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Mesenteric vasoconstriction after endotoxin administration in cats pretreated with aspirin

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Summary

1. Study of the delayed responses to lethal doses of endotoxin in cats is complicated by acute pulmonary vasoconstriction which results in hypotension, cardiac failure and pulmonary oedema. This acute response is abolished if the animal is pretreated with aspirin (10–100 mg/kg). In these cats, pretreated with aspirin, arterial pressure and right atrial pressure remain unchanged in the first 2 h after administration of endotoxin. Later, arterial pressure falls and the animals die but no haemorrhagic lung lesions are visible.

2. These results confirm our previous conclusion that the delayed lethal response to endotoxin is an independent action and not a secondary consequence of the acute response. The mechanism of the action of aspirin is discussed and it is suggested that it prevents the release by endotoxin of vasoactive substances, possibly from platelets.

3. In cats pretreated with aspirin, administration of endotoxin results in a marked mesenteric vasoconstriction. Although arterial pressure does not decrease significantly, superior mesenteric arterial flow decreases to 20% of control in the first hour after endotoxin and remains at this low level until the animal dies. Mesenteric ischaemia may contribute to the cat's death.

4. The mesenteric vasoconstriction is not reduced by prior administration of phenoxybenzamine and is only slightly reduced after phenoxybenzamine, hypophysectomy and nephrectomy. It is concluded that catecholamines, vasopressin and angiotensin play at most a minor role in the mechanism of this vasoconstriction and that other unknown factors are predominant.

Introduction

In cats and dogs, intravenous administration of a lethal dose of endotoxin is followed by an acute fall in arterial pressure. If the animal does not die, the arterial pressure recovers over 20–30 min but then declines again after several hours and the animal dies. We have called these responses the acute and delayed hypotensive responses (Greenway, Lautt & Stark, 1969). In the cat, the acute hypotensive response is due to pulmonary vasoconstriction (Kuida, Gilbert, Hinshaw, Brunson & Visscher, 1961 ; Kuida, Hinshaw, Gilbert & Visscher, 1958).

Weil & Spink (1957) compared the acute response with anaphylactic shock and with the anaphylactoid type of reaction produced by many macromolecules. On the basis of experiments with endotoxin, which was subjected to mild alkaline hydrolysis, we suggested that the acute and delayed phases in the cat were due to

independent mechanisms and the acute phase could be completely abolished without modification to the delayed phase or to the lethal effect (Greenway *et al.*, 1969). Other data suggested that the acute response in the dog required the presence of platelets and other plasma factors (Hinshaw, Kuida, Gilbert & Visscher, 1957; Kobold, Lovell, Katz & Thal, 1964; Vick, 1964) and involved the release of endogenous vasoactive agents (Hinshaw, Vick, Carlson & Fan, 1960; Davis, Meeker & Bailey, 1961; Hinshaw, Jordan & Vick, 1961). It seemed possible that aspirin would block the acute response in the cat since platelet agglutination by endotoxin *in vitro* was inhibited by aspirin (Mustard, Evans, Packham & Nishizawa, 1969) and the acute response to endotoxin in the dog appeared to be reduced after aspirin in experiments reported by earlier workers (Northover & Subramanian, 1962; Hinshaw, Solomon, Erdos, Reins & Gunter, 1967).

This paper describes experiments in which cats were pretreated with aspirin before administration of a lethal dose of endotoxin. The effect of this pretreatment on the acute and delayed responses to endotoxin was investigated. A preliminary report of this work has been given (Murthy & Greenway, 1971).

Methods

Cats (1·7–4·4 kg, mean 2·9 kg) were anaesthetized by intraperitoneal injection of sodium pentobarbitone (Abbott, 30 mg/kg). When reflex limb and eye movements returned, additional doses (8 mg) of sodium pentobarbitone were given through a cannula in a forelimb cutaneous vein. Mean arterial pressure (1 mmHg≡1·333 mbar) was recorded from a cannula in a femoral artery and mean right atrial pressure from a cannula inserted through the right external jugular vein. The surgery was carried out under clean but not sterile conditions.

