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The role of 5-hydroxytryptamine in the feline response to intravenous infusion of live *E. coli*

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1 A standardized septic shock was induced in cats by intravenous infusion of a live *E. coli* bacteria strain. The bacterial infusion induced a rapid haemodynamic response characterized mainly by a pulmonary arterial hypertension and a late phase characterized by systemic hypotension and hypodynamic circulation.

2 Systemic arterial, pulmonary arterial, portal venous, left atrial pressures, max inspiratory-expiratory pressure difference in the trachea, aortic and intestinal blood flows were monitored. Arterial blood samples were taken for recording the number of circulating platelets and white blood cells and for determining the acid-base balance.

3 The effect of pretreatment with ketanserin, a specific 5-hydroxytryptamine$_2$ (5-HT$_2$)-receptor blocker on these haemodynamic reactions was studied.

4 In short term experiments on non-bacteriaemic control cats, ketanserin prevented the pulmonary hypertension induced by intravenous 5-HT infusions but not the increase in intestinal blood flow.

5 Ketanserin induced a reduction of total peripheral (including intestinal) vascular resistance to blood flow but had no effect on aortic blood flow.

6 After infusion of bacteria, ketanserin pretreated cats were more hypotensive due to a relative peripheral dilatation of the resistance vessels. Ketanserin pretreatment had no effect on the pulmonary vascular reactions, the tracheal pressure difference or the number of circulating platelets or white blood cells. Thus, except for a more pronounced hypotension early after bacterial infusion, ketanserin pretreatment did not influence the haemodynamic response.

7 It is concluded that 5-HT is not of significant importance in the pathogenesis of the haemodynamic reactions following experimental bacteraemia.

Introduction

Intravenous infusion of endotoxin or live bacteria is initially followed by a characteristic, rapid increase in pulmonary vascular and airway resistances and a decrease in the number of circulating platelets and leucocytes (Kuida, Hinshaw, Gilbert & Visscher, 1958; Greenway, Lautt & Stark, 1969; Falk, Myrvold & Haglund, 1982c). The pathogenesis of this response is not fully known. It is generally believed, however, that pulmonary-trapping of aggregated platelets and white blood cells causes or at least significantly contributes to the pulmonary vascular and airway reactions by release of vasoactive substances (Kux, Coalson, Massion & Guenter, 1972; Rådegran & McAslan, 1972; Myrvold & Svalander, 1977). One substance proposed to play a pathogenic role is 5-hydroxytryptamine (5-HT) (Koehler, Tsagaris, Kuida & Hecht, 1963; Kusajima. Ozdemir, Webb, Wax & Parker, 1974; Will, 1982). 5-HT is stored in relatively large amounts in the platelets (Holmsen, 1975) and it is reasonable to assume that it is released upon platelet disintegration.

Infusion of 5-HT induces similar vascular and airway responses to those found following infusion of endotoxin or bacteria (Kusajima *et al.*, 1974). The importance of 5-HT release for the pulmonary changes in shock is difficult to assess because there has not been a selective 5-HT receptor blocker available. Use of non-specific blockers such as methysergide has led to conflicting results (Kusajima *et al.*, 1974; Parratt & Sturgess, 1977).

However, a selective 5-HT$_2$-receptor blocker, ketanserin, has recently been developed (Leysen,

Awouters, Kennis, Laduron, Vandenberk & Janssen, 1981; van Nueten, Janssen, von Beek, Xhonneux, Verbeuren & Vanhoutte, 1981). The aim of this study was to investigate to what extent this selective 5-HT_2 blocker influences the pulmonary response and the effects on the general circulation induced by a standardized bacteraemia in cats.

