J. Pharm. Pharmacol. 1999, 51: 1415–1421
Received June 21, 1999
Accepted August 3, 1999

Effects of 5-Hydroxytryptamine on the Transintestinal Electrical Activity and Cardiovascular Function of Fawn-hooded Rats In-vivo

J. HARDCASTLE AND P. T. HARDCASTLE

Department of Biomedical Science, University of Sheffield, Western Bank, Sheffield S10 2TN, UK

Abstract

Fawn-hooded rats, which have abnormal serotonergic function, were used to investigate the receptors involved in 5-hydroxytryptamine (5-HT)-induced intestinal secretion. The effects of 5-HT on secretion by the small intestine and proximal colon, monitored as increased transintestinal electrical activity, and on cardiovascular function, measured as changes in heart rate and blood pressure, were compared in fawn-hooded and Wistar rats.

The maximum fall in heart rate induced by 5-HT (mediated by 5-HT_3 receptors) was greater in fawn-hooded than in Wistar rats. ED50 values (the doses resulting in 50% of the maximum effect) for the 5-HT_2-mediated increases in systolic pressure were lower for both 5-HT and 5-methoxytryptamine in the fawn-hooded group. The prolonged fall in diastolic pressure mediated by 5-HT_1-like receptors was significantly attenuated in fawn-hooded rats, with the maximum responses to 5-HT, 5-methoxytryptamine and 6-hydroxyindalpine reduced to 21%, 42% and 28%, respectively, of the values obtained for Wistar rats. In fawn-hooded rats the small intestine was less sensitive to the effects of 5-HT (ED50 = 47 nmol kg^{-1}; ED50 for Wistar rats = 23 nmol kg^{-1}) and the maximum colonic response to 5-methoxytryptamine was greater (7·0 mV compared with 4·3 mV in Wistar rats), but other indices did not differ for the two strains. The responses to 6-hydroxyindalpine were similar in fawn-hooded and Wistar rats.

It is concluded that although the cardiovascular response of fawn-hooded rats to 5-HT challenge is very different from that of Wistar rats, this difference is not reflected in marked alterations in 5-HT-induced intestinal secretion. This is consistent with 5-HT stimulating secretion via the activation of several different receptor subtypes so that any changes in the receptor profile in fawn-hooded rats results in little alteration in the overall intestinal response.

The fawn-hooded rat is a strain characterized by substantial alterations in serotonergic function. These animals have a haemorrhagic disorder that results from a platelet storage pool deficiency in which 5-hydroxytryptamine (5-HT) content and release is reduced (Raymond & Dodds 1975). They also develop hypertension and proteinuria with age (Kuijpers et al 1986) and there are central nervous system abnormalities consistent with altered serotonergic function (Aulakh et al 1994).

Correspondence: J. Hardcastle, Department of Biomedical Science, University of Sheffield, Western Bank, Sheffield S10 2TN, UK.

The major source of 5-HT in the body is the intestinal tract, where the amine is found predominantly in the enterochromaffin cells of the mucosa, although it is also present in neural and immune elements of the subepithelial tissues (McKay & Perdue 1993). It is well established that 5-HT induces a secretory response throughout the intestinal tract by stimulating electrogenic chloride secretion and inhibiting electroneutral sodium chloride absorption (Hardcastle et al 1981; Zimmerman & Binder 1984). The intestinal response to 5-HT is complex. The amine has several sites of action, with both neural and non-neural compo-

nents contributing to the response (Cooke 1994). In addition, several different 5-HT receptor subtypes have been implicated, including 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_4 (Cooke 1994), and there is evidence for the existence of both prosecretory and antisecretory components of the response (Beesley & Levin 1991; Hardcastle & Hardcastle 1997a, b, 1998).

5-HT also influences cardiovascular function. When administered intravenously it causes a triphasic change in blood pressure—an initial decrease in blood pressure and heart rate mediated by 5-HT_3 receptors, followed by a transient hypertensive phase mediated by 5-HT_2 receptors, and finally a prolonged hypotensive phase mediated by 5-HT_1-like receptors (Kalkman et al 1984). There is evidence of altered cardiovascular function in the fawn-hooded rat which not only develops hypertension with age (Kuijpers et al 1986), but whose blood vessels also have an enhanced constrictor response to 5-HT (Ashmore et al 1991). In addition, the prolonged hypotensive response to 5-HT is attenuated in this strain of rats (Emery et al 1998), consistent with observations of reduced effectiveness of 5-HT_1-like agonists (Aulakh et al 1994).