In the first series of experiments, cats were given aspirin (100 mg/kg) in ammonium acetate solution (1·15 g/100 ml water) followed after 20 min by endotoxin (3 mg/kg). The pressures were recorded for 30 min, then penicillin G (100,000 U) and streptomycin (100 mg) were administered intramuscularly and 5 ml 25% glucose in 5 ml Ringer-Locke solution was given intravenously. The wounds were closed and the animals allowed to recover. Animals which were alive and active after 48 h were considered as survivors.

In the second series of experiments, the cats were prepared as before but in addition, superior mesenteric arterial flow was recorded. The abdomen was opened and a 1–2 cm length of the superior mesenteric artery was dissected free from surrounding tissue without damage to the nerves (McNeill, Stark & Greenway, 1970). The inferior mesenteric artery was ligated. A non-cannulating probe (2 mm diameter) was placed round the superior mesenteric artery and connected to an electromagnetic flowmeter (Nycotron, Oslo). The probe was attached to a micrometer-controlled arterial clamp which served to hold the probe steady and allowed frequent zero checks. Calibration was carried out *in situ* at the end of each experiment (Greenway, Lawson & Mellander, 1967). Mesenteric conductance was calculated by dividing the mesenteric flow by the arterial pressure minus portal pressure in each experiment. Since arterial pressure did not change markedly in these experiments, the graphs for mesenteric flow and conductance are quite similar.

In the third series of experiments, the animals were set up in the same way but in addition, phenoxybenzamine (5 mg/kg) was administered intravenously. In some

animals, hypophysectomy and nephrectomy were carried out as previously described (McNeill *et al.*, 1970).

Endotoxin (Bacto-lipopolysaccharide B from *Salmonella enteritidis*, Difco Laboratories, 3 mg/kg) was suspended in 5 ml 0·9% w/v sodium chloride solution and given intravenously over 30 seconds. Phenoxybenzamine (Dibenzyline, Smith, Kline & French) was dissolved in propylene glycol (250 mg in 25 ml), acidified with four drops of 1 N HCl. Before injection, the required dose (5 mg/kg) was diluted with 5 volumes of 0·9% sodium chloride solution. This dose blocks intestinal vasoconstriction induced by maximal sympathetic nerve stimulation or noradrenaline infused in the quantities released by the adrenal medullae (McNeill *et al.*, 1970). Blood was obtained from donor cats anaesthetized with ether, and heparin (1,500 U/100 ml) was added.

Results

Effects of endotoxin

The arterial and right atrial pressure responses to endotoxin in cats have been described previously (Greenway *et al.*, 1969). Control experiments were carried out to ensure that the ammonium acetate solution used as solvent for the aspirin did not modify the responses. Five cats were given ammonium acetate solution (4 ml/kg) followed 20 min later by endotoxin (3 mg/kg). The mean arterial and right atrial pressure responses are shown in Fig. 1. The responses were similar to

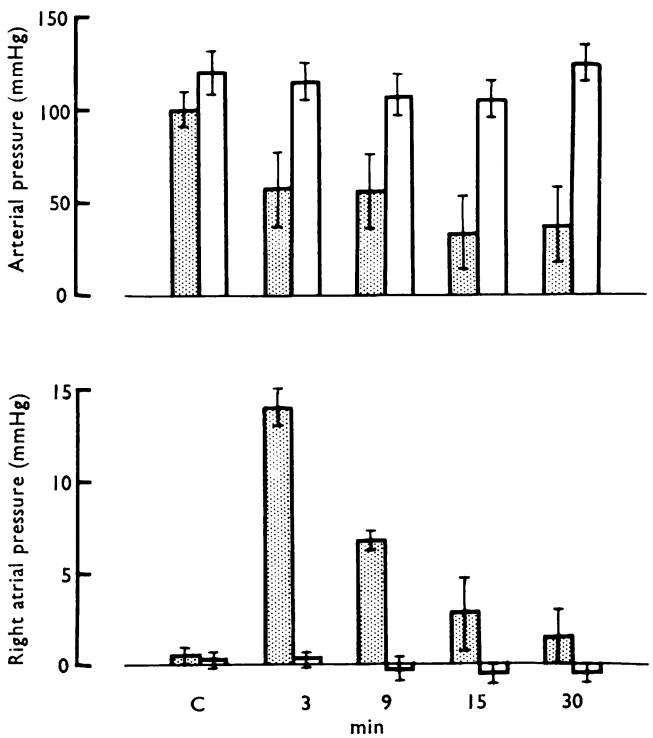

FIG. 1. Arterial and right atrial pressures (means ± S.E.) before (C) and at various times after administration of endotoxin (3 mg/kg) in cats pretreated with ammonium acetate solution (shaded columns, five cats) or aspirin (100 mg/kg) in ammonium acetate solution (open columns, six cats).

those previously described and the responses were not modified by prior administration of ammonium acetate solution. All the cats died within 24 h and on gross examination, the surface of the lungs was covered with red haemorrhagic patches.