Methods

The experiments were performed on 22 cats weighing 3.0–4.8 kg. They were deprived of food for 12 h before the experiments, but had free access to water. Anaesthesia was induced with ether and continued with chloralose (50 mg kg^{-1} body weight) after tracheostomy. The animals were connected to a constant volume respirator and ventilated with 15 ml kg^{-1} body wt at 15 min^{-1}. Thus, the cats were hyperventilated. In pilot experiments the dead space was adjusted to give an arterial P_{CO_2} slightly below normal (Fink & Schoolman, 1963). A slow intravenous infusion of a glucose solution containing bicarbonate (10 mmol $NaHCO_3$ in 100 ml 10% glucose; 0.1–0.2 ml min^{-1}) was started at the time of the induction of anaesthesia and then continued throughtout the experiments to maintain arterial pH at a normal level despite the operative trauma (Haglund & Lundgren, 1972). Body temperature was checked by a thermometer in the oesophagus and was kept at 38°C by means of a heating pad and by ordinary table lamps.

Through a midline laparotomy a segment corresponding to about 75% of the small intestine was isolated with intact vascular and nervous supply. The remainder of the small intestine, colon, spleen, greater omentum, and a major portion of the pancreas were extirpated. Following a left parasternal thoracotomy an electromagnetic flow probe (Nycotron AS, Drammen, Norway) was placed on the ascending aorta to record cardiac output minus coronary flow. The pulmonary artery was cannulated for pressure recordings. The animals were heparinized and the superior mesenteric vein was cannulated. The intestinal venous blood was returned to the portal vein via a photoelectric drop counter. The portal venous pressure was continuously monitored. The left femoral artery was cannulated for systemic arterial blood pressure recording and the left femoral vein for giving intravenous infusions. Maximal inspiration-expiration pressure differences in the trachea were recorded by means of a cannula inserted into the tracheostomy tube. Left atrial pressure was followed after cannulation. Pressures were measured by Statham transducers and together with blood flows recorded on a Grass polygraph. Circulating arterial platelet and white blood cell counts, P_{O_2}, P_{CO_2}, pH and oxygen saturation were measured in arterial blood 5 min before, 5 min, 60 min and 120 min after the start of the *E. coli* infusion. Blood gas analyses were made using an ABL 2 (Acid-Base Laboratory, Radiometer, Copenhagen).

Bacteraemia was induced by infusion of an *Escherichia coli* bacteria strain (*E. coli* 06 K 13 H1) (WHO designation Su 4344/41) from the WHO Collaborative Center for Reference and Research on *Escherichia* (State Serum Institute, Copenhagen, Denmark). The bacteria were cultivated in standard nutrient broth. Prior to the infusion the bacteria were washed in 0.9% w/v NaCl solution (saline). The washed bacteria were then resuspended in saline and infused at a concentration of 10^{10} live cells per ml. The cats were given 1 ml kg^{-1} body wt min^{-1} for 2 min followed by 1 ml kg^{-1} h^{-1} for the next 2 h, after which, the experiments were terminated.

Experimental procedures

In seven cats the effects of 5-HT (25–90 μg) before ($n = 4$) and after ($n = 3$) intravenous infusion of 0.5 mg kg^{-1} body wt ketanserin, (Janssen, Beerse, Belgium) were tested in short term experiments. The remaining 15 cats were divided into two series. Series I ($n = 8$) received ketanserin 5 min before the start of the bacterial infusion. Three cats received 1 mg kg^{-1} and five received 0.5 mg kg^{-1} body wt. In series II the corresponding volume of saline was given 5 min before the start of bacterial infusion.

Microscopy

At the end of each experiment about 3 cm of the middle portion of the small intestine was rapidly excised, cut open, and mounted on cork and fixed in 10% neutral formalin. The blocks were prepared for paraffin-embedding, cut at about 4 μm, mounted and stained according to v. Gieson. The glasses were coded for histological examination. The appearance of the mucosa was graded as described earlier (Åhrén & Haglund, 1973; Falk, Myrvold, Lundgren & Haglund, 1982b) into six grades where grade 0 means normal mucosa and grades 1–5 increasing damage to the villi.

Statistical methods

Data are expressed as mean values ± s.e. When testing statistical significance between the two different series the non-parametric method of Wilcoxon was used (Diem & Lentner, 1970). Differences within each series were tested according to Wilcoxon matched-pairs signed-ranks test (Siegel 1956). A P value less than 0.05 was considered as significant.