The intestinal secretory response to 5-HT in-vivo resembles the prolonged hypotensive phase mediated by 5-HT_1-like receptors with regard to both its time-course and its ED50 (the dose resulting in 50% of the maximum effect) (Hardcastle & Hardcastle 1995), implicating this receptor subtype in the stimulation of secretion. The defective responsiveness of these receptors in the fawn-hooded rat provides an opportunity for further exploration of the involvement of 5-HT_1-like receptors in the intestinal secretory response to 5-HT challenge. Intestinal secretion was monitored as increased transintestinal electrical activity in response to 5-HT, to 5-methoxytryptamine, which lacks affinity for 5-HT_3 receptors (Fozard 1985; Leff & Martin 1988; Craig et al 1990), and to 6-hydroxyindalpine, an agonist at 5-HT_{1P} receptors (Mawe et al 1986; Gershon et al 1990).

Materials and Methods

Chemicals

5-Hydroxytryptamine creatinine sulphate and 5-methoxytryptamine were obtained from Sigma (Poole, UK). 6-Hydroxyindalpine was a gift from SmithKline Beecham Pharmaceuticals (Harlow, UK). Other chemicals were of analytical grade and obtained from commercial suppliers.

Animals

Experiments were performed on male fawn-hooded rats, 250–350 g, obtained from Janvier (Paris, France) and bred in the Sheffield Field Laboratories. Male Wistar rats, 250–300 g, bred in the Sheffield Field Laboratories, were used as controls. All animals were allowed free access to food and water. They were anaesthetized by intraperitoneal injection of sodium pentobarbitone (Sagatal, 60 mg kg^{-1}).

Measurement of transintestinal electrical activity

The transintestinal potential difference was measured across 3-cm segments of mid–small intestine and proximal colon. Each segment was tied at the distal end and filled with 154 mM NaCl through a cannula inserted at the proximal end. The potential difference across each loop was measured between two salt-bridge electrodes, one in contact with the luminal fluid and the other, via a wick electrode, with the peritoneal cavity. Electrodes were connected via calomel half-cells to two differential input electrometers, the outputs of which were displayed on a 2-channel chart recorder (Linseis L6512). Drugs were administered through a cannula in the femoral vein and each dose (in 0·1 mL) was washed in with 0·2 mL 154 mM NaCl. Electrogenic chloride secretion was monitored as a rise in the potential difference and the response to an agonist was taken as the difference between the maximum potential difference achieved after each dose and the value immediately before its addition.

Measurement of cardiovascular function

Arterial blood pressure was monitored at the left carotid artery via a saline–heparin filled cannula connected to a pressure transducer (Druck PDCR75). This was linked to a preamplifier (Lectromed type 5241) and a visual display was obtained on a 2-channel chart recorder (Lectromed Multitrace 2). The blood-pressure signal was fed into a rate-meter (Lectromed type 5250) to provide a continuous display of the heart rate. The triphasic cardiovascular response to 5-HT was measured as an initial fall in heart rate (mediated by 5-HT_3 receptors), followed by a rise in systolic pressure (mediated by 5-HT_2 receptors) and finally a decrease in diastolic pressure (mediated by 5-HT_1-like receptors).

Expression of results

Results are expressed as means ± s.e.m. from the number of animals (n) indicated. An unpaired *t*-test was used to compare values obtained from fawn-hooded rats with those from Wistar rats. ED50 values were calculated as geometric means (95% confidence limits) and statistical analyses were performed on log-transformed data.