Effects of aspirin

In eighteen cats, aspirin (100 mg/kg) in ammonium acetate solution was administered intravenously. The arterial pressure was $109 \pm 5{\cdot}7$ mmHg (mean $\pm$ S.E.) before and $120 \pm 7{\cdot}7$ mmHg 20 min after the aspirin. (1 mmHg$=1{\cdot}333$ mbar). In five of these cats, right atrial pressure was measured; it was $0{\cdot}4 \pm 0{\cdot}5$ mmHg before and $0{\cdot}6 \pm 0{\cdot}7$ mmHg after aspirin. In these five experiments the wounds were closed; all the cats were alive and active 24 h later. In ten cats, the superior mesenteric arterial flow was $(39 \pm 6{\cdot}0$ ml/min)/kg before the aspirin and $95 \pm 6\%$ of this 20 min after the aspirin. In two of these cats no other drugs were given; the arterial pressure and flow did not change significantly ($P > 0{\cdot}1$) over the following 2–3 hours. It is concluded that the administration of aspirin in ammonium acetate solution produces no significant changes in arterial pressure, right atrial pressure and superior mesenteric arterial flow and that the cats will survive this treatment.

Effects of endotoxin after aspirin

In six cats in which arterial and right atrial pressures were recorded, the administration of aspirin (100 mg/kg) was followed 20 min later by endotoxin (3 mg/kg). The responses are shown in Fig. 1. No significant changes in these pressures occurred and at no time after the administration of endotoxin was there an increase in right atrial pressure. After 30 min the wounds were closed and the animals allowed to recover; of the six cats only one survived for 24 h, but on gross examination the lungs appeared normal and no haemorrhagic patches were visible. It is concluded that pretreatment with aspirin prevents the acute hypotension and increase in right atrial pressure, but does not prevent the subsequent death of the animals.

When these data were communicated (Murthy & Greenway, 1971) it was pointed out that this dose of aspirin was large in comparison with normal therapeutic doses used in man. Therefore in three cats, similar experiments were carried out with a smaller dose (10 mg/kg). Right atrial pressure did not increase in any cat while arterial pressure remained unchanged in two cats and decreased by 30 mmHg in the third. Two of the cats died within 48 hours. Thus a dose of 10 mg/kg aspirin is almost as effective as a dose 10 times larger in blocking the acute response to endotoxin in the cat.

Superior mesenteric arterial flow responses

Superior mesenteric arterial flow was measured in eight cats which were given endotoxin after pretreatment with aspirin. The mean superior mesenteric arterial flow before the endotoxin was $(37 \pm 5{\cdot}8$ ml/min)/kg. The results are shown in Fig. 2. Arterial pressure showed a small decrease after endotoxin. This was more consistent than in the previous series of experiments, possibly because of the greater surgical intervention. The mesenteric flow decreased markedly over 45–60 min and thereafter remained at 20–30% of the control level. The onset of the decrease in flow varied in different animals. In four cats, the flow began to decrease 3–9 min after the endotoxin. In the other four cats, the decrease was preceded by an increase

in flow which lasted 15–30 minutes. These variations account for the large standard errors in the first 30 min after endotoxin in Fig. 2. In all the experiments the pressure remained greater than 100 mmHg and the flow remained low for 180–550 min (mean 280 min). After this time, the experiments were either terminated (one cat) or the arterial pressure slowly decreased and the animal died.

It is concluded that in cats pretreated with aspirin, endotoxin causes a marked and persistent mesenteric vasoconstriction.