Results

Intravenous infusion of 5-HT in all animals induced a prompt increase in pulmonary arterial blood pressure of about 5–10 mmHg and an increase in intestinal blood flow of 5–10 ml min^{-1} 100 g^{-1}. There was no concomitant change in arterial blood pressure or aortic blood flow. If ketanserin (0.5 mg kg^{-1}) was infused before the 5-HT injection the change in pulmonary arterial blood pressure was abolished. However, the increase in intestinal blood flow was not influenced by ketanserin.

Intravenous infusion of ketanserin induced a statistically significant drop in arterial blood pressure (Figure 1). This was most pronounced when the higher dose was given (10–40 (median 30) and 0–30 (median 15) mmHg after 1 mg and 0.5 mg kg^{-1} respectively). Intravenous infusion of live bacteria induced a significant early drop in systemic arterial blood pressure in both series. Arterial blood pressure remained low in the ketanserin pretreated series throughout the experiments. In the other series, arterial blood pressure tended to normalize 5 min after the start of the infusion of bacteria and remained at a normal level during the first hour. However, at the end of the experiments there was no difference in arterial blood pressure between the series.

Ketanserin had no effect on pulmonary arterial blood pressure. Bacterial infusion induced a characteristic increase in pulmonary arterial blood pressure and this increase was not influenced by ketanserin. Pulmonary vascular resistance (Table 1) was greatly increased during the first minutes of bacterial infusion and then stabilized at a level slightly above normal. There was no difference between the two series. Ketanserin induced a decrease in total peripheral resistance. This was further accentuated upon bacterial infusion (Table 1). There was no

