PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 178, 333–338 (1985)

MINIREVIEW

Action of Serotonin on the Gastrointestinal Tract (42016)

HERBERT S. ORMSBEE III AND JOSEPH D. FONDACARO[1]

Department of Pharmacology, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

Abstract. Serotonin is localized in the enterochromaffin cells of the gastrointestinal mucosa and within neurons in the enteric nervous system. It can be released into the blood or into the lumen of the gut. Serotonin inhibits gastric acid secretion and may be an endogenous enterogastrone. It appears to stimulate the production and release of gastric and colonic mucus. When placed on the serosal surface of the rabbit ileum *in vitro,* serotonin increases short-circuit current and inhibits the mucosal-to-serosal flux of NaCl. Serotonin potentially is involved in the pathogenesis of diarrhea due to amoebae or cholera. As an enteric neurotransmitter, serotonin affects neural modulation of gut smooth muscle function and may act either directly on mesenteric vascular smooth muscle or through enteric nerves to influence gastrointestinal blood flow. Thus, since serotonin may be involved in multiple physiological processes of digestion, this report reviews and summarizes the role of this ubiquitous substance in the major functions of the gastrointestinal system.

Serotonin (5-hydroxytryptamine) is 3-(β-aminoethyl)-5-hydroxyindole and is found throughout the gastrointestinal (GI) tract, mainly in the mucosa and in significant amounts in the myenteric plexus. The documented pharmacological effects of serotonin are manifold. It inhibits gastric acid secretion, stimulates mucus output, stimulates intestinal secretion, has both excitatory and inhibitory effects on motor function, and can alter mesenteric blood flow. Serotonin also may have physiologically important actions on each of these functions including a role as an enteric neurotransmitter or as an enterogastrone. The relevance of serotonin to particular GI disease states has not been well defined although attempts have been made to implicate either serotonin or serotonin antagonists as potential new therapies.

Localization and Release. The major locus of serotonin in the body appears to be the enterochromaffin cells (EC) of the intestinal mucosa. Immunohistochemically, serotonin-containing cells are found at the base of the crypts and villi of the small intestine (1). Release from the EC has been demonstrated in the rat duodenum *in vitro* by transmural electrical field stimulation (2) and the release appears to be mediated via adrenergic nerves (3). *In vivo,* serotonin is released into the portal circulation by vagal stimulation (4) and by splanchnic nerve stimulation (5). Vagal stimulation also releases serotonin into the gut lumen (6). Thus, extrinsic neuronal release of serotonin may initiate both local and hormonal effects of the amine. Interestingly, Kellum and Jaffe (7) have shown that acid perfusion of the canine duodenum raises portal venous serotonin levels consistent with a feedback inhibition of gastric acid secretion by serotonin, thus suggesting a possible role as an endogenous enterogastrone.

Neuronal actions of serotonin in the GI tract have been suggested for some time (8–10). Extensive work on the enteric serotonergic neurons has been reported over the years supporting an intrinsic neurotransmitter role for serotonin in the myenteric plexus (11). Recent immunocytochemical evaluation of serotonergic neurons in the gut reveals their cell bodies to be in the myenteric plexus with their varicose axons reaching in an anal direction within the myenteric plexus and on to the submucous plexus (2). Enteric serotonergic neurons are interneurons which comprise about 2% of the immunoreactive neurons in the myenteric plexus. They appear to be organized for the control of descending neural pathways and possibly descending motor programs in the gut (13).

Effects on Gastric Acid Secretion. Following either peripheral or central administration, serotonin inhibits acid secretion in a number of species. In the conscious gastric fistula rat,

[1] To whom reprint requests should be sent.

0037-9727/85 $1.50

serotonin inhibited basal acid secretion and pepsin output when administered ip or icv. (14). In the isolated rat stomach preparation, 10^{-5} *M* serotonin inhibited histamine and pentagastrin-stimulated acid secretion without altering basal or bethanechol-stimulated secretion. The serotonin response was antagonized by methysergide and by indomethacin indicating more than one possible mechanism of action (15). In man, methysergide has been shown to increase basal and pentagastrin-stimulated acid secretion, while metergoline actually inhibited secretion, raising questions concerning the action of endogenous serotonin on gastric secretion (16). Endogenous serotonin, released by duodenal acidification, inhibited acid output in canine gastric fistula preparations but did not inhibit acid output from a Heidenhain pouch (17). The H_1 antihistamine/antiserotonin agent, cyproheptadine, inhibits histamine-stimulated acid secretion in the dog making the interpretation of the mechanism of action of serotonin less well defined (18). In summary, serotonin appears to inhibit gastric acid secretion and may be an enterogastrone. Any interpretations of the actions of serotonin based on data with available "serotonin antagonists" must be examined critically.

