The Variable Arterial Pressure Response to Serotonin in Laboratory Animals and Man

By Irvine H. Page, M.D., and J. W. McCubbin, M.D.

Arterial pressure response to serotonin depends largely upon four main actions of the drug: direct vasoconstriction, a von Bezold-like reflex, transient ganglion blockade and peripheral inhibition of neurogenic vasoconstriction. The relative prominence of these actions differs depending upon the dose of serotonin, species tested and degree of pre-existing neurogenic vasoconstriction.

The vasoconstrictor principle in clotted and defibrinated blood was isolated and partially identified by Rapport, Green and Page who named it serotonin. It was further shown by Rapport to be a 5-hydroxy indole base combined with equimolar parts of creatinine and sulfuric acid. Distribution of serotonin in the body may be widespread: Erspamer demonstrated it in mammalian spleen and intestinal mucosa where it was given the name enteramine, later identified by Erspamer and Asero as 5-hydroxytryptamine.

Recently, serotonin was synthesized by Hamlin and Fischer who have provided a generous amount of the material so that its pharmacologic activity might be studied. Page showed the identity of the vascular actions of natural serotonin and synthetic 5-hydroxytryptamine, and he and others have called attention to the widely variable arterial pressure response serotonin evokes in dogs and cats. So varied are the effects of serotonin on arterial pressure that we submit the term amphibaric [Gr. amphis, of both kinds; Gr. baros, weight (pressure)] as one appropriately descriptive of the drug's actions.

Page found the usual response to a test dose of 0.06 or 0.12 mg. of serotonin injected intravenously into normal dogs to be triphasic, consisting of (A) an initial quick fall in arterial pressure with bradycardia followed immediately by (B) a sustained pressor response of from 20 to 60 mm. Hg succeeded in turn by (C) a prolonged depressor response usually of lesser magnitude than the pressor response. This series of events did not comprise a "normal" response, but the one seen most often in normal dogs.

The initial quick fall in arterial pressure (A) was shown to depend largely, but not entirely, upon a von Bezold-like reflex. Through the courtesy of Dr. A. S. Marrazzi, studies are presented here that suggest the initial fall in pressure depends also upon a ganglion blocking action of serotonin. The pressor action of serotonin (B) was shown by perfusion experiments to depend, at least in part, upon a direct vasoconstrictor action. The mechanism of the late and prolonged depressor action of serotonin (C) is considered in this study.

Since Page found that arterial pressure response to serotonin was depressor in neurogenic hypertensive dogs, and pressor in dogs after administration of ganglion blocking agents, experiments were performed to determine by what mechanism the degree of neurogenic vasoconstriction alters vascular response to serotonin.

Methods

Cats, dogs and rabbits were anesthetized with sodium pentobarbital (32 mg. per kilogram) given intravenously or intraperitoneally. Arterial pressure was recorded from a cannulated femoral or carotid artery by a mercury manometer. Test drugs were given through a needle inserted in a femoral vein. Tracheal intubation was done in most experiments and artificial respiration was used when necessary. A slow drip of saline was usually given into a femoral vein. Special technics are described in appropriate sections of the results.
The creatine-sulfate salt of serotonin* was made into a solution containing 0.6 mg. of serotonin per milliliter; doses are given as milligrams of serotonin (5-hydroxytryptamine). Cinobufotenine (dimethyl-5-hydroxytryptamine) flavianate† was made into a solution containing 0.1 mg. of cinobufotenine per milliliter; doses are given as milligrams of cinobufotenine.

Chronic neurogenic hypertension was produced by section of the carotid sinus and aortic depressor nerves.

**RESULTS**

In chronic neurogenic hypertensive dogs, arterial pressure responses to serotonin were entirely depressor and more sustained than depressor responses in normal dogs, often lasting for from 8 to 10 minutes. Rarely, the depressor response was preceded by a small initial rise in pressure. In contrast with responses in normotensive dogs, increase in the dose of serotonin did not tend to make the response pressor. Instead, fall in pressure was greater when the dose of serotonin was increased.

Cinobufotenine, differing from serotonin by possessing two more methyl groups, also caused fall in arterial pressure in neurogenic hypertensive dogs but, on a weight basis, was only about one-half as active as serotonin. In normal dogs, cinobufotenine increased arterial pressure, elicited hyperpnea and, again, was approximately one-half as active as serotonin. Atropine (0.6 to 6.0 mg.) did not lower arterial pressure or reduce the hypotensive action of serotonin in neurogenic hypertensive dogs, though response to 0.05 mg. of Mecholyl was abolished.