Mechanism of mesenteric vasoconstriction

We attempted to study the mechanism of the mesenteric vasoconstriction by the methods we had used previously to analyse the response after a haemorrhage (McNeill *et al.*, 1970; Stark, McNeill & Greenway, 1971). In four cats, phenoxybenzamine (5 mg/kg) was administered intravenously over 5 min and arterial pressure was maintained by infusion of 12 ± 1·9 ml/kg blood. After 40 min aspirin was administered as before, followed after 20 min by endotoxin. After endotoxin, arterial pressure tended to decrease and it was maintained by infusion of 7·7 ± 2·8 ml/kg blood in the first 20 min after endotoxin. After this time, the changes

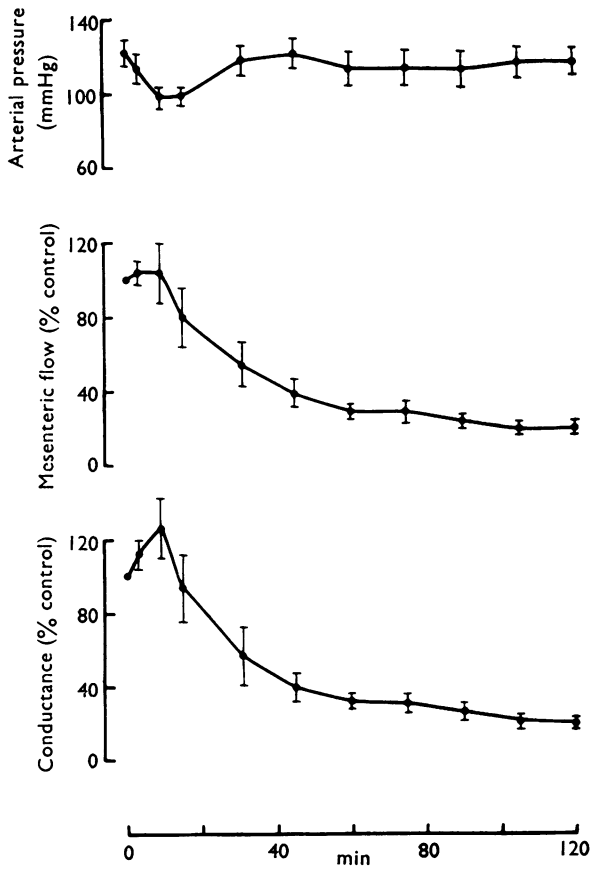

FIG. 2. Arterial pressure and superior mesenteric arterial flow and conductance after administration of endotoxin in cats pretreated with aspirin. The graphs show the means (±S.E.) for eight cats.

in arterial pressure were spontaneous. The responses are shown in Fig. 3. The superior mesenteric arterial flow before the endotoxin was (39 ± 15 ml/min)/kg. After endotoxin, flow and conductance increased initially and then decreased markedly. In the second hour after endotoxin, the flow and conductance were not significantly different from those in animals which did not receive phenoxybenzamine (t test for unpaired data, $P > 0{\cdot}1$).

In seven cats, the pituitary and kidneys were removed and phenoxybenzamine was given. To maintain arterial pressure as the phenoxybenzamine was given, 16 ± 1·9 ml/kg blood was infused intravenously. After 40 min, aspirin was administered as before followed 20 min later by endotoxin. After the endotoxin arterial pressure was maintained by infusion of 12 ± 1·9 ml/kg blood in the first hour and 7·4 ± 2·0 ml/kg in the second hour. The results are shown in Fig. 4. The superior mesenteric flow before endotoxin was (35 ± 7·1 ml/min)/kg. After the endotoxin, flow and conductance increased initially and then decreased to 50–60% of the control by 2 hours. The constriction after 60 min was significantly smaller than that in the control experiments (unpaired t test, $P<0{\cdot}001$) and after administration of phenoxybenzamine alone ($P < 0{\cdot}02$). However, the decrease in

