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SITES OF AUTOREGULATORY ESCAPE OF BLOOD FLOW IN THE MESENTERIC VASCULAR BED

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SUMMARY

1. Stimulation of the sympathetic nerves to the intestinal vascular bed results in an initial decrease in blood flow followed by a recovery towards the control level. This recovery was termed autoregulatory escape by Folkow and his co-workers and they suggested it was associated with a redistribution of blood flow within the intestinal wall. This theory has been examined in cats anaesthetized with pentobarbitone sodium.

2. The sympathetic nerves to the intestinal vascular bed were stimulated for 4 min periods at a submaximal frequency (4 Hz). The blood flows to individual parts of the superior mesenteric arterial bed (whole intestine, mucosal and submucosal layer, muscle layer of intestine, mesentery and lymph nodes, appendix and colon) were measured using radioactive microspheres before, at the peak of the vasoconstriction (30 sec), after autoregulatory escape had occurred (3·5 min) and during the hyperaemia after cessation of nerve stimulation.

3. All parts of the mesenteric vascular bed showed a significant initial vasoconstriction followed by a recovery in the flow to a level not significantly different from the pre-stimulation control flow. All parts showed a significant hyperaemia after cessation of stimulation. The distribution of the superior mesenteric flow at the peak of the vasoconstriction, after autoregulatory escape had occurred and during the hyperaemia after cessation of nerve stimulation was not significantly different from that during the control period.

4. It is concluded that all parts of the mesenteric vascular bed show autoregulatory escape and that this phenomenon is not associated with a redistribution of blood flow within the intestinal wall. Autoregulatory escape must involve relaxation of the same vessels which were originally constricted and various theories on the mechanism of the escape are discussed.

INTRODUCTION

In 1964, Folkow, Lewis, Lundgren, Mellander & Wallentin showed that stimulation of the sympathetic nerves to the intestinal vascular bed in cats produced initial vasoconstriction followed by a recovery of the flow towards the control level in spite of maintained nerve stimulation. They termed this recovery 'autoregulatory escape'. The capillary filtration coefficient (a measure of capillary surface area) decreased for the duration of nerve stimulation, there was a post-stimulatory hyperaemia, and Indian ink was not distributed to the mucosa to the same extent during stimulation as compared with the control period. These observations support their hypothesis that there is a neurogenic redistribution of blood flow from the mucosa to the submucosa (Folkow, Lewis, Lundgren, Mellander & Wallentin, 1964*a*, *b*; Dresel & Wallentin, 1966). Further studies on the arteriovenous extraction of Rb excluded the involvement of true arteriovenous shunts and led to the concept of a dense plexus of thin-walled small vessels which allowed exchange across their walls in the submucosa (Dresel, Folkow & Wallentin, 1966). This concept was elaborated further by Lundgren (1967) and reviewed by Folkow (1967) and Mellander & Johansson (1968). A similar situation has been postulated for the colon (Hultén, 1969).

More recently, substantial evidence against this concept has been presented. As early as 1964, two of the workers who originally demonstrated escape showed that it could be obtained in a preparation of mesentery and lymph nodes after complete removal of the intestine itself (Lundgren & Wallentin, 1964). Ross (1971*a*) showed from studies on the uptake of ^{86}Rb that the distribution of flow between mucosa, submucosa and muscle after escape during noradrenaline infusion was not significantly different from that in a control group of animals. Greenway & Murthy (1972) have presented data to show that the intestinal vascular bed consists only of two parallel-coupled sections, one in the muscle and the other through the submucosa to the mucosa. The vessels in the submucosa were in series with those in the mucosa and submucosal shunts could not be demonstrated. Thus a redistribution of flow from mucosa to submucosa could not occur. In the hepatic vascular bed of the cat, autoregulatory escape was not associated with any redistribution of intrahepatic flow (Greenway & Oshiro, 1972). Thus recent work suggests that autoregulatory escape does not involve a redistribution of flow within the intestine or liver.

However, the work by Ross (1971*a*) was carried out on escape after noradrenaline and this escape was markedly altered after propranolol, suggesting the involvement of β-adrenoceptors in the response. The escape after sympathetic nerve stimulation is not modified by propranolol

and the mechanism could be different. Determination of the site or sites of autoregulatory escape is crucial for discussion of the mechanism and we have therefore re-examined the problem directly using radioactive microspheres to determine the distribution of blood flow within the superior mesenteric arterial bed. This technique has been described and evaluated previously (Greenway & Murthy, 1972).