Effects on Mucus Output. The notion that a physiologic role for serotonin in the GI tract might be to stimulate the production of a protective mucous lining has been put forth by Black and colleagues (19). These investigators demonstrated that serotonin, 5-hydroxytryptophan, and L-tryptophan increase the hexose output of the luminally perfused rat colon. The effect was blocked by chlorpromazine and methysergide, which also behaved as an agonist. In an earlier study (20), it was shown that iv serotonin produced an increase in output of gastric mucus in addition to reducing histamine-stimulated acid secretion. It has been suggested that the mucus-stimulating property of serotonin was not dependent upon its motility-enhancing effect (21). Whether serotonin can stimulate mucus output from the duodenum does not appear to have been thoroughly studied.

Effects on Intestinal Transport. It is well recognized that serotonin causes net water and electrolyte secretion in the small intestine *in vivo* (22–24). These changes are not accompanied by changes in enterocyte adenylate cyclase, cyclic AMP, or cyclic GMP content (22, 24). In *in vitro* Ussing chamber studies, serotonin added to the serosal solution elicits a transient increase in short-circuit current. This response is due to inhibition of mucosal-to-serosal flux of Na and Cl and a stimulation of net Cl secretion (24, 25). However, as Cooke and Carey (26) have shown when electrical field stimulation is applied to the short-circuited guinea pig ileum *in vitro,* serotonin is not the mediator of ileal chloride secretion evoked by activation of enteric nerves. The effects of serotonin are calcium dependent in that removal of Ca^{2+} from the serosal bath or treatment with the Ca^{2+}-channel blocker verapamil prevents the responses (27). No effect is seen with mucosal application of serotonin. In the rat colon *in vivo,* intravenous infusion of serotonin decreases net water and Na absorption from a luminal perfusate (28). *In vitro,* serotonin increases short-circuit current by causing a decrease in net Na and Cl absorption. The decrease in net Cl absorption is greater than that of Na. Again, removal of Ca^{2+} from the serosal solution inhibits all serotonin effects while tetrodotoxin, an inhibitor of neurotransmission, had no effect on serotonin-induced changes in electrolyte transport (28). These studies show that water and electrolyte flux in the small and large intestine are significantly influenced by serotonin acting to alter enterocyte plasma membrane permeability to Ca^{2+}.

Similar studies in the rat jejunum also have demonstrated a net increase in chloride secretion *in vitro* and an increase in potential difference *in vivo,* following serotonin (29). In addition, Hardcastle and co-workers (29) provided evidence that the action of serotonin was primarily on crypt cells rather than villus cells and was not mediated via a change in cellular levels of cAMP. Other recent data from *in vivo* studies in rats and in cats suggest that the intestinal secretory action of serotonin is mediated by a neuronal mechanism (30). In addition, these workers demonstrated that secretion induced *in vivo* by cholera toxin can be inhibited by serotonin tachyphylaxis, thus suggesting a possible role for serotonin in cholera diarrhea. However, such a role for serotonin is questionable since

the presumed intracellular mediator of cholera toxin-induced diarrhea is cAMP (31). Whether serotonin antagonists can exert an antisecretory action against cholera toxin-induced secretion remains to be evaluated.

The role of serotonin in the diarrhea of amebiasis has recently been reported (32). When lysates of *Entamoeba histolytica* were placed on the serosal side of epithelial sheets of either rabbit ileum or rat colon in Ussing chambers, a significant increase in short-circuit current was recorded. This response was calcium dependent and was partially inhibited by the serotonin antagonist bufotenin or by a serotonin antibody. Not only did the lysates mimic the effects on intestinal secretion of serotonin, but serotonin was also discovered to be present in the lysates. These data support the interesting hypothesis that serotonin is the mediator of the diarrhea of amebiasis.