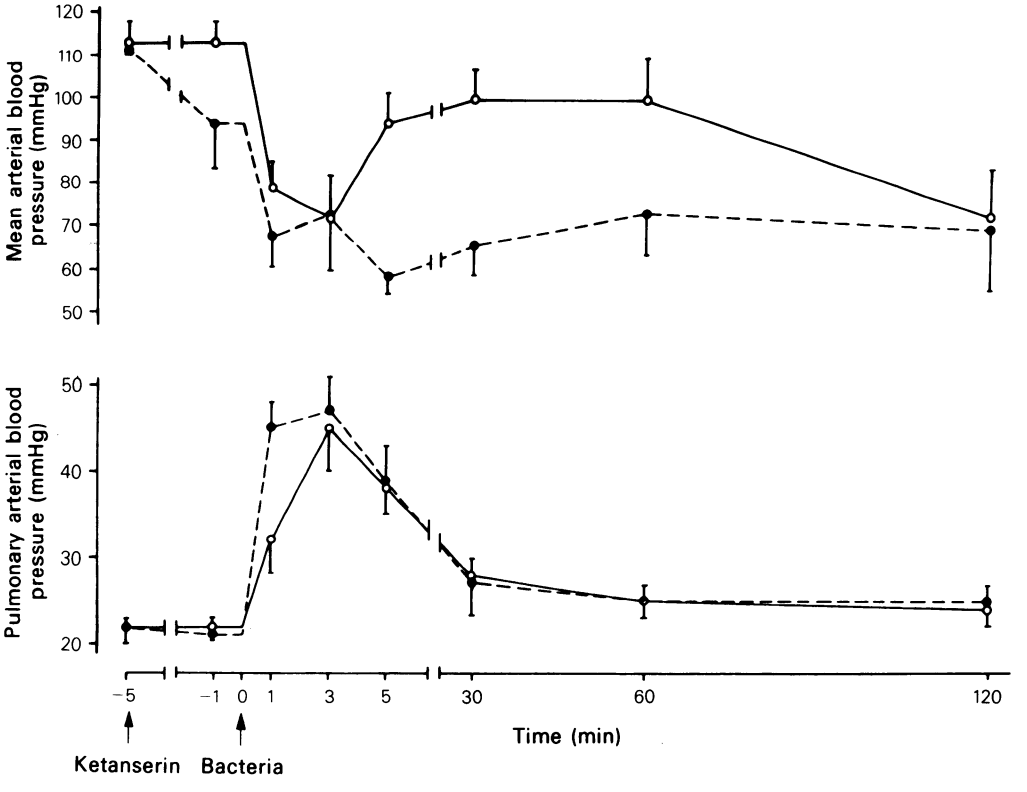

Figure 1 Mean systemic arterial blood pressure and pulmonary arterial blood pressure before and during intravenous infusion of live *E.coli* bacteria. Mean values are shown; s.e.mean indicated by vertical lines. The change in systemic arterial blood pressure was significant ($P < 0.05$) compared to the prebacterial infusion value at 1, 3, 5 and 120 min in the control series (○) and at 1, 5, and 30 min in the ketanserin pretreated series (●). Pulmonary arterial blood pressure was significantly ($P < 0.05$) increased in both series after the start of bacteraemia except at 120 min.

Table 1 Total peripheral resistance (TPR; mmHg × min × kg × ml^{-1}), pulmonary vascular resistance (PVR; mmHg × min × kg × ml^{-1}); and intestinal vascular resistance (IVR; mmHg × min × 100 g × ml^{-1}) to blood flow before and after injection of ketanserin and infusion of bacteria (at time 0)

		Control value	Time					
		−1 min	1	3	5	30	60	120
TPR	Saline	1.5±0.1	0.9±0.1*	1.6±0.1	1.4±0.1	1.4±0.2	1.5±0.2	1.3±0.2
	Ketanserin	1.4±0.1	1.3±0.3	1.3±0.2	0.9±0.1*	1.1±0.1	1.3±0.2	1.3±0.2
PVR	Saline	0.29±0.03	0.39±0.07	1.20±0.20*	0.55±0.06*	0.39±0.03*	0.38±0.04*	0.44±0.06*
	Ketanserin	0.25±0.03	0.93±0.31*	0.83±0.13*	0.54±0.08*	0.43±0.07*	0.41±0.05*	0.37±0.05
IVR	Saline	11.1±1.0	11.0±1.3	13.2±2.0	11.3±1.8	11.1±1.6	9.8±1.6	8.3±1.2
	Ketanserin	9.8±1.3	8.6±0.8	11.1±1.8	5.2±0.6*	6.9±1.4	8.8±1.4	8.9±1.7

Mean values ± s.e. * denotes significant differences ($P < 0.05$) compared to prebacterial infusion control (time −1 min).

difference in the total peripheral resistance to blood flow between the two series at the end of the experiments.

Aortic blood flow was not significantly influenced by the ketanserin infusion. One minute after infusion of live bacteria, aortic blood flow was significantly ($P < 0.05$) reduced in the ketanserin pretreated series but remained unchanged or was slightly increased in the untreated series. Two minutes later a statistically significant decrease in aortic blood flow was noted in both series; 5 min after the start of the bacterial infusion aortic blood flow had stabilized at a level slightly below the preinfusional one. Aortic blood flow was then slightly reduced with time (Figure 2), without any obvious difference between the two series. Ketanserin had no significant effect on the intestinal blood flow (Figure 2). Upon bacterial infusion the untreated series revealed a more pronounced decrease in intestinal blood flow but 5 min after the bacterial infusion this difference had disappeared and during the remainder of the experiments the intestinal blood flow did not differ between the two series. During the first 30 min following bacterial infusion, except for the 3-min value, the intestinal vascular resistance was significantly ($P < 0.05$) lower in the ketanserin pretreated series than in the other series (Table 1).

Portal venous pressure was approximately 10 mmHg in both series. It was not affected by ketanserin or by bacterial infusion, and there was no difference between the two series in portal venous pressure. Left atrial pressure also remained virtually unchanged throughout the experiments without differences between the series. The inspiration-expiration pressure difference in the trachea was increased upon bacterial infusion. Ketanserin pretreatment had no effect on this reaction (Table 2).

Before infusion of live *E.coli* the number of circulating platelets in arterial blood was 348 ± 63 in the untreated, and 329 ± 61 × 10^9 cells l^{-1} in the ketanserin pretreated series. The corresponding values for arterial white blood cells were 5.0 ± 1.3 and 6.0 ± 1.5 × 10^9 cells l^{-1}, respectively. Upon bacterial infusion the number of circulating platelets was reduced to about 50% of the preinfusion values within 5 min (Figure 3). The platelet counts had increased 2 h later. There was no significant difference between the two series. White blood cells in arterial blood were reduced to about 20% upon bacterial infusion and they remained at this low level throughout the experiments. Again, there was no difference between the series.