METHODS

Cats (1·9–3·2 kg body weight) were anaesthetized by I.P. injection of pentobarbitone sodium (Abbott Laboratories, 30 mg/kg). Supplementary doses (2 mg/kg) were given through a cannula in a forelimb cutaneous vein when reflex ear, eye and swallowing movements returned. The trachea was cannulated and arterial pressure was recorded from a femoral artery using a Statham P23AC pressure transducer connected to a Beckman Type R dynograph recorder. The abdomen was opened by a mid-line incision and the anastomotic branch of the superior mesenteric artery was identified. This is the first branch of the superior mesenteric artery and it anastomoses with the inferior mesenteric artery. Its ligation does not deprive any area of flow and it was cannulated for injection of microspheres into the superior mesenteric artery. The total flow in the superior mesenteric artery was measured by a 2 mm diameter non-cannulating flow probe of an electromagnetic flowmeter (Nycotron, Oslo). The probe was set up, zero flow determined and the probe was calibrated *in situ* as previously described (Greenway & Lawson, 1966).

The post-ganglionic sympathetic nerves round the superior mesenteric artery were dissected away from the artery and the distal end was placed in a ring electrode (Greenway, Lawson & Mellander, 1967). The nerves were stimulated by a Grass stimulator (SD 5) using the parameters 15 V, 1–2 msec duration, 4 Hz for 4 min. These parameters were found in four preliminary experiments to cause a vasoconstriction which was approximately 60 % of maximal.

Microspheres (15 ± 5 μm diameter) labelled with ^{141}Ce or ^{51}Cr and suspended in 10 % dextran solution (3M Nuclear Products, Minnesota) were used. A dose of approximately 220,000 microspheres were given into the superior mesenteric artery on each occasion. Three series of experiments were carried out. In all the animals a control period of 30 min was allowed after the arterial pressure and superior mesenteric arterial flow were stable. The sympathetic nerves were then stimulated for 4 min to obtain a control response to nerve stimulation. The time course of this response to sympathetic nerve stimulation is shown in Fig. 1. After the blood flow had returned to the control level, a further control period of 15 min was allowed during which an injection of ^{141}Ce-labelled microspheres was given through the anastomotic artery into the superior mesenteric artery. In the first series of experiments (six cats), the sympathetic nerves were then stimulated again as before and an injection of ^{51}Cr-labelled spheres was given 30 sec after the onset of stimulation, that is, at the peak of the vasoconstriction (Fig. 1). In the second series (six cats), the nerves were stimulated as before and an injection of ^{51}Cr-labelled microspheres was given 3·5 min after the onset of stimulation, that is, after autoregulatory escape had occurred. In the third series (six cats), the nerves were stimulated as before and an injection of ^{51}Cr-labelled spheres was given 1 min after termination of the nerve stimulation, that is, at the peak of the post-stimulation hyperaemia.

At the end of each experiment, the abdominal viscera, lungs and liver were removed and the following procedures were carried out (Greenway & Murthy, 1972).

The lymph nodes, mesentery, pancreas, colon, lungs and liver were cut into small pieces and placed in plastic tubes. The intestine was opened along the mesenteric border and cut into 7 cm lengths. Each length was laid on a paper towel with the mucosal surface in contact with the paper. The muscle layer was then stripped from the submucosa and placed in a plastic tube. Care was taken not to press on the mucosa since this damages it. The remaining tissue was then placed in another plastic tube. In view of our previous observations that submucosal and mucosal vessels are in series (Greenway & Murthy 1972), the submucosa plus mucosa was treated as a unit. The appendix could not be stripped and was placed in a separate tube.