Effects on Motility. Depending upon the localization of study within the GI tract, serotonin has direct and indirect, excitatory and inhibitory actions on GI smooth muscle. In the guinea pig stomach, serotonin has been associated with vagally mediated receptive relaxation primarily by a neural mechanism (8). Exogenous administration of serotonin to the conscious dog produces a dramatic increase in circular muscle contractions resembling phase II of the migrating motor complex in the jejunum and ileum (33). This excitatory response also has been demonstrated by Burks (9) in the isolated perfused canine small intestine. In Burks' preparation, the response to serotonin was reduced after tetrodotoxin, thus indicating a major intrinsic neural component to the response. Studies on the guinea pig ileum support the notion that the primary effect of serotonin in the intestine is a neuronal action, with little direct effect on longitudinal smooth muscle and essentially no direct effect on ileal circular smooth muscle (10). Costa and Furness (10) conclude that in the guinea pig intestine serotonin stimulates (a) excitatory cholinergic nerves, (b) excitatory noncholinergic nerves, and (c) inhibitory noncholinergic nerves. This agrees well with the immunocytochemical evidence discussed earlier that serotonin is a neurotransmitter at enteric interneurons. Both a direct smooth muscle action and an indirect neural action of serotonin have been described in the human colon, *in vitro,* where the response of the tissues to the agonist is relaxation (34).

Neurophysiological investigations have further characterized the role of serotonin in the gut. In the guinea pig ileum, microiontophoretic application of serotonin mimicked the effect of fiber tract stimulation of myenteric neurons producing a slow excitatory postsynaptic potential (EPSP) (35). The effect was blocked by methysergide and by serotonin tachyphylaxis. The neurons stimulated by serotonin appear to be tonic-type mechanosensitive neurons which produce prolonged discharges consistent with a prolonged excitatory or inhibitory action (36). In addition, iontophoretic application of serotonin on the guinea pig ileal myenteric plexus depressed the amplitude of the fast EPSPs from presumed cholinergic neurons (37). Methysergide not only blocked this effect of serotonin, but also depressed the amplitude of the EPSPs. This suggests that serotonin and methysergide may inhibit the release of acetylcholine, presynaptically. These data are in apparent contrast to those of Vizi and Vizi (38) who demonstrated the release of acetylcholine by serotonin in the guinea pig ileum–myenteric plexus preparation studied in the organ bath. It is clear that the conclusions of this experiment and others depend on the precise locus of action of serotonin and serotonin antagonists. Even though there is solid evidence for a transmitter role for serotonin in the gut, the neuronal effects of serotonin are complex and are not yet fully understood.

The multiple actions of serotonin also have been demonstrated on the motor activity of the sphincters in the GI tract. The net effect of exogenous serotonin on the opossum lower esophageal sphincter (LES) is contraction (39). Methysergide reverses the serotonin-induced LES contraction to a relaxation which, in turn, is antagonized by tetrodotoxin, 5-methoxy-*N,N*-dimethyltryptamine and serotonin tachyphylaxis. The authors conclude that serotonin (a) acts directly on LES smooth muscle, (b) stimulates cholinergic excitatory nerves, and (c) stimulates nonadrenergic inhibitory nerves. Moreover, additional pharmacologic evidence suggests that endogenous

serotonin participates in the vagal inhibitory pathway to the LES (40). In the feline sphincter of Oddi, serotonin also has excitatory and inhibitory actions with a net relaxation or biphasic response to exogenous administration (41). As in the LES, the sphincter of Oddi appears to contain serotonin receptors on the smooth muscle, on the excitatory cholinergic neurons, and on the noncholinergic inhibitory neurons. The ileocecal sphincter in the cat also responds to serotonin with excitation and inhibition. Contractile responses appear to be antagonized by cinanserin and relaxation responses by methysergide (42). In contrast to the LES and the sphincter of Oddi, the effects of serotonin on the ileocecal sphincter appear to be directly on the smooth muscle.