The changes induced by infusion of live *E.coli* on arterial pH, P_{O_2} and oxygen saturation are depicted in Table 3. P_{CO_2} remained around 3 kP throughout the experiments in both series. Arterial P_{O_2} was in the prebacterial infusion range during the first 60 min

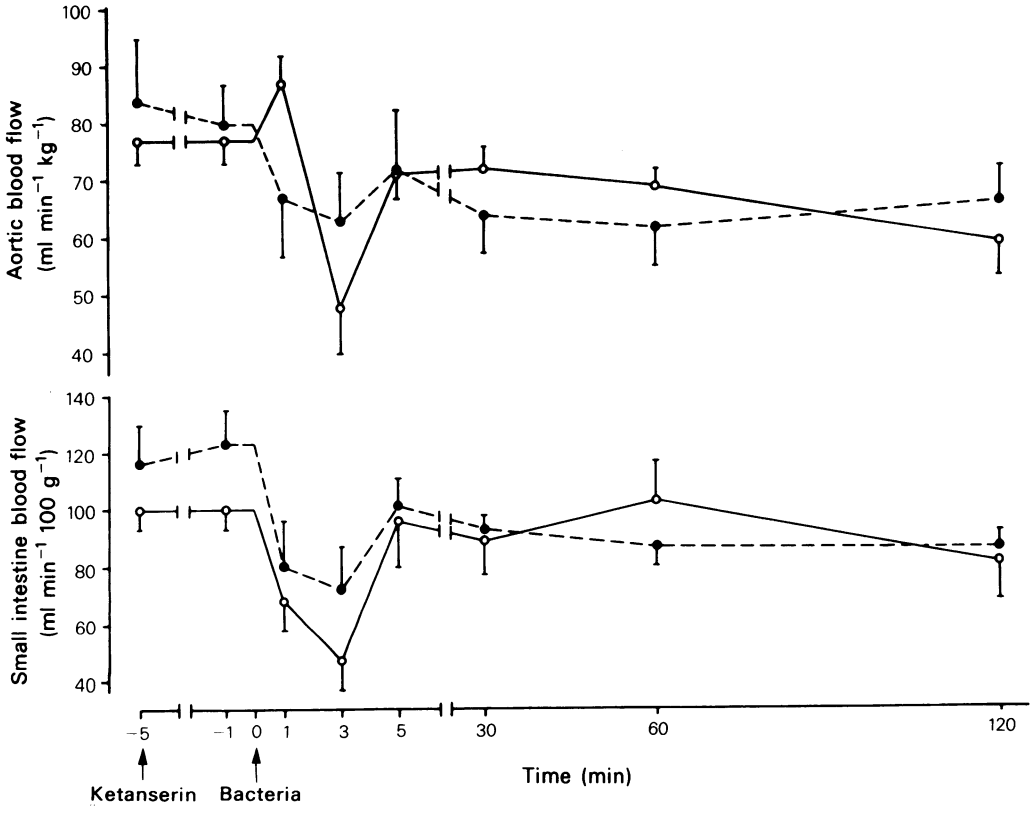

Figure 2 Aortic blood flow and intestinal venous outflow before and during intravenous infusion of live *E.coli* bacteria. Mean values are shown; s.e.mean indicated by vertical lines. In the control series (○) aortic blood flow was significantly ($P < 0.05$) changed after bacteria. In ketanserin pretreated cats (●) the change in aortic blood flow was significant 30, 60 and 120 min after the start of bacteraemia. In both series intestinal blood flow was changed significantly at 1 and 3 min after the start of bacterial infusion.

in the ketanserin-treated cats while it was significantly ($P < 0.05$) reduced at 5 min after bacterial infusion in the controls. The metabolic acidosis at the end of the experiments was more pronounced in the series pre-treated with saline. Otherwise, there was no significant difference between the two experimental series.