Results

Transintestinal electrical activity

The small intestine and the colon both generated basal electrical activity in which the serosal side of the tissue was positive relative to the mucosal side. Basal potential difference values for the fawn-hooded rats (small intestine 5·4 ± 1·4 mV; colon 11·5 ± 0·9 mV, n = 5) did not differ from those recorded for Wistar rats (small intestine 5·6 ± 0·4 mV; colon 10·0 ± 0·7 mV, n = 20, $P > 0·05$ for both). In both groups of animals 5-HT caused dose-dependent increases in the potential difference across the small intestine and the colon (Figure 1). Although maximum responses for the two groups did not differ, the small intestine of the fawn-hooded animals was less sensitive to 5-HT, which was reflected in an increased ED50 value (Table 1). Reduced sensitivity was not observed with 5-methoxytryptamine, although with this agonist the maximum colonic response was greater in the fawn-hooded rats (Figure 1, Table 1). The 5-HT_{1P} agonist 6-hydroxyindalpine was much less effective in increasing the potential difference across the small intestine and colon in both groups of animals; ED50 values were very much greater than those observed with 5-HT ($P < 0·001$ in all cases), and in the Wistar rats it induced a smaller maximum potential difference change than 5-HT in both the small intestine and the colon ($P < 0·05$ in both cases). There were however, no detectable differences between the responses of the two groups of rats to 6-hydroxyindalpine (Figure 1, Table 1).

Cardiovascular function

Basal blood pressure was not elevated in the fawn-hooded rats (Wistar, n = 20, systolic pressure 156 ± 5 mmHg, diastolic pressure 121 ± 4 mmHg; fawn-hooded, n = 5, systolic pressure 111 ± 8 mmHg, diastolic pressure 92 ± 9 mmHg), although the heart rate was higher (Wistar, 396 ± 6 beats min^{-1}; fawn-hooded, 452 ± 12 beats min^{-1}; $P < 0·001$). In Wistar rats the triphasic change in blood pressure was observed on administration of 5-HT, with the onset of the electrical responses of