The effects of serotonin and serotonin antagonists have been evaluated in two species on the intrinsic pattern of gastrointestinal motor activity known as the migrating myoelectric or motor complex (MMC). In the dog, cyproheptadine blocked the initiation and migration of MMCs along the small intestine and significantly increased the period of the MMC (43). These data suggesting a role for serotonin in the regulation of the canine MMC were supported by similar results with another serotonin antagonist, 5-methoxy-*N,N*-dimethyltryptamine and with the serotonin synthesis inhibitor, parachlorophenylalanine. Methysergide appeared to behave as a partial serotonin agonist, enhancing contractile activity throughout the small intestine and disrupting the MMC. In contrast, recent data in conscious sheep demonstrate that methysergide significantly increases the number of MMC cycles recorded (44). These data suggest that in the sheep serotonin also plays a regulatory (and potentially inhibitory) role on the MMC. Together these studies provide one functional correlation to the anatomical and neurophysiological evidence in support of intrinsic serotonergic neuronal pathways in the gut.

Effects on Mesenteric Blood Flow. The influence of serotonin on the mesenteric circulation is paradoxical and appears to be subject to dose, preparation, species, and motor activity. Hashimoto and Kumakura (45) showed, in anesthetized dogs, that perfusion of the mesenteric vasculature with 1–100 μg of serotonin produced vasoconstriction. Later, Adar and Salzman (46) reported that intravenous injections of 30 μg/kg in anesthetized dogs caused similar reductions in mesenteric blood flow. In the former study, the vascular response was associated with vigorous intestinal motor activity. This relationship with motility has been observed with other agents, such as acetylcholine, and it is difficult to assess what is the primary response (47). Some evidence suggests that the major effect of serotonin is on intestinal motor function in this relationship. In anesthetized dogs, Chou and Dabney (48) reported that perfusion of the canine mesenteric arterial supply *in situ* with 2 μg/min of serotonin decreased ileal compliance while not significantly altering vascular resistance. This decrease in ileal wall compliance may have masked a vasodilator response since in half the animals examined, vascular resistance decreased while ileal compliance fell only slightly. This suggests that when serotonin does increase visceral motor activity, mechanical compression of the mesenteric microcirculation manifests as a vasoconstriction (47).

In the chloralose anesthetized cat, Biber *et al.* (49) showed that both intraarterial infusion and injection of serotonin produced intestinal vasodilation. Prior treatment with tetrodotoxin reversed the vasodilation to vasoconstriction. The vasodilator response was unaffected by intestinal motor activity in this species. Also, infusion of 20–50 mg/min increased the capillary filtration coefficient (CFC) as well as mesenteric blood flow. Lower doses (10–15 mg/min) increased CFC without changing blood flow suggesting a change in capillary permeability. *In vitro,* serotonin increased isometric tension in both mesenteric arteries and veins (49). This report shows that the paradoxical effect of serotonin may be explained by the differences in the site of action. *In vitro* methods generally permit study only of larger vessels. This may explain the contraction of vessels *in vitro* to serotonin while *in vivo,* blood flow was increased indicating that resistance vessels of the mesenteric microvasculature respond to serotonin by relaxation.

While these studies shed some light on the action of serotonin on GI blood flow, more

definitive studies are necessary to fully delineate the role of this biogenic amine in the regulation of the mesenteric circulation.