Microscopical examination of the intestinal tissue specimens revealed no or only very slight mucosal damage in five cats of both series. Thus, three ketanserin-treated and two control cats had significant mucosal damage. There was no difference between the series.

Discussion

In normotensive cats, ketanserin blocks the pulmonary arterial pressure response induced by 5-HT but not the increase in intestinal blood flow. This latter lack of effect does not mean that ketanserin is not a 5-HT_2-receptor blocker. It has been shown that the effect of 5-HT on the intestinal vascular bed is complex (Granger, Richardson, Kvietys & Mortillaro, 1980). For instance, 5-HT may release vasoactive substances in the splanchnic area such as vasoactive intestinal polypeptide (VIP, Eklund, Fahrenkrug, Jodal, Lundgren, Schaffalitzky de Muckadell & Sjöqvist, 1980) which in turn may be responsible for the major part of the vascular effect. If this is the explanation for the sustained intestinal vascular effect following ketanserin, one may conclude that the releasing effect of 5-HT is apparently not blocked by ketanserin.

Ketanserin induced a significant, although not very pronounced reduction of the peripheral resistance to blood flow. The total peripheral resistance as well as the peripheral resistance of the intestinal vascular bed was reduced about 15 and 20%, respectively (Table 1). Aortic blood flow was not changed by

ketanserin and, consequently, mean arterial blood pressure was reduced. In the doses used in this study an arterial pressure reduction of 15% was seen in normotensive animals. Intestinal blood flow remained unchanged following ketanserin injection. Ketanserin induced no change in portal venous pressure, left atrial or pulmonary arterial blood pressures, nor was the tracheal max inspiratory-expiratory pressure difference influenced.

Intravenous infusion of live *E.coli* into a cat induces a characteristic cardiovascular response described in detail previously (Falk, Kaijser, Myrvold & Haglund, 1980). The early phase is characterized by a pronounced increase in pulmonary arterial blood

Table 2 Inspiratory–expiratory pressure difference (mmHg) before and after injection of ketanserin and start of bacterial infusion (time 0)

		Time					
	Control value	−1	1	3	5	30	60	120
Saline	5.3±0.4	5.3±0.4	6.4±0.5*	9.4±0.4*	7.4±0.6*	6.6±0.4*	6.4±0.4*	6.3±0.3
Ketanserin	5.2±0.7	5.2±0.7	8.3±0.6*	8.0±0.8*	7.1±0.7*	6.7±0.6*	6.6±0.7	6.8±0.8

Mean values±s.e. * denotes a significant difference ($P<0.05$) compared to the prebacterial infusion value (time −1).

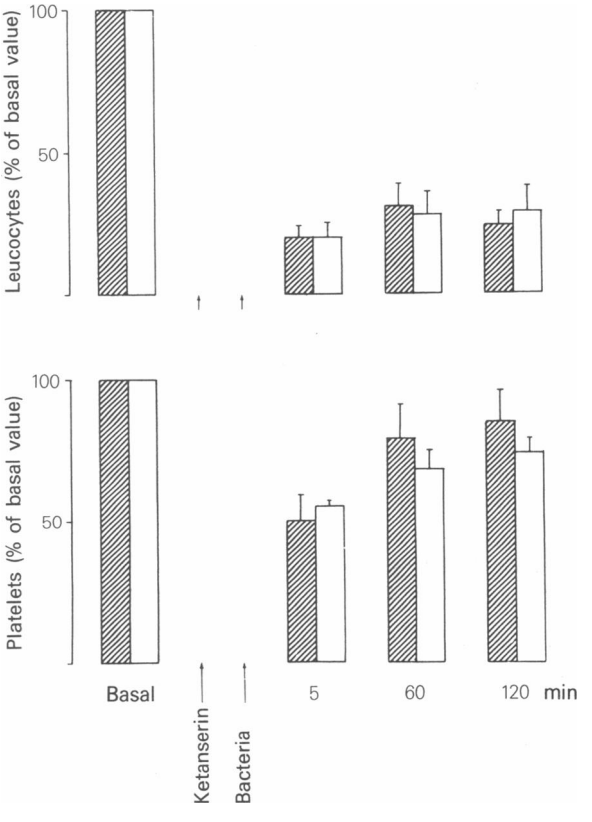

Figure 3 The number of circulating leucocytes and platelets before and during intravenous infusion of live *E.coli* expressed as a percentage of the prebacterial infusion, control level. Hatched columns denote pretreatment with ketanserin and open columns, controls. Mean values are shown; s.e.mean indicated by vertical lines. The reduction of circulating leucocytes was statistically significant at all times in both series, as was the change in platelets in the control series. In the ketanserin series, platelet reduction was significant at 5 min.

