A VEXING HORMONE—SEROTONIN

JAMES W. McCUBBIN, M.D.
Division of Research

SEVERAL years ago we wrote editorially that serotonin should provide "tenure for the pharmacologist." As it has turned out, this prophecy was gross understatement. And, despite many hundreds of publications on serotonin since, it is frustrating to have to record now that it is still not known surely what physiologic role or roles serotonin may play. It has been referred to appropriately as "a hormone in search of a function," and it should be of succor to the pharmacologic and allied sciences for some time to come. It occurs normally in several body tissues, and it can be shown to have powerful effects on nearly all biologic systems. The sorting out of what normal and abnormal functions serotonin may mediate is a large and intriguing task for the future, but it is timely now to offer a progress report on the present status of our knowledge concerning some of the effects of serotonin on the cardiovascular system.

Serotonin was first isolated in the Research Division. This fact is generally known—but it is not so well known that the discovery is a fine example of serendipity. A series of experiments was not going well because of interference by a vasoconstrictor material that appeared when blood clotted. A plan was devised to isolate this interfering "nuisance" in order that the experiments could proceed—and it turned out to be 5-hydroxytryptamine—serotonin. Fortunately, the importance of the isolation was recognized and was reported in 1948. Of course, the then more important experiments with which serotonin was interfering are now largely forgotten.

Although the vasoconstrictor effect of serotonin was the first one observed, the usual effect of very small and more nearly possible physiologic amounts is vasodilation and fall in arterial pressure. This is the case when there is normal or increased neurogenic vasoconstriction. In the absence of sympathetic vasomotor activity, serotonin is invariably vasoconstrictor and pressor. Thus, degree of activity of the sympathetic nervous system, and hence degree of neurogenic vasoconstriction, appears to be by far the most important determinant of response to serotonin. This deduction led quite naturally to the hypothesis that small amounts of normally occurring serotonin may participate in the regulation of blood flow by influencing degree of response to neurogenic vasoconstrictor impulses.

The mechanism of the inhibiting action of serotonin on neurogenically mediated vasoconstriction is unique, so far as is known. Sympathetic nerve endings in the cardiovascular system are of three known types: (1) constrictor and (2) dilator receptors that are stimulated by adrenergic neurohumors, and (3) dilator receptors that respond to acetylcholine and similar agents. Perfusion experiments employing different portions of the vascular bed have permitted measurement of the effect of

serotonin on these different receptors. Dilator receptors responsive to acetylcholine were made insensitive by administration of atropine, but the vasodilator action of serotonin was unchanged, indicating that these receptors do not participate in the response. Next, it was considered that serotonin may block adrenergic constrictor receptors or interfere with the action of the humoral mediator, norepinephrine. It was found that serotonin did not modify response to administered norepinephrine though, at the same time, it caused marked inhibition of constrictor responses to sympathetic nerve stimulation. The remaining possibility was that serotonin has an effect on adrenergic vasodilator receptors.

Epinephrine, unlike norepinephrine, stimulates both adrenergic constrictor and dilator receptors, though the net effect in most vascular beds is generally vasoconstriction. It was observed that serotonin caused slight inhibition of the constrictor response to epinephrine; this suggested that the stimulating effect of epinephrine on dilator receptors was somehow enhanced by serotonin. Electric stimulation of sympathetic nerves can be expected to activate both constrictor and dilator receptors, though, as with epinephrine, the net effect is vasoconstriction. If, during stimulation, response of the dilator receptors is made more prominent by serotonin, there would be decrease in the total vasoconstrictor response, or relative vasodilation. This surmise was supported by other experiments. When the vasodilator receptors were made inactive by administration of a selective blocking agent, the ability of serotonin to inhibit neurogenic vasoconstriction was completely lost.

This interplay between serotonin and the sympathetic vasomotor system is but one of the many ways in which serotonin can modify cardiovascular function, but it may be one of the more important. The story is considerably more complicated than has been indicated; this brief outline of the investigation of a mechanism of action of a naturally occurring hormone is meant to indicate the general manner in which these problems are explored, and to suggest the reasons for our interest in cardiovascular control systems.

Serotonin also has a central effect on vasomotor centers that modifies sympathetic outflow to the cardiovascular system. It occurs normally in brain tissue and in especially high concentrations in the hypothalamus. Our interest in what it might be doing there developed, not unusually, through a round-about series of observations. We were investigating the mechanisms by which reserpine lowers arterial pressure and inhibits cardiovascular reflexes. Measurements of electric activity of the splanchnic nerve, which is largely preganglionic, revealed that part of the hypotensive activity of reserpine depends upon an effect on the central nervous system. After intravenous injection of reserpine, splanchnic activity slowly diminished. To support the conclusion that reserpine has a central effect that causes diminution of sympathetic outflow, very small doses were given into a lateral ventricle. When given intravenously these small dosages had no effect on splanchnic activity or arterial pressure. When given into a lateral ventricle, however, they caused lowering of arterial pressure and marked inhibition of cardiovascular reflexes. It had

been shown previously by others that reserpine causes release of serotonin and norepinephrine from their bound forms in body tissues. These separate observations led to the postulate that the central effect of reserpine on vasomotor activity may depend upon release of these amines. Accordingly, serotonin was injected into a lateral ventricle to determine if it would mimic the action of reserpine given in the same manner. It did, and norepinephrine was found to have the same effect.

Since serotonin and norepinephrine in appropriate dosages are both vasoconstrictor agents, it was considered that their central effects might depend in some manner on this property. This may be the case, for superimposed injection of a vasodilator drug diminished or eliminated the central inhibitory effect of both serotonin and norepinephrine. Further, central injection of vasodilator drugs also opposed the inhibitory action of reserpine. Thus, the central effect of reserpine on vasomotor activity appears likely to depend upon release of serotonin and norepinephrine from their bound forms, and the inhibitory effect of these amines possibly depends upon their ability to cause vasoconstriction and local change in blood flow. Whether or not slow, continuous release of small amounts of serotonin and norepinephrine occurs normally and is a factor in the physiologic regulation of vasomotor activity, and therefore arterial pressure, is an interesting problem to be explored in the future.

These are but two general aspects of the pharmacology of serotonin which have occupied us, but we hope that they give a hint of the possible importance of serotonin in the regulation of arterial pressure. The title indicates the hormone is "vexing." Thus far, because of our unsuccessful efforts to date to determine precisely the functions serotonin may normally mediate, it is just this.