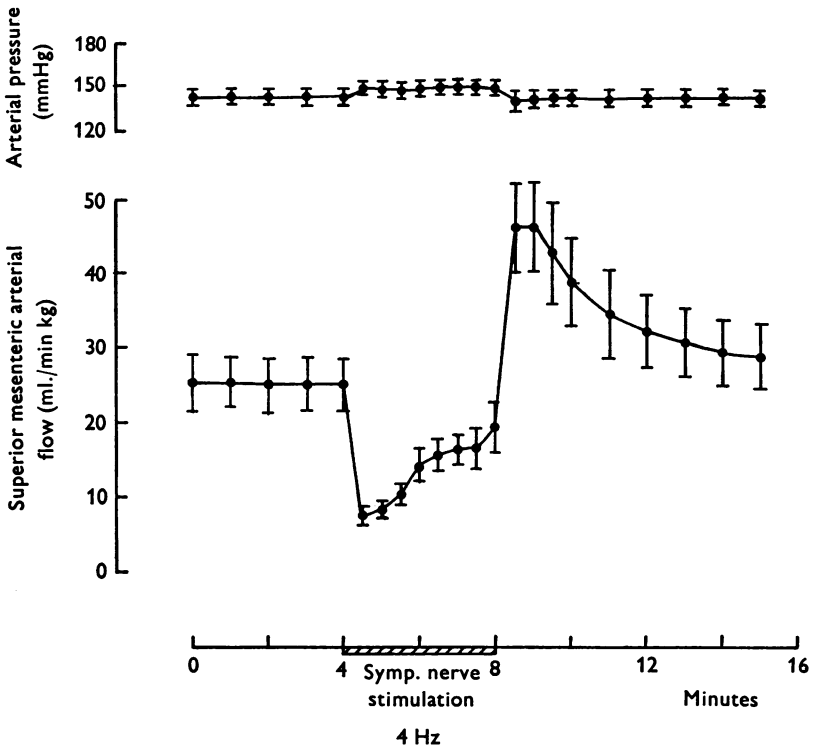

Fig. 1. Means (± S.E.) of the arterial pressures and superior mesenteric arterial flows during the control period of post-ganglionic sympathetic nerve stimulation in the eighteen cats.

The tissue samples were weighed and the radioactivity was counted in a two-channel auto-gamma spectrometer (Intertechnique Ltd). Corrections for overlap of radioactivity between the two channels were made (Greenway & Oshiro, 1972). Fractional flow to each piece of tissue was calculated from the principle of Stewart-Hamilton as described by Wagner, Rhodes, Sasaki & Ryan (1969):

$$f = F \cdot \frac{q}{Q},$$

where f is the fractional flow to the tissue, F is the total blood flow in the superior mesenteric artery at the time the microspheres were given, q is the radioactivity in

the piece of tissue and Q is the total injected radioactivity obtained by the summation of the counts in all the samples. As previously reported (Greenway & Murthy, 1972), counts in the lungs were negligible and counts in the livers were less than 1 % of the injected radioactivity, indicating that all the microspheres were trapped in the superior mesenteric arterial bed.

RESULTS

Control data on the tissue weights and on the distribution of superior mesenteric arterial blood flow have been presented previously (Greenway & Murthy, 1972). These earlier experiments established the stability and reproducibility of the flows and showed that the microspheres were uniformly mixed in the mesenteric blood stream.

In the present experiments, three series of six cats were used. Total superior mesenteric arterial flow was calculated from the flowmeter readings and regional flows were calculated from this total flow and the proportional distribution of the first dose of microspheres (^{141}Ce). The values for the control period before stimulation of the sympathetic nerves are shown in Table 1. The groups were compared by a random block analysis of variance with multiple comparisons by the test of least significant difference. No significant differences were found and thus, the flow distribution in these three groups of animals is comparable during the control period. The flow to the colon showed a marked variability between

TABLE 1. Comparison of control data (mean and S.E.) in the three groups of six cats

	Group 1	Group 2	Group 3	S.E. of mean
Body weight (kg)	2·50	2·33	2·47	(0·17) n.s.
Total superior mesenteric arterial flow (ml./min kg)	20·8	22·7	27·0	(4·0) n.s.
Flow to intestine (ml./min kg)	17·4	17·0	21·5	(4·1) n.s.
Flow to mucosal and submucosal layers (ml./min kg)	15·0	15·2	19·1	(3·9) n.s.
Flow to muscle layer (ml./min kg)	2·39	1·78	2·37	(0·5) n.s.
Flow to mesentery and lymph nodes (ml./min kg)	0·88	1·31	1·81	(0·3) n.s.
Flow to appendix (ml./min kg)	0·76	0·85	1·31	(0·3) n.s.
Flow to colon (ml./min kg)	1·67	3·55	2·63	(1·1) n.s.

n.s., not significant.

animals. This was reported previously (Greenway & Murthy, 1972) and was due to the variable portion of the colon supplied by the superior mesenteric artery.