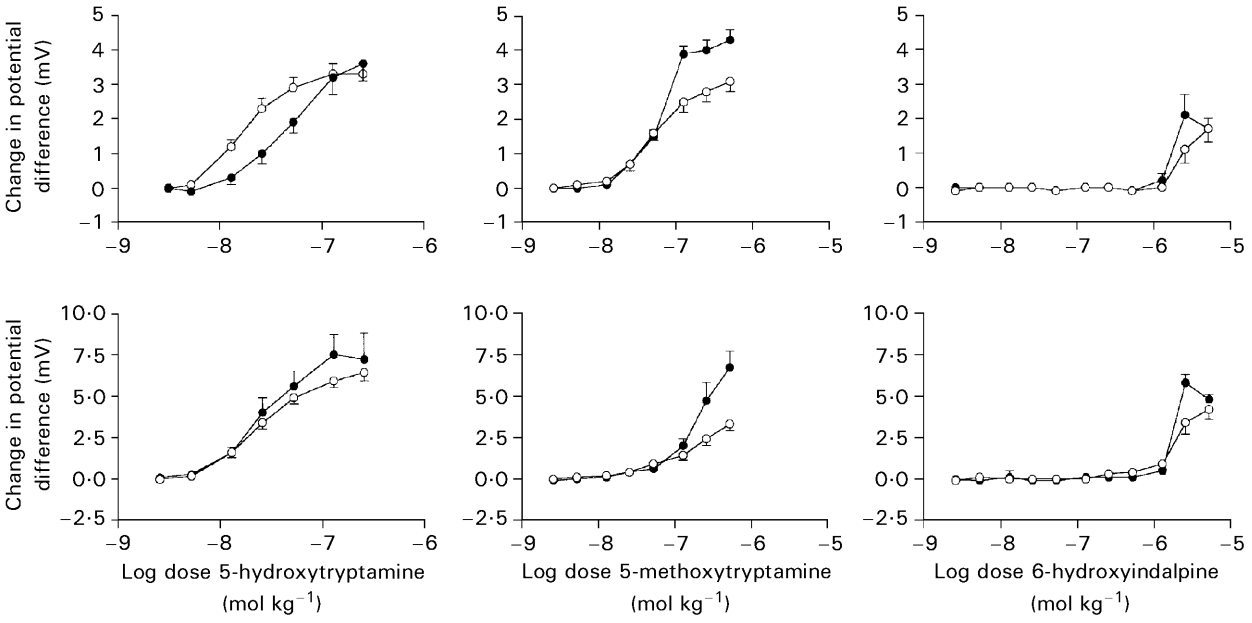

Figure 1. Effect of 5-HT (n = 5 for fawn-hooded rats, n = 20 for Wistar rats), 5-methoxytryptamine (n = 5 for fawn-hooded rats, n = 14 for Wistar rats) and 6-hydroxyindalpine (n = 5 for fawn-hooded rats, n = 6 for Wistar rats) on the potential difference across the mid-intestine (upper) and proximal colon (lower) of fawn-hooded (●) and Wistar (○) rats. The change in potential difference is plotted as a function of the logarithm of the dose and each point is the mean ± s.e.m. of results from the number of animals indicated. In some instances the error bar is smaller than the symbol.

Table 1. Comparison of the intestinal responses of fawn-hooded and Wistar rats to intravenous administration of 5-HT, 5-methoxytryptamine and 6-hydroxyindalpine.

	Change in potential difference					
	Wistar rats			Fawn-hooded rats		
	n	Mid-small intestine	Proximal colon	n	Mid-small intestine	Proximal colon
5-HT						
Maximum	20	3·5 ± 0·3	6·5 ± 0·4	5	3·4 ± 0·5	7·9 ± 1·1
ED50		19	27		47**	28
		15–23	23–32		28–78	18–42
5-Methoxytryptamine						
Maximum	14	3·3 ± 0·3	4·1 ± 0·5	5	4·1 ± 0·3	7·0 ± 0·8*
ED50		59	192		70	204
		41–84	139–266		47–104	149–281
6-Hydroxyindalpine						
Maximum	6	1·9 ± 0·5	4·4 ± 0·6	5	2·2 ± 0·6	5·9 ± 0·4
ED50		2811	2296		2444	5906
		2018–3917	1667–3162		1484–4023	1118–31203

Changes in the potential difference (mV) across the mid-small intestine and proximal colon, expressed as the maximum response (mean ± s.e.m.), and ED50 values (nmol kg^{-1}; geometric means; 95% confidence limits) were from the number (n) of animals indicated. An unpaired *t*-test was used to assess the significance of differences between the two groups of animals. $*P < 0.01$, $**P < 0.001$.

the small intestine and colon coinciding with the prolonged hypotensive phase (Figure 2). In the fawn-hooded rats all three phases of the cardiovascular response were significantly different from those of the Wistar rats. The maximum fall in heart rate was increased and the transient hypertensive phase was more sensitive to 5-HT, which was reflected in a lower ED50 value. In contrast the prolonged hypotensive phase was greatly attenuated—the maximum decrease in diastolic pressure was only 21% of that observed for the Wistar rats (Figure 3, Table 2). Administration of 5-methoxytryptamine elicited both the transient hypertensive and prolonged hypotensive phases, without an alteration in heart rate (Figure 3). Again in the fawn-hooded rats the ED50 value was lower for the hypertensive phase, and the maximum fall in diastolic pressure was reduced to 42% of that observed for the Wistar rats (Figure 3, Table 2). 6-Hydroxyindalpine did not alter heart rate nor increase systolic pressure in either group of animals. It did, however, cause a prolonged fall in diastolic pressure, with a maximum effect that for fawn-hooded rats was only 28% of that obtained for the Wistar rats (Figure 3, Table 2).

Discussion

Intravenous administration of a bolus dose of 5-HT elicits a complex cardiovascular response with three distinct phases—a short-lasting depressor phase with intense bradycardia, a transient pressor phase and a prolonged hypotensive phase. The first of these is a reflex response, the Bezold–Jarisch effect, activated by 5-HT_3 receptors located on afferent nerve terminals of the vagus in the heart and lungs (Evans et al 1990). The second phase is because of direct action at 5-HT_2 receptors on vascular smooth muscle, and the third phase involves both direct and indirect mechanisms that result in the relaxation of vascular smooth muscle (Bradley et al 1986). This vasodilation is considered to result from the activation of 5-HT_1-like receptors (Bradley et al 1986), although recent studies have suggested that the cloned 5-HT_7 subtype might be involved (De Vries et al 1997; Terrón 1997). The receptor subtype responsible for the prolonged hypotensive phase might also have a role in stimulating intestinal secretion, because the intestinal potential difference starts to rise during this phase. A 5-HT_{1P} agonist, 6-hydroxyindalpine, was used to investigate the involvement of this receptor subtype.

