, F., Loots, W., De Gryse, A. 1984. Restoration of post-thrombotic peripheral collateral circulation in the cat by ketanserin, a selective 5-HT_2 receptor antagonist. *Arch. Int. Pharmacodyn. Ther.* 270:268–79
54. Orlandi, C., Blackshear, J. L., Hollenberg, N. K. 1986. Increase in sensitivity to serotonin of the canine hindlimb collateral arterial tree via the 5-hydroxytryptamine-2 receptor. *Microvasc. Res.* 32:121–30
55. Verheyen, A., Lauwers, F., Vlaminckx, E., Wouters, L., De Clerck, F. 1987. Effects of vasoactive agonists on peripheral collateral arteries in situ perfused rat hind quarters. *Abstr. Belg. Cardiol. Soc., 5th, Brussels*, pp. A7
56. Welch, K. M. A., Hashi, K., Meyer, J. S. 1973. Cerebrovascular response to tintracarotid injection of serotonin before and after middle cerebral artery

occlusion. *J. Neurol. Neurosurg. Psychiatr.* 36:724–35
57. Helenski, C., Schaub, R. G., Roberts, R. 1980. Improvement of collateral circulation after aortic thrombosis with indomethacin therapy. *Thromb. Haemostas.* 44:69–71
58. Ilich, N., Hollenberg, N. K., Williams, D. H., Abrams, H. L. 1979. Time course of increased collateral arterial and venous endothelial cell turnover after renal artery stenosis in the rat. *Circ. Res.* 45:579–82
59. Odori, T., Paskins-Hurlburt, A., Hollenberg, N. K. 1983. Increase in collateral arterial endothelial cell proliferation induced by captopril after renal artery stenosis in the rat. *Hypertension* 5:307–11
60. DeCree, J., Leempoels, J., Geukens, H., Verhaegen, H. 1983. Placebo controlled doubleblind trial of ketanserin in the treatment of intermittent claudication. *Lancet* 2:775–79
61. Maseri, A., Chierchia, S., Davies, G. 1986. Pathophysiology of coronary occlusion in acute infarction. *Circulation* 73:233–39
62. Young, M. A., Vatner, S. F. 1986. Regulation of large coronary arteries. *Circ. Res.* 59:579–96
63. Brazenor, R. M., Angus, J. A. 1981. Ergometrine contracts isolated canine coronary arteries by a serotonergic mechanism: no role for alpha adrenoceptors. *J. Pharmacol. Exp. Ther.* 218:530–36
64. Myers, J. H., Mecca, T. E., Webb, R. C. 1985. Direct and sensitizing effects of serotonin agonists and antagonists on vascular smooth muscle. *J. Cardiovasc. Pharmacol.* 7:S44–S48
65. Brazenor, R. M., Angus, J. A. 1982. Actions of serotonin antagonists on dog coronary artery. *Eur. J. Pharmacol.* 81:569–76
66. Nickerson, M. 1962. Mechanism of the prolonged adrenergic blockade produced by haloalkylamines. *Arch. Int. Pharmacodyn.* 140:237–50
67. Cohen, R. A. 1986. Contractions of isolated canine coronary arteries resistant to S_2-serotonergic blockade[1]. *J. Pharmacol. Exp. Ther.* 237:548–52
68. Bove, A. A., Dewey, J. D. 1983. Effects of serotonin and histamine or proximal and distal coronary vasculature in dogs: comparison with alpha-adrenergic stimulation. *Am. J. Cardiol.* 52:1333–39
69. Brum, J. M., Sufan, Q., Lane, G., Bove, A. A. 1984. Increased vasoconstrictor activity of proximal coronary arteries with endothelial damage in intact dogs. *Circulation* 70:1066–73
70. Folts, J. D., Crowell, E. B., Rowe, G. G. 1976. Platelet aggregation in partially obstructed vessels and its elimination with aspirin. *Circulation* 54: 365–70
71. Bush, L. R., Campbell, W. B., Kern, K., Tilton, G. D., Apprill, P., et al. 1984. The effects of A_2-adrenergic and serotonergic receptor antagonists on cyclic blood flow alterations in stenosed canine coronary arteries. *Circ. Res.* 55:642–52
72. Ashton, J. H., Benedict, C. R., Fitzgerald, C., Raheja, S., Taylor, A., et al. 1986. Serotonin as a mediator of cyclic flow variations in stenosed canine coronary arteries. *Circulation* 73:572–78
73. Bush, L. R., Campbell, W. B., Maximilian, L., Tilton, G. D., Willerson, J. T. 1984. Effects of the selective thromboxane synthetase inhibitor dazoxiben on variations in cyclic blood flow in stenosed canine coronary arteries. *Circulation* 69:1161–70
74. Ashton, J. H., Schmitz, J. M., Campbell, W. B., Ogletree, M. L., Raheja, S., et al. 1986. Inhibition of cyclic flow variations in stenosed canine coronary arteries by thromboxane A_2/prostaglandin H_2 receptor antagonists. *Circ. Res.* 59:568–78