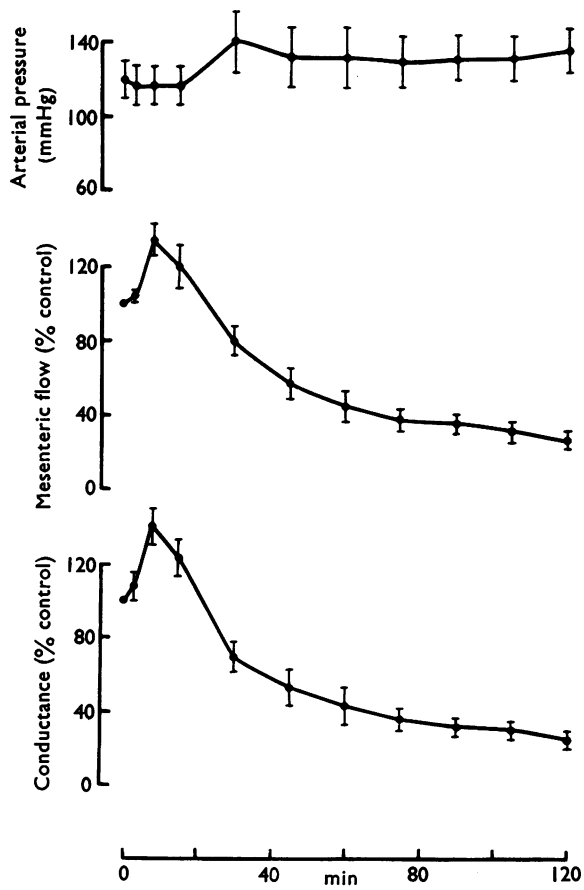

FIG. 3. Arterial pressure and superior mesenteric arterial flow and conductance after administration of endotoxin in cats pretreated with phenoxybenzamine and aspirin. Arterial pressure was maintained by infusion of blood. The graphs show the means (±S.E.) for four cats.

conductance was still highly significant when compared with the control pre-endotoxin level (paired t test, $P<0{\cdot}001$).

It is concluded that administration of phenoxybenzamine alone did not significantly alter the intestinal vasoconstriction after endotoxin in cats pretreated with aspirin. In cats in which phenoxybenzamine was given and the pituitary and kidneys removed, the constriction was significantly reduced but conductance still decreased to half the control level.

Discussion

In the cat, study of the delayed responses to lethal doses of endotoxin is complicated by acute pulmonary vasoconstriction which in our experience kills half the animals in a few minutes. Although it was previously shown that the acute response could be abolished without abolishing the delayed lethal effect if the endotoxin was first subjected to mild alkaline hydrolysis, this separation could only be obtained in two-thirds of the cats (Greenway *et al.*, 1969). This procedure seemed to us to be unsatisfactory for studying the delayed response since one-third of the experiments was wasted and, perhaps of more importance, the endotoxin was

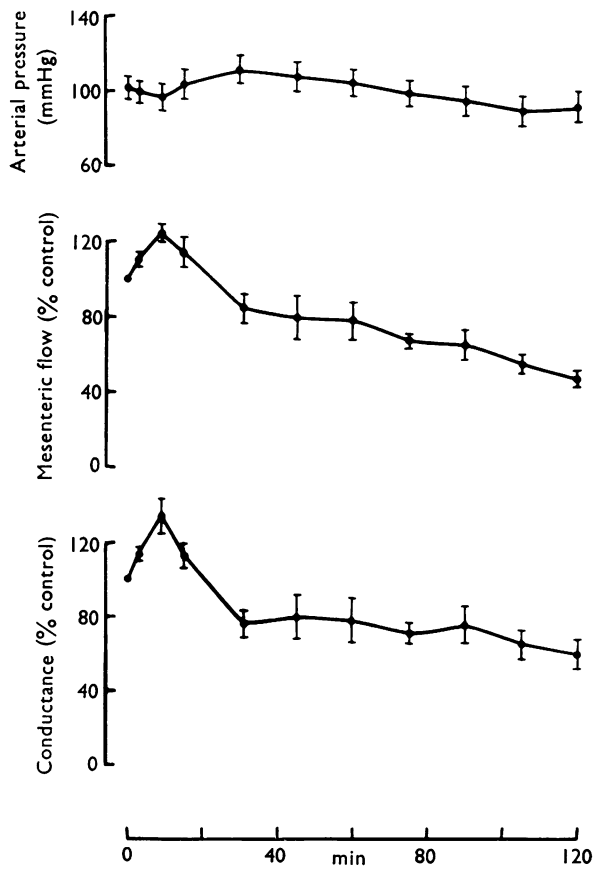

FIG. 4. Arterial pressure and superior mesenteric arterial flow and conductance after administration of endotoxin in cats pretreated with phenoxybenzamine and aspirin after hypophysectomy and nephrectomy. Arterial pressure was maintained by infusion of blood. The graphs show the means (±S.E.) for seven cats.

modified in an unknown way by the alkaline hydrolysis. Pretreatment with aspirin was consistently effective in blocking the acute response and preventing the haemorrhagic lesions of the lungs. These results confirm our previous conclusion that the delayed lethal response is an independent action of endotoxin and not a secondary consequence of the acute respose.