Although the triphasic cardiovascular response to 5-HT was observed for both fawn-hooded and Wistar rats, there were marked differences between them. The maximum fall in heart rate was greater in fawn-hooded rats, although the ED50 value was not altered. Both 5-HT and 5-methoxytryptamine elicited a pressor response, but the greater sensitivity of fawn-hooded rats was reflected in ED50

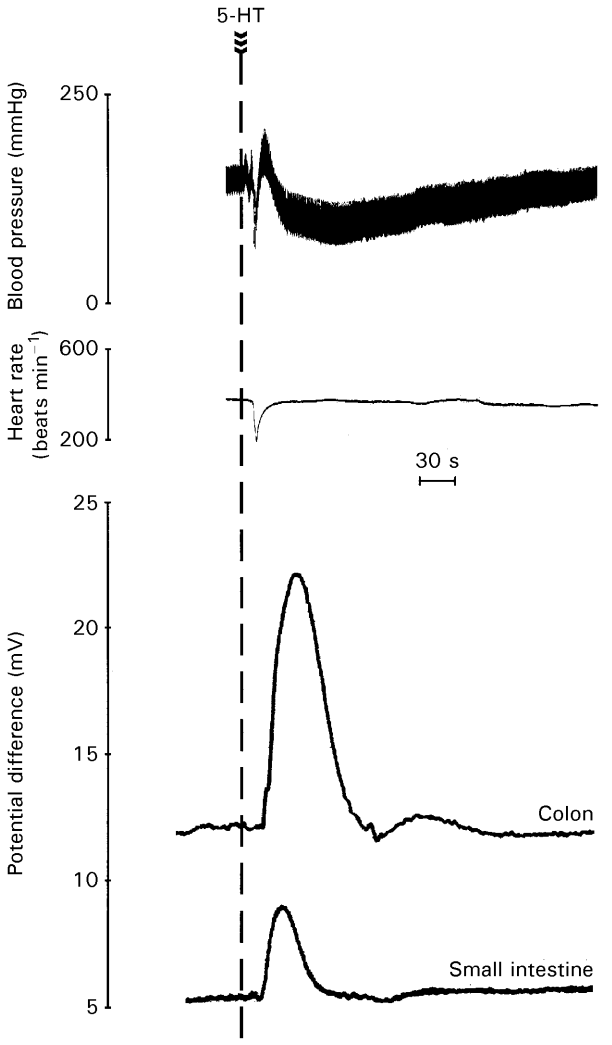

Figure 2. Effect of intravenous administration of 5-HT (130 nmol kg^{-1}) on cardiovascular function and transintestinal potential difference. The typical triphasic blood pressure response, the change in heart rate, and the increases in potential difference across the small intestine and the colon are shown.

values that were 2·6 (5-HT) and 3·7 (5-methoxytryptamine) times lower than those obtained for Wistar rats. Significant changes in the pressor response to 5-HT were not detected in a previous study comparing fawn-hooded and Wistar rats (Emery et al 1998), although only the effects of a single submaximum dose of 5-HT were tested. Enhanced 5-HT-induced contraction has been observed in isolated arterial preparations from fawn-hooded rats; this was attributed to increased sensitivity of the smooth muscle itself, because neither removal of the endothelium nor pretreatment with a cyclooxygenase inhibitor altered the response (Ashmore et al 1991). The prolonged hypotensive phase was greatly attenuated in the fawn-hooded rat, in which the maximum responses to 5-HT, 5-methoxytryptamine and 6-hydroxyindalpine were all reduced to less than half the values observed in Wistar rats. Similar effects have been reported by Emery et al (1998). A reduction in the maximum response could reflect a smaller number of receptors. Alternatively indirect mechanisms contributing to the response could be altered. It has been shown, for example, that nitric oxide contributes to the hypotensive phase in Wistar rats (Franks et al 1994); this pathway might be less effective in fawn-hooded rats.