The mean data for arterial pressure and superior mesenteric arterial flow during the control nerve stimulation in all the cats are shown in Fig. 1. It can be seen that stimulation of the post-ganglionic sympathetic nerves reduced arterial flow from 25 to 7·7 ml./min.kg body wt., 30 sec after the onset of stimulation. Autoregulatory escape then occurred; the flow returned towards the control level and after 4 min had reached 19 ml./min kg. After stimulation was stopped there was a hyperaemic period and flow reached 46 ml./min kg, 1 min after cessation of stimulation. It then returned to the control level. The values given in the later sections of the results differ slightly but not significantly from these mean values since they represent the second period of nerve stimulation in each of the individual series of experiments.

Blood flows during and after nerve stimulation

In each of the groups of cats, total superior mesenteric arterial flow was calculated from the electromagnetic flowmeter readings and regional flow were calculated from this total flow and the proportional distribution of the second dose of microspheres (^{51}Cr). For each animal, these flows were expressed as proportions of the flow during the control period. In Group 1, these values were obtained at the peak of the vasoconstriction 30 sec after the onset of nerve stimulation; in Group 2 after autoregulatory escape had occurred 3·5 min after the onset of nerve stimulation and in Group 3, during the peak of the hyperaemia 1 min after cessation of nerve stimula-

TABLE 2. Blood flows expressed as proportions of the flows during the control periods for the three groups of cats: Group 1 during the peak vasoconstriction; Group 2 after autoregulatory escape had occurred; and Group 3 during the hyperaemia after cessation of nerve stimulation. Statistical comparisons to unity (no change in blood flow) were made by random block analysis of variance and tests of least significant difference (* $P < 0.05$; ** $P < 0.01$)

	Group 1	Group 2	Group 3	S.E. of mean
Total superior mesenteric arterial flow	0·32**	1·17	2·20**	(0·17)
Flow to intestine	0·34**	1·33	2·17**	(0·16)
Flow to mucosal and sub-mucosal layer	0·34**	1·33	1·99**	(0·14)
Flow to muscle layer	0·36**	1·46	4·26**	(0·23)
Flow to mesentery and lymph nodes	0·28**	0·77	2·34*	(0·50)
Flow to appendix	0·26**	1·39	2·59*	(0·46)
Flow to colon	0·41*	0·94	4·06*	(0·39)

tion. The ratio to the control value was used in order to allow random block analysis of variance without losing the pairing of the experimental and control data in each animal. The values are shown in Table 2. It can be seen that all regions of the mesenteric vascular bed showed a significant vasoconstriction (Group 1). After escape had occurred, the flow through all regions were not significantly different from the control flows. Comparison of Group 1 against Group 2 by the method of least significant difference showed that these values were significantly different ($P < 0{\cdot}01$) in all regions except the colon where the variability between animals was very great. Thus a significant autoregulatory escape occurred in all parts of the vascular bed except the colon. After cessation of stimulation (Group 3) the flow increased significantly above the control level in all regions. Thus all parts of the vascular bed showed a hyperaemia after cessation of nerve stimulation.

Distribution of blood flows during and after nerve stimulation

The analysis in the previous section shows that all regions of the superior mesenteric vascular bed showed an initial vasoconstriction, autoregulatory escape and a post-stimulatory hyperaemia. The data in Table 2 suggest that the changes were approximately similar in each of the regions of the vascular bed but this point was re-examined more rigorously.