During the acute neurogenic hypertension that follows immediately after section of the buffer nerves, the depressor action of serotonin was augmented, but the change in response was not so striking as in chronic neurogenic hypertensive animals. Depressor responses were of lesser magnitude, not so sustained, and were more often preceded by an initial small pressor response.

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* Dr. R. K. Richards and Dr. K. K. Hamlin, Jr., of Abbott Laboratories, kindly provided the serotonin.
† Dr. K. K. Chen kindly provided the cinobufotenine.

Since the depressor action of serotonin is more prominent in dogs hypertensive due to section of the buffer nerves, and since this hypertension results, presumably, from increased transmission of impulses over the sympathetic nervous system, the effect of interruption of this activity on response to serotonin was determined.

Dogs with acute or chronic neurogenic hypertension, or normal dogs with primarily depressor response to serotonin, reacted similarly to serotonin after administration of intracisternal procaine or ganglion blockade with hexamethonium or tetraethylammonium chloride (TEAC); responses all became entirely pressor (table 2). This change in response from depressor to pressor was found not to depend upon simple lowering of blood pressure since similar hypotensions could be induced by infusion of sodium nitroprusside without abolishing the depressor action of serotonin.

Since TEAC is also markedly depressor in neurogenic hypertensive animals (Page and McCubbin†) and its action also becomes pressor when neurogenic vasomotor outflow is abolished, as after intracisternal procaine or cord section, there is a similarity between the actions of serotonin and TEAC in these animals. To determine whether the depressor action of serotonin also depends upon ganglion blockade, innervated legs of neurogenic hyp-
pertensive dogs were perfused with a constant output pump. To assure that drugs given into the body could not reach the perfused leg, the leg was dissected entirely free from the body (referred to as "recipient") with an electrocautery knife with care to damage as little as possible the sciatic and femoral nerves and the femoral artery and vein. The vessels were cannulated and the leg perfused with blood from a donor animal passed through a roller pump. Serotonin given into the recipient caused the usual deep depressor response characteristic of neurogenic hypertensive dogs, but failed to alter perfusion pressure in the leg as measured by a mercury manometer introduced into the arterial side of the perfusion system. TEAC caused a marked systemic hypotensive response and caused marked lowering of leg perfusion pressure as well (fig. 1).

It seems clear that the hypotensive action of serotonin does not depend upon central inhibition of neurogenic outflow or upon ganglion blockade, and that its hypotensive effect must depend upon a more peripheral action. To test this, serotonin was given directly into the arterial side of the leg perfusion system where it caused vasodilation, this time without affecting arterial pressure in the recipient. When neurogenic tone was reduced by administration of intracisternal procaine or by blocking ganglia with TEAC or hexamethonium, or by nerve section, responses in the perfused leg to directly administered serotonin were reversed from depressor to pressor, as in the body.

Drs. A. S. Marrazzi and E. R. Hart have been kind enough to measure the influence of serotonin on nerve impulse transmission through the ciliary ganglion and permit the results to be included in this report. Technic was that described by C. turn Suden and A. S. Marrazzi.

In a dog lightly anesthetized with sodium pentobarbital, submaximal and constant intensity shocks were delivered to the preganglionic oculomotor nerve at the rate of 2 per second; postganglionic action potentials in

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the ciliary nerve were recorded on a cathode ray screen where they were photographed continuously. Local blood supply of the ganglion was preserved so that injected materials might reach ganglion synapses. Times at which postganglionic action potentials were recorded are indicated on the blood pressure curve (fig. 2A). Following a stimulus artefact, the control trace (fig. 2B) shows a low wave complex from fibers passing through the ciliary ganglion without synapsing; superimposed is the longer and slower C wave, the postsynaptic response. Space between dots represents 10 milliseconds. Ten seconds after close injection of 0.5 gamma per kilogram of serotonin into the carotid artery, the second record (fig. 2C) shows that action potentials in the nonsynapsing fibers are unaltered, but that the postsynaptic action potentials have been almost completely obliterated. The effect was transient: record 2D, taken 26 seconds after injection of serotonin, is similar to the control tracing.

Serotonin had approximately one-half the ganglion blocking action of adrenaline.

These results accord with those obtained in the perfused dog's leg. Serotonin did not have a prolonged blocking action that might explain its sustained depressor effect. Its quick, transient blocking action corresponds in time with the initial fall in pressure shown by Page to depend in large part upon a von Bezold-like reflex. In those experiments, vagus section did not, however, completely eliminate the depressor response; the residual effect may be due to the ganglion blocking action of serotonin observed by Marrazzi and Hart.