75. DeCaterina, R., Carpeggiani, C., L'Abbate, A. 1984. A double-blind, placebo-controlled study of ketanserin in patients with Prinzmetal's angina. *Circulation* 69:889–94
76. Allcock, J. M., Drake, C. G. 1965. Ruptured intracranial aneurysms; the role of arterial spasm. *J. Neurosurg.* 22:21–29
77. Fisher, C. M., Robertson, G. H., Ojemann, R. 1977. Cerebral vasospasm with ruptured saccular aneurysm: the clinical manifestations. *Neurosurgery* 1:245–48
78. Allen, G. S., Ahn, H. S., Preziosi, T. J., Battye, R., Boove, S. C., et al. 1983. Cerebral arterial spasm—a controlled trial of nimodepine in patients with subarachnoid hemorrhage. *N. Engl. J. Med.* 308:619–24
79. Ellis, E. F., Nies, A. S., Oates, J. A. 1977. Cerebral arterial smooth muscle contraction by thromboxane A_2. *Stroke* 8:480–83
80. Harper, A. M., MacKenzie, E. T. 1977. Cerebral circulatory and metabolic effect of 5-hydroxytryptamine in anesthetized baboons. *J. Physiol.* 271:721–33
81. Thompson, J. A., Wei, E. P., Kontos, H. A. 1984. Inhibition by ketanserin of

serotonin induced cerebral arteriolar constriction. *Stroke* 15:1021–24
82. Vallfors, B., Dahlstrom, A., Bostrom, S., Ahlman, H. 1985. Influence of ketanserin on 5-hydroxytryptamine-induced cerebrovascular spasm in the cat. *J. Cardiovasc. Pharmacol.* 7:S60–S63
83. Halpern, A., Kuhn, P. H., Shaftel, H. E., Samuels, S. S., Shaftel, N., et al. 1960. Raynaud's disease. Raynaud's phenomenon and serotonin. *Angiology* 11:151–67
84. Winkelmann, R. K., Goldyne, M. E., Linscheid, R. L. 1976. Hypersensitivity of scleroderma cutaneous vascular smooth muscle to 5-hydroxytryptamine. *Br. J. Dermatol.* 95:51–56
85. Seibold, J. R. 1985. Serotonin and Raynaud's Phenomenon. In *Serotonin and the Cardiovascular System,* ed. P. M. Vanhoutte, pp. 189–97. New York: Raven. 288 pp.
86. Seibold, J. R., Terregino, C. A. 1986. Selective antagonism of S_2-serotonergic receptors relieves but does not prevent cold induced vasoconstriction in primary Raynaud's phenomenon. *J. Rheumatol.* 13:337–40
87. Stranden, E., Roald, O. K., Krohg, K. 1982. Treatment of Raynaud's phenomenon with the 5-HT_2-receptor antagonist ketanserin. *Br. Med. J.* 285:1069–71
88. Van Nueten, J. M., De Ridder, W., Vanhoutte, P. M. 1984. Ketanserin and vascular contractions in response to cooling. *Eur. J. Pharmacol.* 99:329–32
89. Hollenberg, N. K., Harrington, D. P., Garnic, J. D., Adams, D. F., Abrams, H. L. 1983. Renal angiography in the oliguric state. In *Abrams Angiography,* ed. H. L. Abrams, 2:1299–1325. Boston: Little, Brown. 1816 pp. 3rd ed.
90. Kimberly, R. P., Grill, J. R., Bowden, R. E., Keiser, H. R., Plotz, P. H. 1978. Elevated urinary prostaglandins and the effects of aspirin on renal function in lupus erythematosus. *Ann. Int. Med.* 89:336–41
91. Ciabattoni, G., Cinotti, G. A., Pierucci, A., Simonetti, B. M., Manzi, M., et al. 1984. Effects of sulindac and ibuprofen in patients with chronic glomerular disease. *N. Engl. J. Med.* 310:279–83
92. Spinazzola, A. J., Sherrod, T. R. 1957. The effects of serotonin (5-hydroxytryptamine) on renal hemodynamics. *J. Pharmacol. Exp. Ther.* 119:114
93. McCubbin, J. W., Kaneko, Y., Page, I. H. 1962. Inhibition of neurogenic vasoconstriction by serotonin. Vasodilator action of serotonin. *Circ. Res.* 11: 74–83
94. Erspamer, V. 1953. Pharmacological studies on enteramine (5-hydroxytryptamine). Influence of sympathomimetic and sympatholytic drugs on the physiological and pharmacological actions of enteramine. *Arch. Int. Pharmacodyn Ther.* 93:293–316
95. Vyden, J. K., Lent, D., Nagasawa, K., Carvalho, M., Serruya, A., Corday, E. 1974. The effects of serotonin on regional hemodynamics in the vascular system. *J. Clin. Pharmacol.* 14:434–41
96. Emannel, D. A., Scott, J., Collins, R., Haddy, F. J. 1959. Local effect of serotonin on renal vascular resistance and urine flow rate. *Am. J. Physiol.* 196: 1122–26
97. Wright, C. E., Angus, J. A. 1983. Haemodynamic response to ketanserin in rabbits with Page hypertension: Comparison with prazosin. *J. Hypertension* 1:183–90