The proportion of the ^{51}Cr microspheres in each region was expressed as a ratio of the proportion of the ^{141}Ce microspheres in each region for each cat. This gives the relative flows to each region as a ratio of that during the control period. Values close to unity indicate there was no change in the distribution of flow within the region. This method was again used to allow a random block analysis of variance without losing the pairing of experimental and control values in each animal. This analysis is presented

TABLE 3. The relative flows to each region expressed as a ratio of those during the control period for the three groups of cats: Group 1 during the peak vasoconstriction; Group 2 after autoregulatory escape had occurred; and Group 3 during the hyperaemia after cessation of nerve stimulation. Statistical comparison to unity (no change in distribution of flow) was made by random block analysis of variance and tests of least significant difference (* $P < 0{\cdot}05$)

	Group 1	Group 2	Group 3	S.E. of mean
Whole intestine	1·01	1·13	1·01	(0·06)
Mucosal and sub-mucosal layers	0·99	1·13	0·94	(0·07)
Muscle layer	1·23	1·23	1·52*	(0·17)
Mesentery and lymph nodes	1·01	0·65	0·97	(0·17)
Appendix	1·14	1·14	1·19	(0·47)
Colon	1·80	0·80	1·69	(0·50)

in Table 3. The data show that the distribution of flow was not significantly altered during the initial vasoconstriction, or during autoregulatory escape. However, the post-stimulatory hyperaemia was significantly greater in the muscle layer of the intestine than in other parts of the vascular bed.

DISCUSSION

Escape of vascular smooth muscle during the continued presence of agonists (both constrictor and dilator) has been demonstrated under many conditions and Ross (1971*b*, *c*) has reviewed the literature up to 1970. These escape phenomena often have different characteristics and Ross suggested that an inability of a vascular bed to maintain a response in the continued presence of a stimulus (either nervous or humoral) should be termed 'escape' or 'flow recovery' and that the term 'autoregulatory escape' should be dropped. However, we suggest that the term 'autoregulatory escape' should be restricted to types of escape which show the following specific characteristics: (1) another vascular parameter (for example, regional blood volume) measured simultaneously does not escape; (2) escape occurs at all frequencies of nerve stimulation or all doses of agonists and not only during maximal or supramaximal stimulation; (3) escape can be demonstrated during reflex activation of the sympathetic nerves (Oberg, 1964; Greenway *et al.* 1967); (4) cessation of stimulation is followed by a hyperaemic period indicating a sustained effect of the stimulus even though flow may have escaped to the control level; (5) the escape is not modified by atropine, propranolol, antihistamines or prostaglandin synthetase inhibitors; and (6) the escape can be demonstrated during both constant pressure conditions and constant flow conditions.

True autoregulatory escape defined by these criteria has so far only been demonstrated in response to sympathetic nerve stimulation in the intestinal (Folkow *et al.* 1964) and hepatic arterial (Greenway *et al.* 1967) vascular beds in cats. In several other vascular beds (for example, the kidney) its occurence remains equivocal until all the criteria are studied. The importance of these criteria lies in the fact that they exclude a great many of the mechanisms suggested for autoregulatory escape.

The data presented in this paper show that autoregulatory escape during sympathetic nerve stimulation in the intestinal bed is not associated with a redistribution of blood flow. Escape occurs in all areas supplied by the superior mesenteric artery. Thus a lack of any redistribution of flow is now demonstrated in both the intestinal and the hepatic arterial bed (Greenway & Oshiro, 1972). It seems impossible that a vasodilatation in some series-coupled site in the vessel could restore flow to the control level in spite of a maintained vasoconstriction at some other site which alone

reduces flow to 30% or less. Thus during autoregulatory escape, the same smooth muscle elements which initially contracted must relax again. This conclusion is similar to that reached by others on the basis of other experimental data (Richardson & Johnson, 1969; Ross, 1971*b*, *c*).

A major problem with this conclusion is that it becomes difficult to explain the maintained reduction in intestinal capillary filtration coefficient (c.f.c.) (Folkow *et al.* 1964*a*). If the arterioles relax again during escape, why does the capillary surface area not return towards the control level? There are two possible ways of explaining this. First, calculation of c.f.c. involves an assumption of the percentage of the known increment in venous pressure which is transmitted back to the capillaries. Due to the intense constriction of the capacitance vessels during sympathetic nerve stimulation, this percentage might be substantially reduced and CFC would then be underestimated. Secondly, Richardson (1974) has suggested that intestinal flow and c.f.c. are independent variables, controlled by different smooth muscle. On this basis, changes in c.f.c. have no bearing on the mechanism of autoregulatory escape.

