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THE RELEASE OF PANCREATIC GLUCAGON AND INHIBITION OF INSULIN IN RESPONSE TO STIMULATION OF THE SYMPATHETIC INNERVATION

BY S. R. BLOOM AND A. V. EDWARDS

From the Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London, W12, and the Physiological Laboratory, University of Cambridge, Cambridge CB2 3EG

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SUMMARY

1. The changes in the concentration of glucagon and insulin in arterial plasma which occur in response to splanchnic nerve stimulation have been investigated in adrenalectomized dogs, cats and sheep.

2. In dogs, stimulation of both splanchnic nerves at a low frequency (2·0 c/s) for 10 min produced a small but statistically significant increase in plasma glucagon concentration and appeared to inhibit the release of insulin. Stimulation at a higher frequency (10·0 c/s) produced a much greater increase in plasma glucagon concentration, which was normally accompanied by a rise in plasma glucose concentration.

3. Qualitatively similar changes in plasma glucagon and insulin concentration were observed in both sheep and cats in response to adrenergic stimulation.

4. Intramesenteric infusions of glucagon at a dose of 5·0 ng kg^{-1} min^{-1} in dogs produced a comparable rise in plasma glucagon concentration to that elicited by splanchnic nerve stimulation at high frequency (10·0 c/s) and invariably caused a rise in plasma glucose concentration.

5. In dogs given exogenous glucose, release of glucagon in response to splanchnic nerve stimulation was unaffected by induced hyperglycaemia. Secretion of insulin was partially inhibited by stimulation at 2·0 c/s and completely suppressed at higher frequency (10·0 c/s).

6. It is concluded that stimulation of the sympathetic innervation to the pancreatic islets, at frequencies within the physiological range, stimulates the release of glucagon and inhibits that of insulin in each of these species.

INTRODUCTION

There is now abundant evidence to show that stimulation of the autonomic innervation to the pancreatic islets modifies the secretion of both insulin and glucagon and a comprehensive review of the literature has recently been published (Woods & Porte, 1974). The sensitivity of the glucagon release mechanism to stimulation via the sympathetic innervation in the young calf suggests that variations in the rate at which this hormone is secreted must be a consequence of normal tonic changes in sympathetic efferent activity (Bloom, Edwards & Vaughan, 1973*b*). This mechanism provides a satisfactory explanation for the rapid increase in plasma glucagon concentration which occurs during feeding in this species in association with pronounced tachycardia and hypertension (Bloom, Edwards, Hardy, Malinowska & Silver, 1975*b*). Stimulation of the sympathetic innervation to the liver and pancreas also produces a rapid rise in plasma glucose concentration which can be ascribed to the combined glycogenolytic effects of pancreatic glucagon and noradrenaline released from sympathetic nerve endings in the liver.

The experiments described in the present paper were undertaken in order to establish the sensitivity of the pancreatic islets to stimulation via the sympathetic innervation in species other than the calf. In addition the possibility that hyperglycaemia might modify pancreatic endocrine responses to adrenergic stimulation has been investigated.

Certain of these results have been published previously in preliminary form (Bloom & Edwards, 1975).

METHODS

Animals

The experiments were carried out on adult mongrel dogs, cats and sheep. The dogs and cats were fed on Purina Cat or Dog Chow (Ralston Purina of Canada Ltd) *ad libitum* for a minimum period of 10 days before use (the diet for cats was supplemented with milk). The sheep were maintained on a diet of grass, supplemented with good quality hay and concentrates.

Experimental procedures

Anaesthesia was induced and maintained by the administration of sodium pentobarbitone (May and Baker). The preparatory surgical procedures were closely similar to those employed previously (Bloom *et al.* 1973*b*; Edwards, 1971). Both adrenal glands were removed in each case and in dogs and cats both splanchnic nerves were cut immediately below the diaphragm in order that the peripheral ends could be stimulated by means of separate fluid electrodes. Nerves were stimulated independently for 2–3 sec in order to ensure effective electrical contact. The experiments were then commenced 45 min later; a standard 20 V square-wave stimulus (pulse width 1 msec) was employed throughout. Sheep tolerate bilateral splanchnic