The mechanism of the action of aspirin is not clear. The papers cited in the introduction suggest that the acute response to endotoxin involves the release of endogenous factors and platelets have been implicated as one possible source of these factors. Collier (1969) has reviewed the pharmacology of aspirin and suggests that it antagonizes some humoral mediators by a local action which does not involve a receptor antagonism. Since aspirin inhibits platelet agglutination by endotoxin *in vitro* (Mustard *et al.*, 1969), histamine release (Haining, 1956) and anaphylactic shock (Campbell, 1948), it seems reasonable to postulate that aspirin prevents the release of the vasoactive factors involved in the acute pulmonary response. The nature of these factors and the mechanism of action of aspirin remains to be elucidated.

Extrapolation of studies on endotoxin in one species to other species is extremely hazardous. Pulmonary lesions after endotoxin have been reported in primates and man (McLean, Duff & MacLean, 1968; Coalson, Hinshaw & Guenter, 1970) and may play an important role in human septic shock. There is no evidence that the mechanism of the pulmonary changes in man is related to that in the cat. However it appears reasonable to suggest that the effects of aspirin on these pulmonary lesions are worthy of investigation. Although the doses of aspirin (100 mg/kg) used in most of our experiments were very large, smaller doses (10 mg/kg) were also effective. Such doses could be tested in primates or man. It is unlikely that aspirin treatment would reverse pulmonary damage which had already occurred, but it might prevent further progression of the lesions.

Although the acute response to endotoxin is abolished, the cats still show a delayed hypotension which leads to death. Hinshaw *et al.* (1967) claimed that survival was increased after endotoxin in dogs pretreated with aspirin but in their study the doses of endotoxin were very small (0.4 mg/kg). Thus while aspirin pretreatment may have a marginal effect on survival, it does not appear to protect against the lethal effects of larger doses of endotoxin. Although we cannot exclude the possibility that the delayed responses to endotoxin are substantially modified by pretreatment with aspirin, the advantage of being able to study these delayed responses in the absence of the massive cardiovascular disturbance which results from pulmonary vasoconstriction, seemed to justify such a study. We therefore examined the mesenteric vascular responses in cats pretreated with aspirin.

After pretreatment with aspirin, administration of endotoxin causes a persistent marked mesenteric vasoconstriction, and superior mesenteric flow decreases to 20% of the control flow. This degree of mesenteric ischaemia was similar to that seen after haemorrhage (McNeill *et al.*, 1970) but the mesenteric vasoconstriction was much greater after endotoxin since arterial pressure was not reduced and the decrease in flow was entirely due to vasoconstriction. Non-occlusive mesenteric ischaemia is harmful in cats (Glenn & Lefer, 1970), dogs (Chiu, McArdle, Brown, Scott & Gurd, 1970; Selkurt, 1959; Williams, Anastasia, Hasiotis, Bosniak & Byrne, 1968) and man (Jordan, Boulafendis & Guinn, 1970; Ottinger & Austen, 1967) and this may be one cause of the subsequent hypotension and death of the cats. Intravenous

infusion of vasopressin ((10–20 mU/min)/kg) for 3–4 h caused death within 48 h in cats (Greenway, unpublished observations). Such doses produce marked intestinal and splenic vasoconstriction with only small to moderate increases in arterial pressure (Cohen, Sitar, McNeill & Greenway, 1970). Until experiments can be done in which the mesenteric vasoconstriction after administration of endotoxin is prevented, it is not possible to state whether this is the only cause of death.