It was considered that serotonin might
interfere with the action of humoral mediators liberated from sympathetic nerve endings. Production of hypertension by infusion of noradrenaline did not, however, cause response to serotonin to become depressor; instead, there was usually augmentation of its pressor action (fig. 3). Hypertension due to increased intracranial pressure also failed to reverse the action of serotonin from pressor to depressor, cats was also abolished and reversed to a pressor one by ganglion blockade with hexamethonium or TEAC (fig. 4). Pithing did likewise and simultaneously augmented the pressor action of angiotonin and noradrenaline. The action of cinobufotenine in normal cats differed from that of serotonin by raising arterial pressure and eliciting hyperpnea. It was regularly pressor in doses of 0.04 mg.

**Fig. 2.** Recordings of action potentials in the ciliary nerve produced by test shocks delivered to the preganglionic oculomotor nerve as influenced by serotonin. The tracing at the top indicates the times during the blood pressure response when the action potentials shown below were recorded. These data and recordings were kindly supplied to the authors by Drs. A. S. Marrazzi and E. R. Hart.

but, in this experiment, the stimulus is so strong that the hypotensive action of TEAC also often failed to appear.

Bilateral adrenalectomy in both cats and dogs failed to modify significantly response to serotonin either immediately after the operation or after four days of maintenance therapy with adrenal cortical extract.

The normal depressor action of serotonin in rabbits was like that in cats rather than dogs; it evoked purely depressor responses. Bilateral section of the vagus nerves or atropine reduced the hypotensive response but did not abolish it. But arterial pressure response to serotonin in rabbits was reversed from depressor to pressor after ganglion blockade with hexamethonium or TEAC.
To determine whether respiratory stimulation after intravenous injection of serotonin might contribute to rise in arterial pressure, response was measured in dogs before and after injection of 5 mg. of succinyl choline, which abolished respiratory movements. Responses were the same despite failure of serotonin to stimulate respiration after administration of succinyl choline.

**ARTERIAL PRESSURE RESPONSE TO SEROTONIN IN HYPERTENSIVE PATIENTS**

Since the difference in response between normotensive and neurogenic hypertensive dogs is striking, it was considered that vascular response to serotonin in patients with hypertension might provide an index of the degree of participation of the nervous system in the mechanism of hypertension in individual patients.

Arterial pressure response to serotonin was measured in 20 hypertensive patients. A Peterson catheter was inserted through a 21 gage needle into the brachial artery and arterial pressure recorded continuously by means of a capacitance manometer and ink oscillograph. Drugs were injected through a polyethylene catheter inserted into an antecubital vein.

Response to serotonin in these patients...
resembled that in dogs rather than in cats and rabbits; small doses (0.06 or 0.12 mg.) commonly elicited minor fall in arterial pressure of 10/5 to 20/15 mm. Hg, usually with but slight pressor component in the response. Larger doses (0.3 to 1.8 mg.) produced the typical triphasic response observed in dogs; the depressor components of the response were somewhat less prominent in hypertensive human beings than in dogs. Pressor responses to the larger doses of serotonin were usually small, averaging 10/5 to 20/15 mm. Hg. As in dogs, atropine (0.6 mg.) often converted response to small doses of serotonin from depressor to pressor. Variation in response was marked but the difference in response existing between normotensive and neurogenic hypertensive dogs was unusual among the patients. A few did show pure depressor responses, however, and it is hoped that this group of patients may also show a good response to paravertebral sympathectomy.

Serotonin was an unpleasant drug to receive compared with equipressor doses of adrenaline, noradrenaline or angiotonin. It caused more discomfort than even large doses of TEAC. Most common complaints were nausea, tightness across the chest and dizziness. Many patients were observed to blush and simultaneously complain of a generalized tingling sensation. Nearly all had the sensation of gasping and would hyperventilate briefly. A few said they felt as if their bladders or bowels would empty. This array of side-effects was all of short duration, however, lasting for about the same length of time serotonin had an effect on arterial pressure.

**DISCUSSION**

Probably the most important mechanism controlling vascular reactivity to serotonin is degree of activity of the autonomic nervous system: when neurogenic vasoconstrictor tone is absent, whatever the species, response to serotonin is pressor; when neurogenic vasoconstriction is increased by section of the buffer nerves, response to serotonin is strikingly depressor. In these respects, serotonin has an effect on blood pressure like that of TEAC, the hypotensive action depending upon ganglion blockade and the hypertensive action, in part, upon direct constriction of blood vessels. Though effects on blood pressure of the two drugs are similar, their mechanisms of action are not the same. The major hypotensive action of serotonin was found to be due, not to interruption of impulse transmission through ganglia, but to a peripheral action.