nerve section comparatively poorly as do various other herbivorous species (Edwards, 1971). For this reason only a single nerve was sectioned and stimulated in sheep in these experiments. Arterial blood pressure was measured continuously by means of a pressure transducer connected to a polyethylene catheter inserted into the femoral artery with the tip in the abdominal aorta; blood samples for chemical analysis or assay and haematocrit estimations were withdrawn from this catheter as required. Samples destined for glucagon or insulin assay were treated with aprotonin (Trasylol: F.B.A. Laboratories, 10,000 k.i.u./ml.) before centrifugation (10% dilution v/v) and the plasma was stored at −20° C. Portal and central venous pressures were also monitored continuously during each experiment.

When required 20% glucose (w/v) in 0·9% (w/v) NaCl solution was administered by rapid intravenous injection 1 min after the start of stimulation.

Glucagon (Novo) was dissolved in 0·9% NaCl and infused into the portal circulation through a narrow bore catheter inserted into an ileal branch of the mesenteric vein.

Estimations

Plasma glucose concentration was estimated with glucose oxidase using the Beckman Glucose Analyzer. At the end of each experiment small pieces of liver were removed for glycogen analysis as described previously (Edwards, 1971). Plasma glucagon and insulin were measured by radio-immunoassay (Bloom *et al.* 1973*b*).

Results have been expressed as the change in concentration from the values at time = 0 in order to provide a direct comparison of the responses. Statistical analyses were made according to the methods of Snedecor & Cochran (1967).

RESULTS

Responses to splanchnic nerve stimulation of adrenalectomized dogs

The effects of stimulation of the peripheral ends of both splanchnic nerves at 10·0 and 2·0 c/s for 10 min were examined in ten adrenalectomized dogs. In the group tested at the higher frequency mean plasma glucagon concentration fell slightly during the first 2½ min but rose steadily thereafter to achieve a maximum incremental value of 244 ± 81 pg/ml. (S.E. of mean) at 12½ min and then subsided towards the initial concentration (Fig. 1). Individual variation within the group was considerable, due to differences in the times at which maximum glucagon concentrations occurred in the different individuals, none of which failed to respond to the stimulus. Much less variation between individuals was encountered in dogs tested at low frequency (2·0 c/s) and the rise in mean plasma glucagon concentration, although comparatively small (Fig. 1), was found to be statistically significant (mean maximum increment at 7½ min: 29 ± 4 pg/ml.; $P < 0{\cdot}01$). The changes in mean aortic blood pressure and haematocrit which occurred during these experiments were closely similar to those recorded previously under the same conditions (Edwards, 1971, 1972*a*, *b*).

The changes in mean plasma glucose concentration in response to

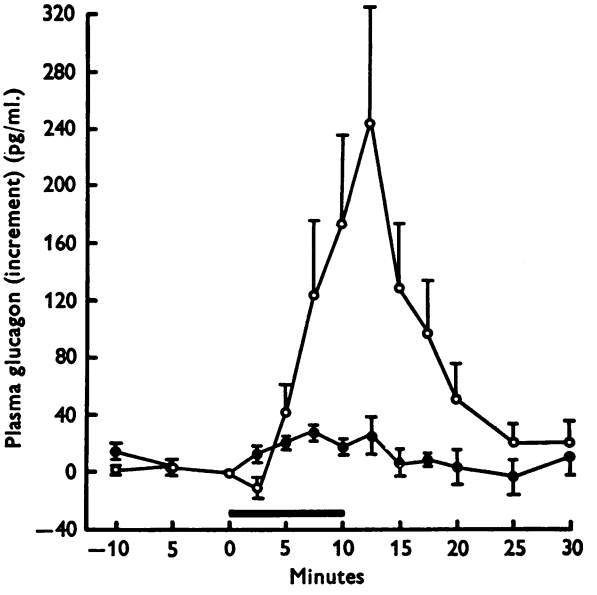

Fig. 1. Comparison of changes in mean plasma glucagon concentration in ten adrenalectomized dogs in response to stimulation of the peripheral ends of both splanchnic nerves for 10 min. Open circles, 10·0 c/s (n = 5); filled circles, 2·0 c/s (n = 5); horizontal bar, duration of stimulus; vertical bars, S.E. of each mean value.