1. Nemoto N, Kawaoi A, Shikata T. Immunohistochemical demonstration of serotonin (5-hydroxytryptamine) containing cells in the human and rat intestines. Biomed Res **3**:181–187, 1982.
2. Pettersson G, Ahlman H, Dahlstrom A, Kewenter J, Larsson I, Larsson PA. The effect of transmural field stimulation on the serotonin content in rat duodenal enterochromaffin cells—in vitro. Acta Physiol Scand **107**:83–87, 1979.
3. Pettersson GB, Newson B, Ahlman H, Dahlstrom A. In vitro studies of serotonin release from rat enterochromaffin cells: studies of gut serotonin release. J Surg Res **29**:141–148, 1980.
4. Siepler JK, Ahlman HJ, Bhargava HN, Donahue PE, Nyhus LM. A pharmacokinetic analysis of the vagal release of 5-hydroxytryptamine in the cat. J Neural Transm **47**:99–105, 1980.
5. Larsson I, Ahlman H, Bhargava HN, Dahlstrom A, Pettersson G, Kewente J. The effects of splanchnic nerve stimulation on the plasma levels of serotonin and substance P in the portal vein of the cat. J Neural Transm **46**:105–112, 1979.
6. Ahlman H, DeMagistris L, Zinner M, Jaffe BM. Release of immunoreactive serotonin into the lumen of the feline gut in response to vagal nerve stimulation. Science (Washington, DC) **213**:1254–1255, 1981.
7. Kellum JM, Jaffe BM. Release of immunoreactive serotonin following acid perfusion of the duodenum. Ann Surg **184**:633–636, 1976.
8. Bulbring E, Gershon MD. 5-Hydroxytryptamine participation in the vagal inhibitory innervation of the stomach. J Physiol **192**:823–846, 1967.
9. Burks TF. Mediation by 5-hydroxytryptamine of morphine stimulant actions in dog intestine. J Pharmacol Exp Ther **185**:530–539, 1973.
10. Costa M, Furness JB. The sites of action of 5-hydroxytryptamine in nerve-muscle preparations from the guinea-pig small intestine and colon. Brit J Pharmacol **65**:237–248, 1979.
11. Gershon MD, Erde SM. The nervous system of the gut. Gastroenterology **80**:1571–1594, 1981.
12. Furness JB, Costa M. Neurons with 5-hydroxytryptamine-like immunoreactivity in the enteric nervous system: Their projections in the guinea-pig small intestine. Neuroscience **7**:341–349, 1982.
13. Costa M, Furness JB, Cuello AC, Verhofstad AAJ, Steinbusch HWJ, Elde RP. Neurons with 5-hydroxytryptamine-like immunoreactivity in the enteric nervous system: Their visualization and reactions to drug treatment. Neuroscience **7**:351–363, 1982.
14. Bugajski J, Hano J, Danek L, Wantuch C. The action of serotonin on basal gastric secretion in the conscious rat after intraventricular and intraperitoneal administration. Arch Int Pharmacodyn Ther **225**:29–38, 1977.
15. Canfield SP, Spencer JE. The inhibitory effects of 5-hydroxytryptamine on gastric acid secretion by the rat isolated stomach. Brit J Pharmacol **78**:123–130, 1983.
16. Caldara R, Ferrari C, Barbieri C, Romussi M, Rampini P, Telloli P. Effect of two antiserotoninergic drugs methysergide and metergoline on gastric acid secretion and gastrin release in healthy man. Eur J Clin Pharmacol **17**:13–18, 1980.
17. Jaffe BM, Kopen DF, Lazan DW. Endogenous serotonin in the control of gastric acid secretion. Surgery **82**:156–163, 1977.
18. Berkowitz JM, Warner RP, Janowitz HD, Miller IF. Effects of some pharmacologic agents on gastric cation secretion: Ratio of hydrogen to potassium ions. Proc Soc Exp Biol Med **135**:804–808, 1970.
19. Black JW, Bradbury JE, Wyllie JH. Stimulation of colonic mucus output in the rat. Brit J Pharmacol **66**:456P–457P, 1979.
20. Black JW, Fisher EW, Smith AN. The effects of 5-hydroxytryptamine on gastric secretion in anesthetized dogs. J Physiol **141**:27–34, 1958.
21. White TT, Magee DF. The influence of serotonin on gastric mucus production. Gastroenterology **35**:289–291, 1958.
22. Donowitz M, Charney AN. Effect of serotonin treatment on intestinal transport in the rabbit. Amer J Physiol **232**(Endocrinol Metab Gastrointest Physiol **1**):E85–E94, 1977.
23. Kisloff B, Moore EW. Effect of serotonin on water and electrolyte transport in the *in vivo* rabbit small intestine. Gastroenterology **71**:1033–1038, 1976.
24. Donowitz M. Ca^{++} in the control of active intestinal Na and Cl transport: Involvement in neurohumoral action. Amer J Physiol **245**(Gastrointest Liver Physiol **8**):G165–G177, 1983.
25. Donowitz M, Tai Y-H, Asakof N. Effect of serotonin on active electrolyte transport in rabbit ileum and gallbladder. Amer J Physiol **239**(Gastrointest Liver Physiol **2**):G463–G472, 1980.
26. Cooke HJ, Carey H. Effects of cisapride, a serotonin antagonist, on neural stimulation of guinea pig ileal mucosa. Fed Proc **43**:1093, 1984.
27. Donowitz M, Asakof N, Pike G. Serotonin-induced changes in rabbit ileal active electrolyte transport are calcium dependent and associated with increased ileal calcium uptake. J Clin Invest **66**:341–352, 1980.
28. Zimmerman TW, Binder HJ. Serotonin-induced alteration in colonic electrolyte transport in the rat. Gastroenterology **86**:310–317, 1984.
29. Hardcastle J, Hardcastle PT, Redfren JS. Action of 5-hydroxytryptamine on intestinal ion transport in the rat. J Physiol **320**:41–55, 1981.
30. Cassuto J, Jodal M, Tuttle R, Lundgren O. 5-