Possibly serotonin acts as do the adrenergic blocking agents to prevent the constrictor action of adrenaline and/or noradrenaline released from sympathetic nerve endings. While these studies offer no direct proof that this is not the case, the reinjection of serotonin during hypertension due to infusion of noradrenaline showed an enhanced pressor action rather than a depressor one. We were unable to test the possibility that serotonin prevents release of adrenergic mediators at sympathetic nerve endings.

The late sustained fall in pressure due to elimination of neurogenic tone differs from and is not to be confused with the initial very brief fall in pressure preceding the pressor response. The latter is inhibited by vagus section or atropine and is probably, in part, a von Bezold effect as suggested by Page. The residual effect not eliminated by vagus section may depend upon a quick, transient interruption of impulse transmission through ganglia, as observed by Marruzzi and Hart. Reid and Rand attributed the initial brief fall in pressure to pulmonary vasoconstriction and considered the late and more sustained depressor effect of serotonin to depend upon a different and unknown mechanism, one that we believe to be an inhibition of neurogenic vasomotor tone.

Since small doses of serotonin usually produce depressor response in normal dogs and men, and larger doses pressor responses, it is probable that only small amounts of serotonin are necessary to inhibit neurogenic tone; it is only with large doses that the direct vasoconstrictor action of serotonin is sufficiently unmasked to be apparent. It is also probable that the pressor action of serotonin is more short-lived than the indirect depressor effect since, with a single dose, a sustained fall in
pressure usually appears after the initial pressor response.

Different degrees of normal resting neurogenic vasoconstriction might explain the species difference in response to serotonin. There is some evidence that the sympathetic nervous system is more active in cats than in dogs, and it is known that cats tolerate sympathectomy poorly compared with dogs and man. If neurogenic vaso-motor tone is more prominent in cats than in dogs and man, serotonin responses might be expected to be predominantly depressor. It is probable that the serotonin-induced von Bezold-like reflex is also more prominent in cats than in dogs.

Serotonin is a naturally occurring compound, and the possibility that it has a physiologic regulatory function on neurogenic vasoconstriction of arterioles should be kept in mind. Such a hypothesis has special interest in view of recent work concerning the effect of serotonin on contraction of invertebrate smooth muscle. Twarog has found that serotonin occurs in the byssus retractor and induces relaxation when it is added to the bathing media after muscle contraction due to electrical stimulation or to acetylcholine. She has suggested that the normal physiologic role of serotonin in this preparation is to induce relaxation. Thus, there is an analogy between the action of serotonin on the byssus retractor and its action on blood vessels of vertebrates stimulated by nerve impulses.

Adrenalectomy did not greatly alter the pattern of response to serotonin. Though Reid and Rand found that serotonin had a direct stimulating action on the adrenal medulla, adrenalectomy did not appreciably alter the pressor response to the doses of serotonin used in these experiments.

The introduction of two methyl groups into the serotonin molecule (cinobufotenine) changes its vascular action from depressor to pressor in cats. Despite the different response in cats, cinobufotenine has the same actions as serotonin in neurogenic hypertensive dogs; arterial pressure is reduced instead of raised. Chen, Jensen and Chen have shown previously that cinobufotenine has both cardiac stimulant and direct vasoconstrictor actions.

**Summary**

1. Arterial pressure response to serotonin is the resultant of several variables, of which four are of major importance: (1) a direct vasoconstrictor action; (2) a von Bezold-like reflex; (3) transient autonomic ganglion blockade and (4) peripheral inhibition of neurogenic vasoconstriction. Adrenalectomy had little effect on response.

2. Inhibition of neurogenic vasoconstriction was prominent in animals made hypertensive by section of the buffer nerves and resulted in entirely depressor responses to serotonin; when neurogenic tone was abolished, response to serotonin became strongly pressor. Inhibition of neurogenic vasoconstriction by serotonin did not depend upon ganglion blockade, or upon change in central vasomotor outflow, but upon a peripheral inhibiting or relaxing effect; suggestive evidence was obtained that this effect does not depend upon interference with the vasoconstrictor action of noradrenaline.

3. Dogs and hypertensive man responded similarly to serotonin but differently from cats and rabbits; the von Bezold effect and inhibition of neurogenic vasoconstriction may be more prominent actions of serotonin in cats and rabbits.

4. Cinobufotenine, on a weight basis, was approximately one-half as active as serotonin but had qualitatively similar actions except in cats where it was usually pressor when serotonin was depressor.

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Circ Res. 1953;1:354-362
doi: 10.1161/01.RES.1.4.354

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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