Stimulation of secretion was observed with all three agonists tested. It is clear that 5-HT_1-like receptors contribute to this response, because the selective 5-HT_{1P} agonist, 6-hydroxyindalpine, mimicked the effects of 5-HT on the transintestinal potential difference. Moreover, the onset and duration of the increased potential difference coincided with the 5-HT_1-mediated hypotensive phase of the cardiovascular response. In fawn-hooded rats 6-hydroxyindalpine-induced secretion was unchanged, even though its effects on cardiovascular function were reduced. This suggests that the 5-HT_1-like receptors involved in secretion differ from those responsible for the prolonged hypotension. The secretory actions of the other agonists tested, 5-HT itself and 5-methoxytryptamine, were also similar in fawn-hooded and Wistar rats, with only minor differences being detected. This might not be surprising in view of the complexity of 5-HT-induced secretion which involves several different mechanisms, including both prosecretory and antisecretory pathways (Beesley & Levin 1991; Hardcastle & Hardcastle 1997a, b, 1998). The cardiovascular data obtained in the current study clearly indicate that in fawn-hooded rats some effects of 5-HT are enhanced whereas others are reduced. If similar changes occur to the components of the intestinal response to 5-HT, it is possible they might counteract one another and as only the overall effect is measured little change is noted.

This study has revealed significant differences between fawn-hooded and Wistar rats in their responses to 5-HT challenge. Whilst these are particularly pronounced with regard to cardiovascular function, they are less obvious in relation to intestinal transport and confirm that the secretion induced by 5-HT cannot simply be associated with one type of receptor, but results from the complex interplay of several different receptors and pathways.