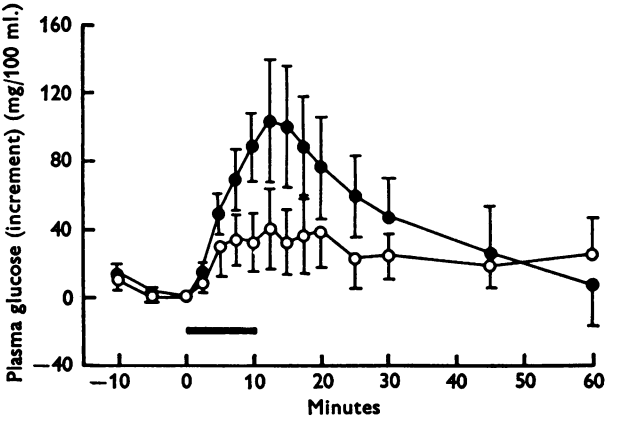

Fig. 2. Changes in mean plasma glucose concentration in response to stimulation of the peripheral ends of both splanchnic nerves for 10 min in adrenalectomized dogs. ○, 2·0 c/s (n = 5); ●, 10·0 c/s (n = 5). Horizontal bar, duration of stimulus; vertical bars, S.E. of each mean value.

splanchnic nerve stimulation at both 2·0 and 10·0 c/s are shown in Fig. 2. The liver glycogen concentration was found to vary widely between individuals with consequential effects on the extent of the hyperglycaemic response (see for instance Fig. 3).

Stimulation of the splanchnic sympathetic innervation was found to produce a profound inhibition of insulin release in these animals and the extent to which plasma insulin concentration rose when the stimulus was discontinued appeared to be related to the degree of hyperglycaemia

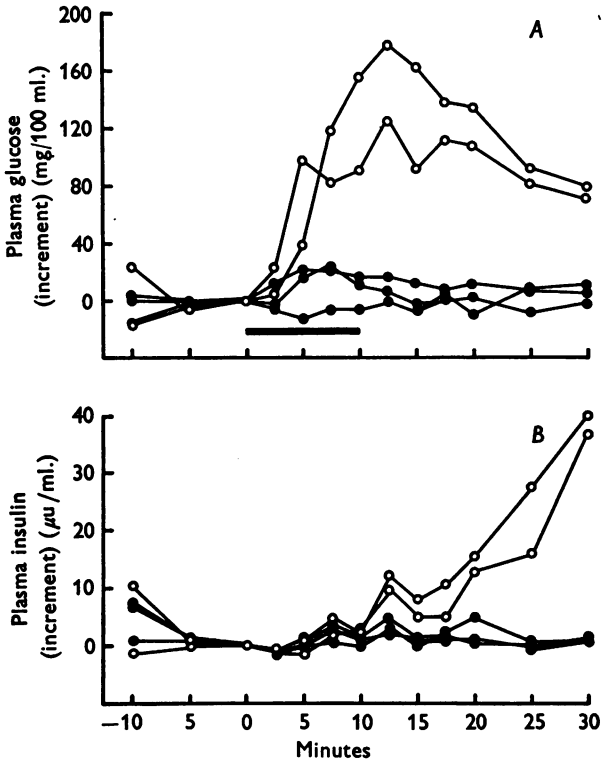

Fig. 3. Responses to stimulation of the peripheral ends of both splanchnic nerves at 2·0 c/s for 10 min in five adrenalectomized dogs. *A*, plasma glucose; *B*, plasma insulin. Open circles, liver glycogen > 20·0 mg/g; filled circles, liver glycogen < 0·5 mg/g; horizontal bar, duration of stimulus.

produced. This is shown most clearly when the individual results from the group stimulated at low frequency are compared (Fig. 3). Three of these animals were found to have virtually no glycogen in the liver at the end of the experiment (< 0·5 mg/g) and splanchnic nerve stimulation produced no significant change in either plasma glucose or insulin

concentration. In the remaining two animals, in which the liver glycogen concentrations were comparatively high (> 20·0 mg/g) splanchnic nerve stimulation at low frequency produced a rapid rise in plasma glucose concentration but no significant change in plasma insulin concentration (Fig. 3). After stimulation was discontinued plasma insulin concentration rose sluggishly in both animals.