During autoregulatory escape, the flow may rise to levels above the prestimulatory control (Folkow *et al.* 1964; C. V. Greenway, unpublished observations), autoregulatory escape occurs during constant flow perfusion (Dresel & Wallentin, 1966; Greenway *et al.* 1967) and as the present study shows, there is no redistribution of flow within the organs. This combination of data eliminates the possibility that either escape or the subsequent hyperaemia are due to local accumulation of metabolites secondary to a period of reduced flow; the hyperaemia is not therefore a reactive hyperaemia.

The possibility of the development of a transitory refractoriness (desensitization) of α-receptors was proposed by Shanbour & Jacobson (1971). This hypothesis fails to explain how the flow can escape to above the prestimulatory control level and how on cessation of stimulation there is a hyperaemic period. It is also difficult to explain why arteriolar but not venular α-receptors should show this refractoriness.

Sympathetic nerve stimulation may cause a slow progressively increasing release of a vasodilator agent (Shanbour & Jacobson, 1971). Such an agent must progressively accumulate in spite of the increasing flow, it must be released in a wide variety of tissues (smooth muscle, mucosa, hepatic parenchyma, mesentery, lymph glands, etc.) and its accumulation or its action must not be modified in the presence of atropine, propranolol, antihistamines or prostaglandin synthetase inhibitors (C. V. Greenway and G. E. Lister, unpublished observations). On cessation of stimulation, the agent must be removed considerably more slowly than the transmitter itself (noradrenaline). It must be a highly effective

antagonist of noradrenaline since the concentration of noradrenaline in the vicinity of the nerve terminals is reputed to be high (Folkow, Haggendal & Lisander, 1967). Finally, it must be released or act only on arterioles and not on capacitance vessels. At the present time, the existence of a second transmitter with these properties seems unlikely.

Although it is thus possible to suggest that certain hypotheses on the mechanism of autoregulatory escape are unlikely, it is much more difficult to present a hypothesis which will explain all the observed characteristics of this phenomenon. One possibility involves changes in the arteriolar smooth muscle cells causing them to relax in spite of the continuing presence of noradrenaline. Little is known about the properties of arteriolar smooth muscle but two phenomena found in certain other types of smooth muscle may be relevant.

Autoregulatory escape might involve a failure of myogenic propagation in the arteriolar wall since sympathetic nerve terminals lie round the outside of the arteriolar wall and activation of the inner muscle cells may be by myogenic propagation. This has been demonstrated in isolated segments of rat portal vein (Johansson & Ljung, 1968). On cessation of nerve stimulation, the normal myogenic arteriolar tone may be inhibited until myogenic propagation is re-established thus accounting for the hyperaemic phase. Why myogenic propagation should fail during maintained nerve stimulation cannot be explained at present. If this suggestion were correct, autoregulatory escape as defined earlier should not occur during infusions of noradrenaline since the noradrenaline reaches all the muscle cells and myogenic propagation is probably of less importance. However, this question has not yet been studied critically; although escape during noradrenaline infusions has been proposed and denied under various conditions, the criteria for autoregulatory escape have not been studied.

A second hypothesis may be considered. Bose (1975) has recently shown that accumulation of intracellular Na^+ causes relaxation of a spontaneously active smooth muscle preparation (taenia coli). This effect was not seen in multi-unit smooth muscle or splenic capsule. If prolonged sympathetic nerve stimulation resulted in a progressive increase in intracellular Na^+ in arteriolar smooth muscle, this could explain autoregulatory escape including the observation that flow can return to above the pre-stimulatory control level. Since on cessation of nerve stimulation, restoration of low levels of intracellular Na^+ would take time, the hyperaemic phase can also be explained.

Two further questions remain to be answered. First, does autoregulatory escape occur in any vascular beds in man? Secondly, is autoregulatory escape a failure of a physiological mechanism (arteriolar vasoconstriction) or does it have a definite physiological function? Escape is most pronounced

in organs which cannot function with a low blood flow (liver, intestine, kidney) and least in organs with some resistance to hypoxia (muscle, fat, skin). Thus it is possible that escape has specifically evolved to prevent prolonged intense vasoconstriction which might cause ischaemic tissue damage during prolonged sympathetic activation. If this is so, sympathetic overactivity is unlikely to be a major factor in the causation of circulatory shock (Shanbour & Jacobson, 1971).

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