Serotonin and the Vascular System
Role in Health and Disease, and Implications for Therapy

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Summary

Serotonin released from aggregating platelets can reach sufficient concentrations to affect local vascular function in a number of ways. The monoamine can cause contraction of blood vessels by its direct action on smooth muscle or by potentiating the effect of other vasoconstrictor agents. It can also induce vasodilatation by a direct relaxing effect on smooth muscle, by inhibition of adrenergic nerves, and by release of an uncharacterised relaxing factor from endothelial cells. One of its most likely physiological roles is to aid in haemostasis by promoting platelet aggregation and by causing local vasoconstriction at sites of injury. It probably has a role in some forms of vascular pathology as well: it may contribute to vasospasm of cerebral, coronary, and digital arteries, particularly if there is endothelial dysfunction or damage.

Much evidence has implicated serotonin (5-hydroxytryptamine) in the pathogenesis of migraine. Serotonergic agonists, such as ergotamine, and antagonists, such as methysergide and pizotifen, are both used in therapy of migraine. Promising but conflicting early results have not yet defined a place for serotonergic antagonists in other vasospastic disorders. The antihypertensive efficacy of one serotonergic antagonist, ketanserin, raises questions about the possible involvement of serotonin in either the initiation or the maintenance of the elevated peripheral vascular resistance in several forms of hypertension, including essential hypertension.

The vasoconstricting agent present in serum after blood has clotted was identified in 1949 as serotonin (5-hydroxytryptamine) [Page 1954; Rapport 1949; fig. 1]. In 1952 the autacoid that is concentrated in enterochromaffin cells, and which stimulates the gut, also was recognised to be serotonin (Erspermer & Asero 1952). Serotonin was soon afterward isolated in the brain, and with the discovery of the antagonistic properties of lysergic acid diethylamide (Gaddum 1953), the recognition of the function of serotonin as a neurotransmitter followed. Serotonin has complex and sometimes opposite effects on the cardiovascular system, depending on the species, the route of administration and the experimental conditions, which prompted the term ‘amphibaric hormone’ (Page & McCubbin 1953). A particular difficulty in unravelling the effects of serotonin has been the lack of specific antagonists against its different actions. Recently, a number of serotonergic receptor subtypes have been
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classified. One of the most useful tools in this respect is ketanserin, a selective blocker of receptors mediating contraction to serotonin in peripheral vascular smooth muscle; it has made possible a greater understanding – and more speculation – about the role of serotonin in the control of vascular function.

Important quantities of serotonin are found in enterochromaffin cells in the gut, platelets, and serotonergic neurons in the central nervous system (CNS) and the gastrointestinal wall. Serotonin crosses the blood-brain barrier poorly, and the serotonin located within the CNS is synthesised locally. Central serotonergic neural pathways are involved in cardiovascular regulation (see Kuhn et al. 1980). Apart from that which is synthesised in and confined to the CNS, serotonin originates from gastrointestinal enterochromaffin tissue (Thompson 1971). When it is released from these cells, part of it gains access to the plasma. Free serotonin is avidly taken up by platelets (Linggaerde 1977), or destroyed by the liver and by the pulmonary endothelium (Thompson 1971; Strum & Junod 1972). Whether significant concentrations of free serotonin are present in peripheral plasma is uncertain, given the difficulty of ensuring freedom from contamination by release from platelets during the preparation of the specimen (Erspamer 1961; Sjaastad 1975). Estimates of free plasma concentrations of serotonin range from 3 to 20 µg/L (Crawford 1965; Engbaek & Voldby 1982; Genetke et al. 1968; Somerville 1976).

Outside the CNS, cells sensitive to exogenous serotonin are located in many tissues, including the bronchi and the gastrointestinal tract. Receptors are present, too, in many parts of the cardiovascular system, mediating diverse effects. The question can be asked whether concentrations of serotonin ever increase to the extent that they stimulate these receptors and produce a physiological or pathological response. Outside of the intestinal vasculature the only immediate source of serotonin that could exert cardiovascular effects is serotonin released from platelets. Turpie et al. (1982) recently reviewed the evidence for increased platelet consumption in various cardiovascular diseases. Serotonin, along with other vasoactive substances such as calcium, adenosine diphosphate (ADP), and thromboxane A₂, is released when platelets are activated (Holmsen 1975). Keeping in mind its rapid disposition by endothelial monoamine oxidase and by reuptake into platelets, one might predict that effects of serotonin would predominate at discrete sites where platelet activation occurs rather than contribute to the general homeostasis of the cardiovascular system.

1. Pharmacology of Serotonin

The complexity of the vascular effects of serotonin depends on its ability to affect the function of many cells. Serotonin probably has little direct effect on the myocardium, but it can stimulate vagally mediated chemoreflexes, causing cardiac slowing and a decrease in cardiac output by eliciting a von Bezold-Jarisch reflex (Page 1954). It can also have an inotropic effect, probably by increasing release of noradrenaline (norepinephrine) from adrenergic nerve endings (Buccino et al. 1967; Fillion et al. 1971). However, the most relevant effects of serotonin relate to its action on blood vessels.