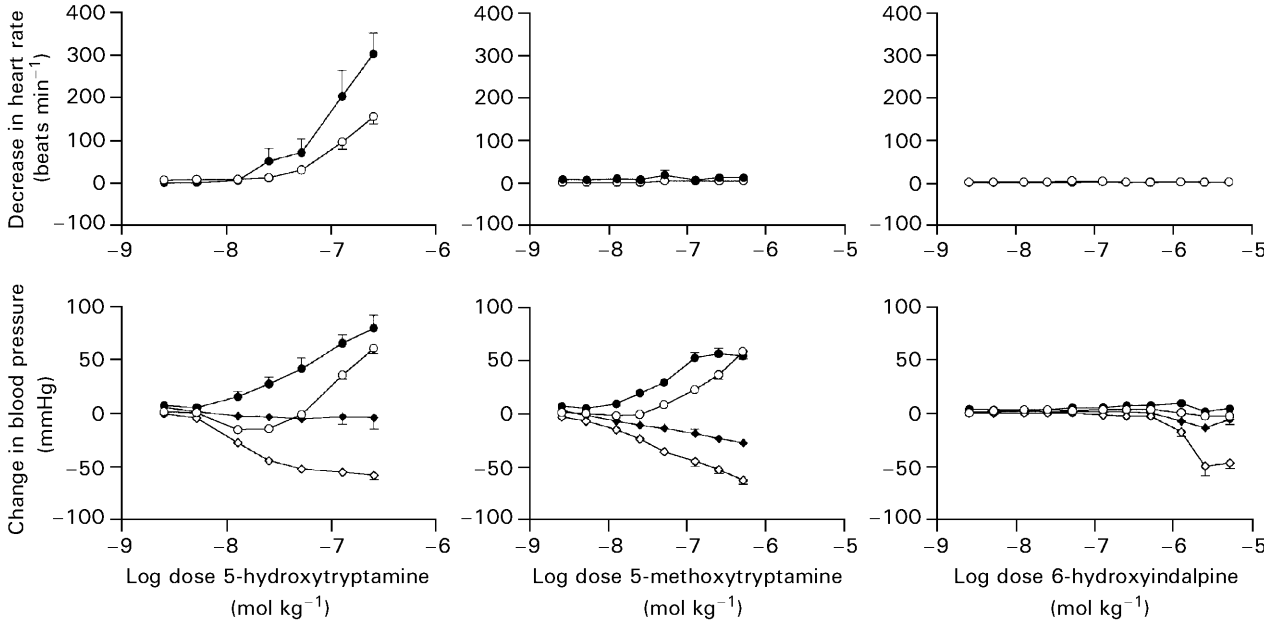

Figure 3. Effect of 5-HT (n = 5 for fawn-hooded rats, n = 20 for Wistar rats), 5-methoxytryptamine (n = 5 for fawn-hooded rats, n = 14 for Wistar rats) and 6-hydroxyindalpine (n = 5 for fawn-hooded rats, n = 6 for Wistar rats) on the heart rate (upper) and blood pressure (lower) of fawn-hooded (●, ◆) and Wistar (○, ◆) rats. Decreases in heart rate, increases in systolic pressure (●, ○) and prolonged decreases in diastolic pressure (◆, ◇) are plotted as a function of the logarithm of the dose and each point is the mean ± s.e.m. of results from the number of animals indicated. In some instances the error bar is smaller than the symbol.

Table 2. Comparison of the cardiovascular responses of fawn-hooded and Wistar rats to intravenous administration of 5-HT, 5-methoxytryptamine and 6-hydroxyindalpine.

	n	Decrease in heart rate (beats min^{-1})	Increase in systolic blood pressure (mmHg)	Prolonged decrease in diastolic blood pressure (mmHg)
Wistar rats				
5-HT				
Maximum	20	159 ± 17	66 ± 7	62 ± 4
ED50		112	115	16
		94–133	98–136	13–20
5-Methoxytryptamine				
Maximum	14	23 ± 5	75 ± 9	66 ± 4
ED50		–	227	56
			160–322	40–80
6-Hydroxyindalpine				
Maximum	6	11 ± 5	4 ± 2	54 ± 6
ED50		–	–	1637
				1337–2004
Fawn-hooded rats				
5-HT				
Maximum	5	306 ± 52*	79 ± 10	13 ± 3**
ED50		104	44**	–
		71–150	22–89	
5-Methoxytryptamine				
Maximum	5	4 ± 4	57 ± 5	28 ± 3**
ED50		–	62**	–
			50–75	
6-Hydroxyindalpine				
Maximum	5	2 ± 2	9 ± 1	15 ± 2**
ED50		–	–	–

Results, expressed as the maximum response (mean ± s.e.m.) and as the ED50 (nmol kg^{-1}; geometric means; 95% confidence limits) are from the number (n) of animals indicated. An unpaired *t*-test was used to assess the significance of differences between the two groups of animals. *$P < 0.01$, **$P < 0.001$.

Acknowledgements

We gratefully acknowledge Dr C. J. Emery for providing the fawn-hooded rats and for fruitful discussions. We would also like to thank Julie Chapman for skilled technical assistance.

References

Ashmore, R. C., Rodman, D. M., Sato, K., Webb, S. A., O'Brien, R. F., McMurtry, I. F., Stelzner, T. J. (1991) Paradoxical constriction to platelets by arteries from rats with pulmonary hypertension. Am. J. Physiol. 260: H1929–H1934

Aulakh, C. S., Tolliver, T., Wozniak, K. M., Hill, J. L., Murphy, D. L. (1994) Functional and biochemical evidence for altered serotonergic function in the fawn-hooded rat strain. Pharmacol. Biochem. Behav. 49: 615–620

Beesley, A., Levin, R. J. (1991) 5-Hydroxytryptamine induces electrogenic secretion and simultaneously activates a modulating inhibitory neural circuit in rat small intestine *in vitro*. Exp. Physiol. 76: 607–610

Bradley, P. B., Engel, G., Fenuik, W., Fozard, J. R., Humphrey, P. P. A., Middlemiss, D. N., Mylecharane, E. J., Richardson, B. P., Saxena, P. R. (1986) Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. Neuropharmacology 25: 563–576

Cooke, H. J. (1994) Neuroimmune signaling in regulation of intestinal ion transport. Am. J. Physiol. 266: G167–G178

Craig, D. A., Eglen, R. M., Walsh, L. K. M., Perkins, L. A., Whiting, R. L., Clarke, D. E. (1990) 5-Methoxytryptamine and 2-methyl-5-hydroxytryptamine-induced desensitization as a discriminative tool for the 5-HT_3 and putative 5-HT_4 receptors in guinea pig ileum. Naunyn Schmiedebergs Arch. Pharmacol. 342: 9–16

