Serotonin Receptors in Human Coronary Arteries

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Serotonin (5-hydroxytryptamine, 5-HT) was first identified in serum in 1949 by M. Rapport. At that time, the importance of 5-HT was quite modest: The serum vasoconstrictor that appeared when blood was allowed to clot was an important source of artifactual vasoconstriction in investigations aimed at discovering substances possibly causing hypertension. Since then, however, a great interest has been endowed to 5-HT research, as indicated by the remarkable number of full publications in this area of research.

In mammals, about 90% of 5-HT present in the body is stored in the gastrointestinal tract, mainly in enterochromaffin cells. Of the remaining 5-HT, most is present in cells of the central nervous system and circulating platelets. Part of the 5-HT that is released by enterochromaffin cells overflows to the capillary blood and reaches the liver through the portal circulation. In the liver, most of it is degraded enzymatically. Of the remaining fraction, little escapes the uptake by the pulmonary endothelium that inactivates it by means of monoamine oxidase and catechol-O-methyltransferase. The final fraction of 5-HT present in the plasma is taken up avidly by platelets, which store it in their dense granules. As a consequence, as long as platelets do not aggregate, peripheral arterial blood contains little or no free 5-HT. However, whenever platelet aggregation is initiated and dense granules release their contents, 5-HT is liberated in the blood and can exert its pathophysiological effects through activation of specific membrane receptors.

5-HT Receptors

The first major attempt to classify serotonergic receptors was by Gaddum and Picarelli in 1957, who described "D" and "M" receptors in the guinea pig ileum according to whether the response to 5-HT was blocked by phenoxybenzamine or morphine. Later, binding sites for 5-HT in brain tissues have been subclassified into 5-HT1 and 5-HT2 serotonergic binding sites. The former have a greater affinity for agonists and can be characterized by binding of [3H]serotonin; the latter have a higher affinity for antagonists and can be labeled with [3H]spiropiridol. More recently, a number of other 5-HT receptors have been identified (for a review, see Reference 4). It is worth noting that the 5-HT1-like receptor subclass is itself a heterogeneous group, as suggested by a number of studies.

In this issue of Circulation, Kaumann et al report the results obtained in experiments conducted in vitro on human epicardial coronary arteries isolated from patients undergoing heart transplantation for a variety of heart diseases. In this article, Kaumann et al describe the existence of both 5-HT1-like and 5-HT2 receptors in human epicardial coronary arteries and that the relative contribution of 5-HT1-like receptors in evoking contractions in response to 5-HT is predominant with respect to 5-HT2 receptors. These conclusions are based on the findings that 5-HT-induced contraction of human coronary arteries is only partially blocked by ketanserin, a selective 5-HT2 receptor antagonist, and that sumatriptan, a pure 5-HT1 receptor agonist clinically used for the treatment of migraine, is also capable of eliciting coronary constriction, although to a lesser extent with respect to 5-HT. Furthermore, binding assays using transfected receptors indicate that the human coronary 5-HT1 receptor more closely resembles the 5-HT1D receptor.

5-HT has complex and sometimes opposite effects on blood vessels, its net results being dependent on the species, the route of administration, the experimental conditions under which the amine is released or administered, and the presence of a functional endothelium. A particular difficulty in unraveling the vascular effects of serotonin has been the lack of selective antagonists against its different receptors. Recently, however, a number of 5-HT receptor antagonists, such as ketanserin, have become available for experimental and clinical studies. These new drugs have proved to be extremely useful in increasing our understanding of the pathophysiological role of 5-HT in a variety of cardiovascular disorders. A few years ago, the consensus in the field was that the arterial constriction induced by 5-HT was almost invariably mediated by activation of 5-HT2 receptors, with the possible exception of cerebral arterial vessels. Later studies, however, described that under some circumstances, 5-HT-induced coronary constriction can be partly mediated by activation of 5-HT1 receptor subtypes.

The report by Kaumann and colleagues provides further evidence that both 5-HT1 and 5-HT2 receptors are involved in the vasoconstrictor action of 5-HT in...
human coronary arteries. This finding, although not entirely original, further emphasizes the complexity of the vascular roles for 5-HT receptor subtypes. In addition, Kaumann and colleagues report evidence that 5-HT receptors predominate over 5-HT receptors in causing vasoconstriction of human coronary arteries. This observation, however, is in contrast with previous work reported in the literature. Indeed, some studies have described that the 5-HT-induced contraction of human coronary arteries is predominantly mediated by 5-HT receptor subtypes, although 5-HT-like receptors may also play a role. In addition, it is evident from the study of Kaumann and colleagues that a large interpatient variability exists in terms of the relative contribution of 5-HT-mediated contraction. Thus, the disagreement with previous studies, the large interpatient variability, and the fact that coronary arteries were harvested from patients with a variety of cardiovascular disorders who were on a number of medications should induce caution in assigning more importance to 5-HT receptors in mediating 5-HT-induced coronary vasoconstriction.