In cats, occlusion of the superior mesenteric artery, haemorrhage and endotoxin result in the appearance of a myocardial depressant factor in plasma (Glenn & Lefer, 1970) and this may be an important mechanism by which mesenteric ischaemia results in death. However, it is probably not the only mechanism since inhibition of production of this factor does not prevent death even though it delays it (Lefer, 1970). Other factors with cardiovascular or respiratory depressant actions may be released (Bergan, Gilliland, Troop & Anderson, 1964; Rangel, Dinbar, Stevens, Byfield & Fonkalsrud, 1970). Kobold & Thal (1963) demonstrated the release of histamine, serotonin, catecholamines and polypeptides into portal blood during mesenteric ischaemia in dogs. Portal hyperkalaemia (Bergan *et al.*, 1964 ; Rangel *et al.*, 1970) may contribute further to the haemodynamic changes during and after mesenteric ischaemia. Until the mesenteric vasoconstriction can be prevented, it is difficult to decide whether the lethal action in cats is due to vasoactive substances released from the ischaemic gut or to some other action of endotoxin.

Recently it has been shown that mesenteric vasoconstriction does not occur after administration of endotoxin in primates (Brobmann, Ulano, Hinshaw & Jacobson, 1970; Hinshaw, 1968; Wyler, Forsyth, Nies, Neutze & Melmon, 1969) and it may be that human responses to endotoxin are different from those in the cat. However, further study of the responses in the cat may still be of value in understanding the fundamental pharmacological actions of endotoxin.

We attempted to analyse the mechanisms of this mesenteric vasoconstriction after endotoxin by the techniques previously used to study the intestinal and splenic vasoconstriction after haemorrhage (McNeill *et al.*, 1970; Stark *et al.*, 1971; Greenway & Stark, 1971). However, after removal of the animal's compensatory mechanisms, endotoxin caused a severe hypotension. This was not due to cardiac depression or to pulmonary vasoconstriction since right atrial pressure did not increase and intravenous infusion of blood could be used to maintain arterial pressure without increasing right atrial pressure. It was not due to hepatic venoconstriction such as occurs in the dog since portal pressure did not increase (Murthy, unpublished observations). Thus a primary event after administration of endotoxin appeared to be release of factors which cause arterial or venous vasodilatation. This response, which was only unmasked by removal of the animal's compensatory constrictor mechanisms, requires further investigation. In these experiments, it was overcome by infusion of donor blood to maintain arterial pressure.

The mesenteric vasoconstriction was not modified after administration of phenoxybenzamine in doses which have previously been shown to block mesenteric vascular responses to sympathetic nerve stimulation and infusions of noradrenaline in amounts likely to be released by the adrenal medullae (McNeill *et al.*, 1970). Thus the sympathetic innervation of the intestine and circulating noradrenaline appears to play no part in this vasoconstriction after endotoxin. A similar conclusion was reached in regard to the intestinal and splenic vasoconstriction after

haemorrhage in the cat (McNeill *et al.*, 1970; Stark *et al.*, 1971). These conclusions are at variance with previous reports. It has been claimed that intestinal vasoconstriction after haemorrhage, administration of endotoxin or occlusion of the superior mesenteric arteries in dogs was blocked by phenoxybenzamine (Lillehei, Longerbeam, Bloch & Manax, 1964; Nahor, Milliken & Fine, 1966). However, no details of the flow measurements are given and arterial pressure was not controlled. In other reports, the vasoconstriction was blocked after infiltration of lignocaine into the coeliac ganglion (Nahor *et al.*, 1966; Wangensteen, Geissinger, Lovett, Glenn & Lefer, 1971). However, direct effects of lignocaine on the mesenteric vascular bed were not excluded and the control mesenteric flows were abnormally low.

Removal of the pituitary and kidneys reduced the intestinal vasoconstriction significantly after endotoxin. A reasonable interpretation of these data is that angiotensin and vasopressin play some role in the vasoconstriction after endotoxin but their role is much less important than their role after haemorrhage (McNeill *et al.*, 1970; Stark *et al.*, 1971). A substantial vasoconstriction remained after removal of these compensatory mechanisms and this residual response was much greater than the residual response after haemorrhage. This suggests that vasoconstrictor factors other than the secretions of the pituitary and kidney are of primary importance in the mechanism of the intestinal vasoconstriction after endotoxin. It is not yet clear whether these factors are released locally in the intestine or are circulating in the blood.

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