De Vries, P., Villalon-Carlos, M., Heiligers, J. P. C., Saxena-Pramod, R. (1997) Nature of 5-HT_1-like receptors mediating depressor responses in vagosympathectomized rats: close resemblance to the cloned 5-ht_7 receptor. Naunyn Schmiedebergs Arch. Pharmacol. 356: 90–99

Emery, C. J., Phillips, H. M., Marriott, H. M., Laude, E. A., Bee, D. (1998) Pulmonary and systemic action of 5-HT in the Fawn Hooded rat: a model of inherited pulmonary and systemic hypertension. J. Physiol. 511: 108P–109P

Evans, R. G., Michalick, J., Ludbrook, J. (1990) Excitation of 5-hydroxytryptamine$_3$ receptors and nicotinic ganglionic cholinoceptors on vagal cardiopulmonary afferents in rabbits. Eur. J. Pharmacol. 183: 1111

Fozard, J. R. (1985) 5-Methoxytryptamine (5-MeOT) discriminates between excitatory neuronal 5-hydroxytryptamine (5-HT) receptors in the guinea pig ileum. J. Pharmacologie 16: 498

Franks, C. M., Hardcastle, J., Hardcastle, P. T. (1994) Involvement of nitric oxide in the response to 5-hydroxytryptamine in the rat in-vivo. J. Pharm. Pharmacol. 46: 387–389

Gershon, M. D., Wade, P. R., Kirchgessner, A. L., Tamir, H. (1990) 5-HT receptor subtypes outside the central nervous system. Neuropsychopharmacology 3: 385–395

Hardcastle, J., Hardcastle, P. T. (1995) Evidence that the secretory response of rat intestine to 5-hydroxytryptamine in-vivo involves more than one 5-hydroxytryptamine receptor subtype. J. Pharm. Pharmacol. 47: 744–749

Hardcastle, J., Hardcastle, P. T. (1997a) Several receptor subtypes contribute to 5-hydroxytryptamine-induced secretion by rat ileum in-vitro. J. Pharm. Pharmacol. 49: 1126–1131

Hardcastle, J., Hardcastle, P. T. (1997b) Comparison of the intestinal secretory response to 5-hydroxytryptamine in the rat jejunum and ileum in-vitro. J. Pharm. Pharmacol. 49: 1114–1120

Hardcastle, J., Hardcastle, P. T. (1998) 5-Hydroxytryptamine-induced secretion by rat jejunum in-vitro involves several 5-hydroxytryptamine receptor subtypes. J. Pharm. Pharmacol. 50: 539–547

Hardcastle, J., Hardcastle, P. T., Redfern, J. S. (1981) Action of 5-hydroxytryptamine on intestinal ion transport in the rat. J. Physiol. 320: 41–55

Kalkman, H. O., Engel, G., Hoyer, D. (1984) Three distinct subtypes of serotonergic receptors mediate the triphasic blood pressure response to serotonin in rats. J. Hypertens. 2 (Suppl. 3): 143–145

Kuijpers, M. H. M., Provoost, A. P., de Jong, W. (1986) Development of hypertension and proteinuria with age in fawn-hooded rats. Clin. Exp. Pharmacol. Physiol. 13: 201–209

Leff, P., Martin, G. R. (1988) The classification of 5-hydroxytryptamine receptors. Med. Res. Rev. 8: 187–202

Mawe, G. M., Branchek, T. A., Gershon, M. D. (1986) Peripheral neural serotonin receptors: identification and characterization with specific antagonists and agonists. Proc. Natl Acad. Sci. USA 83: 9799–9803

McKay, D. M., Perdue, M. H. (1993) Intestinal epithelial function: the case for immunophysiological regulation. Cells and mediators. Dig. Dis. Sci. 38: 1377–1387

Raymond, S. L., Dodds, W. J. (1975) Characterization of the fawn-hooded rat as a model for hemostatic studies. Thromb. Diathes. Haemorrh. 33: 361–369

Terrón, J. A. (1997) Role of 5-ht_7 receptors in the long-lasting hypotensive response induced by 5-hydroxytryptamine in the rat. Br. J. Pharmacol. 121: 563–571

Zimmerman, T. W., Binder, H. J. (1984) Serotonin-induced alteration of colonic electrolyte transport in the rat. Gastroenterology 86: 310–317