Table 3 Arterial pH, P_{O_2} (kP), and oxygen saturation (%) before and after start of bacterial infusion

		pH	P_{O_2}	*O_2 saturation*
Control value before bacterial infusion	Saline	7.50 ± 0.02	12.4 ± 0.9	97 ± 1
	Ketanserin	7.46 ± 0.01	11.6 ± 0.9	95 ± 1
5 min after	Saline	7.47 ± 0.03	7.94 ± 0.89*	88 ± 3*
	Ketanserin	7.48 ± 0.02	13.1 ± 1.4	96 ± 1
60 min	Saline	7.28 ± 0.04*	7.14 ± 0.29*	81 ± 3*
	Ketanserin	7.32 ± 0.02*	10.3 ± 1.7	89 ± 3*
120 min	Saline	7.12 ± 0.05*	9.23 ± 0.77*	83 ± 4*
	Ketanserin	7.27 ± 0.03*	8.1 ± 0.6*	86 ± 3*

Mean ± s.e. * denotes significant difference ($P < 0.05$) compared to the control value

pressure and pulmonary vascular resistance, a rapid and reversible drop in systemic arterial blood pressure without significant changes in aortic blood flow. After a few minutes, arterial blood pressure is more or less restored while aortic blood flow is significantly reduced. The later phase is characterized by a progressive decline in systemic arterial blood pressure (Greenway *et al.*, 1969; Falk *et al.*, 1982c). Pulmonary arterial blood pressure is normal in this phase but pulmonary vascular resistance is increased. In the late phase, aortic blood flow is reduced progressively.

The haemodynamic changes in the small intestine, representing an important part of the peripheral vascular bed, have been studied in some detail during experimental bacteraemia. In the early phase, intestinal blood flow was decreased approximately 35% and intestinal blood flow resistance was increased about 60%. The portal venous pressure most often remains unchanged. In the late phase of the haemodynamic response to bacteraemia, intestinal blood flow is progressively reduced while intestinal resistance to blood flow remains in the prebacteraemic range (Falk *et al.*, 1980; Falk, Myrvold & Haglund, 1982a). Despite the rather modest changes in intestinal blood flow, 2 h of experimental bacteraemia in the cat induces microscopical mucosal damage of the small intestine in about 50% of cases (Falk *et al.*, 1982b). Furthermore, a direct relationship between the development of the intestinal mucosal lesions and cardiovascular deterioration in experimental bacteraemia has been suggested (Falk, Myrvold & Haglund, 1982c).

In the present series of experiments it was found that the ketanserin pretreated cats were unable to restore systemic arterial blood pressure to the preseptic level. However, in the late phase there was no arterial blood pressure difference between pretreated and untreated cats. There was no difference in pulmonary arterial blood pressure or pulmonary vascular resistance between the two series of animals. Ketanserin has no significant effect on the aortic blood flow reactions to bacteraemia, nor on intestinal blood flow. The max inspiratory-max expiratory pressure difference in the trachea was not influenced by ketanserin pretreatment. However, the arterial hypoxia induced by the bacteraemia was postponed 60 min by ketanserin. This was not secondary to preventing platelet or leucocyte reduction in arterial blood. The reason for the effect on arterial P_{O_2} is not known.

In summary, blockade of the 5-HT_2 receptors did not influence the feline haemodynamic response to experimental bacteraemia. It could thus be concluded that 5-HT dose not seem to be an important factor in the pathogenesis of this response, in contrast to what was suggested before a specific 5-HT receptor blocker was available (Koehler *et al.*, 1963; Kusajima *et al.*, 1974; Will, 1982).

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