hydroxytryptamine and cholera secretion. Physiological and pharmacological studies in cats and rats. Scand J Gastroenterol **17**:695–703, 1982.
31. Moss J, Vaughan M. Mechanism of activation of adenylate cyclase by choleragen and *E. coli* heat-labile enterotoxin. In: Field M, Fordtran JS, Schultz SG, eds. Secretory Diarrhea. Bethesda, American Physiological Society, pp107–126, 1980.
32. McGowan K, Kane A, Asarkof N, Wicks J, Guerina V, Kellum J, Baron S, Gintzler AR, Donowitz M. Entamoeba histolytica causes intestinal secretion: Role of serotonin. Science (Washington, DC) **221**:762–764, 1983.
33. Ormsbee HS III, Silber DA, Hardy FE Jr. Evidence for serotonergic regulation of canine migrating motor complex (MMC). Gastroenterology **80**:1244, 1981.
34. Burleigh DE. Evidence for more than one type of 5-hydroxytryptamine receptor in the human colon. J Pharm Pharmacol **29**:538–541, 1977.
35. Wood JD, Mayer CJ. Serotonergic activation of tonic-type enteric neurons in guinea pig small bowel. J Neurophysiol **42**:582–593, 1979.
36. Wood JD. Neurophysiology of the enteric nervous system. In: Brooks C McC, Koizumi K, Sato A, eds. Integrative Functions of the Autonomic Nervous System. Amsterdam, Elsevier/North-Holland Biomedical Press, p177, 1979.
37. North RA, Henderson G, Katayama Y, Johnson SM. Electrophysiological evidence for presynaptic inhibition of acetylcholine release by 5-hydroxytryptamine in the enteric nervous system. Neuroscience **5**:581–586, 1980.
38. Vizi VA, Vizi ES. Direct evidence of acetylcholine releasing effect of serotonin in the Auerbach plexus. J Neural Transm **42**:127–138, 1978.
39. Rattan S, Goyal RK. Effects of 5-hydroxytryptamine on the lower esophageal sphincter *in vivo*. Evidence for multiple sites of action. J Clin Invest **59**:125–133, 1977.
40. Rattan S, Goyal RK. Evidence of 5-HT participation in vagal inhibitory pathway to opossum LES. Amer J Physiol **234**:E273–E276, 1978.
41. Behar J, Biancani P. Neural control of the sphincter of Oddi. A physiological role of 5-hydroxytryptamine in the regulation of basal sphincter of Oddi motor activity in the cat. J Clin Invest **72**:551–559, 1983.
42. Ouyang A, Cohen S. Multiple 5-hydroxytryptamine receptors on feline ileum and ileocecal sphincter. Amer J Physiol **244**:G426–G434, 1983.
43. Ormsbee HS III, Silber DA, Hardy FE Jr. Serotonin regulation of the canine migrating motor complex. J Pharmacol Exp Ther **231**:436–440, 1984.
44. Ruckebusch Y, Bardon T. Involvement of serotonergic mechanisms in initiation of small intestine cyclic motor events. Dig Dis Sci **29**:520–527, 1984.
45. Hashimoto K, Kumakura S. The pharmacological features of the coronary renal mesenteric and femoral arteries. Japan J Physiol **15**:540–551, 1965.
46. Adar R, Salzman EW. Serotonin and the mesenteric circulation. Brit Med J **25**:444, 1974.
47. Fondacaro JD. Intestinal blood flow and motility. In: Shepherd AP, Granger DN, eds. Physiology of the Intestinal Circulation. New York, Raven Press, pp107–120, 1984.
48. Chou C-C, Dabney JM. Interrelation of ileal wall compliance and vascular resistance. Amer J Dig Dis **12**:1198–1208, 1967.
49. Biber B, Fara J, Lundgren O. Intestinal vascular responses to 5-hydroxytryptamine. Acta Physiol Scand **87**:526–534, 1973.