Of note is the demonstration that sumatriptan is a pure 5-HT agonist. This compound was introduced for the treatment of migraine on the assumption that it caused vasoconstriction only of cerebral arterioles that are particularly rich in 5-HT receptors. However, Kau mann et al have convincingly shown that sumatriptan, under the experimental conditions used, can indeed constrict human epicardial coronary arteries. This finding, associated with a number of recent studies that indicate that sumatriptan administration may precipitate angina pectoris and even cause myocardial infarction, calls for great caution in use.

**In Vivo Studies of the Coronary Circulation**

Because of the existence of a number of different cellular systems that potentially may be affected by 5-HT, the effects of 5-HT are much more complex in vivo. First, once 5-HT is released by activating platelets, the first targets probably are the platelets themselves. Indeed, the monoamine activates serotoninergic receptors of the 5-HT subtype on the platelet membrane. This accelerates the turnover of phosphoinositides, resulting in an activation of the platelets and release of other vasoactive substances, such as thromboxane A, which may result in coronary vasoconstriction as well. The importance of this platelet-mediated coronary vasoconstriction is outlined by studies conducted in dogs with experimental coronary stenosis and endothelial injury in which platelet activation leads to a marked coronary vasoconstriction at the site of platelet–vessel wall interaction. It is worth emphasizing that this vasoconstriction can be prevented or significantly reduced by administration of selective 5-HT receptor antagonists, suggesting a prominent role of these 5-HT receptor subtypes in causing this platelet-related coronary vasoconstriction.

At the arteriolar level and in a number of large conduit vessels, 5-HT causes the relaxation of vascular smooth muscle and thus dilation. There is general agreement that this 5-HT-induced vasodilatation is mediated through activation of 5-HT receptors located on endothelial cells with the consequent release of endothelium-derived relaxing factor (in the form of nitric oxide or a nitroso-derivative yielding nitric oxide). Thus, it can be anticipated that the effects of 5-HT in the intact coronary circulation will be complex. Indeed, Brum et al reported that in anesthetized dogs, 5-HT caused dose-dependent constriction of coronary arteries with injured endothelium. In contrast, Chu and Cobb showed that in conscious dogs without endothelial damage, 5-HT caused a dose-related biphasic response characterized by an initial increase in coronary artery diameter followed by a delayed vasoconstriction. Hence, the in vivo vascular responses to 5-HT will depend, at least in part, on the integrity of the endothelial cell lining. If the latter is intact, it will form a diffusion barrier preventing the monoamine from permeating into the media; in addition, the endothelial cells take up the monoamine and degrade it enzymatically or store it. The 5-HT reaching 5-HT serotoninergic receptors on the endothelial cells will trigger the release of endothelium-derived relaxing factor. This not only will cause relaxation of the underlying vascular smooth muscle but also will help to prevent platelet adhesion and curtail platelet aggregation.

Studies conducted in humans also provide evidence that 5-HT has complex effects on the coronary circulation. In patients with normal coronary arteries, 5-HT causes a dose-dependent increase in coronary blood flow as well as an increase in the diameter of the coronary artery where the amine was infused. These vasodilating effects were mediated through activation of non-5-HT receptors, since they were not blunted but instead potentiated after administration of ketanserin. In contrast, in patients with coronary atherosclerotic lesions, intracoronary infusions of 5-HT caused a dose-dependent vasoconstriction evidenced by a decrease in both coronary artery diameter and flow. Interestingly, the vasoconstricting effects of 5-HT in patients with coronary atherosclerosis were completely blocked after administration of ketanserin, thus suggesting a role of activation of 5-HT subtype receptors.

In another study, intracoronary infusion of 5-HT in patients with angiographically normal coronary arteries caused a biphasic response in proximal segments with dilation at low doses and constriction at high doses, a response also observed in dogs. In the same study, intracoronary infusion of 5-HT in patients with coronary artery disease caused only vasoconstriction leading to myocardial ischemia: Ischemia resulted from epicardial coronary spasm in patients with variant angina but from small vessel constriction in those with chronic stable angina; both epicardial spasm and distal coronary vessel constriction failed to respond to ketanserin. This observation suggests that activation of 5-HT-like receptors, either at hyperreactive sites in patients with variant angina or in the distal epicardial vessels of patients with chronic stable angina, may contribute to or cause myocardial ischemia when 5-HT is released during intracoronary platelet activation.

**Conclusions**

Several lines of evidence indicate that 5-HT may be important in modulating coronary artery tone in patients with atherosclerotic coronary lesions and in those with variant angina in the presence of intracoronary platelet activation. Establishing precisely the relative roles of 5-HT-like and 5-HT-like receptors in human
disease is difficult on the one hand because the variable findings in different reports and even in the same study of in vitro experiments reflect the varied conditions of the patients from whom the coronary segments were obtained. On the other hand, the behavior of selected segments tested in vitro under carefully controlled conditions may reflect only partially the behavior in vivo when vessels are exposed to a host of positive and negative vasomotor feedback loops.

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