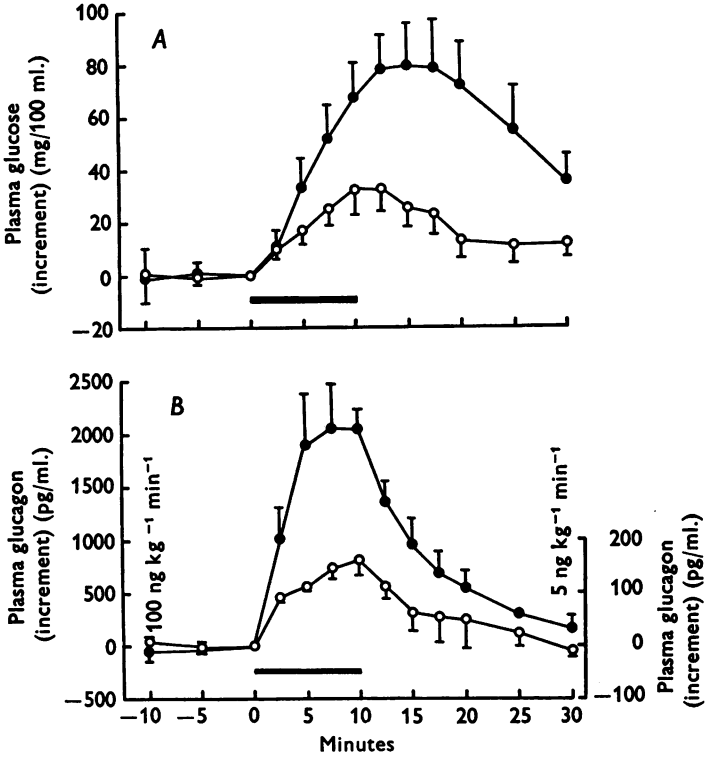

Fig. 4. Responses to intramesenteric infusions of exogenous glucagon for 10 min in adrenalectomized dogs with cut splanchnic nerves. ○, 5·0 ng kg^{-1} min^{-1} ●, 100·0 ng kg^{-1} min^{-1} (n = 4). *A*, plasma glucose; *B*, plasma glucagon. Horizontal bars, duration of infusion; vertical bars, S.E. of each mean value.

Responses to intramesenteric infusions of exogenous glucagon in dogs

The changes which occur in response to exogenous glucagon were examined in eight adrenalectomized dogs under the same experimental conditions as those employed to test the effects of splanchnic nerve stimulation (sodium pentobarbitone anaesthesia; both splanchnic nerves cut).

Glucagon was infused intramesenterically at a dose of either 5·0 or 100·0 ng kg^{-1} min^{-1} for 10 min. The higher dose produced an abrupt

increase in the concentration of glucagon in the arterial plasma, which rose to maximum mean incremental values of 2046 ± 421 and 2036 ± 195 pg/ml. at 7½ and 10 min respectively. The close similarity between these two values, at the end of the infusion, shows that near equilibrium between glucagon exit and entry rates had been achieved at this time. When the infusion was discontinued the mean values declined approximately exponentially during the next 20 min (Fig. 4). The mean rate of disappearance of glucagon during this period was found to be 13 % min^{-1} and the half life of the hormone was *ca.* 5 min. The theoretical glucagon pool at the end of the infusion was estimated to be 770 ng/kg, which, when divided by the mean plasma concentration at that time, produces a value of 380 ml./kg for the glucagon space under these conditions. Infusion of glucagon at this dose caused a pronounced hyperglycaemia; mean plasma glucose concentration rose steadily to a maximum incremental value of 79·3 ± 14·6 mg/100 ml. at 15 min and subsided thereafter. Intramesenteric infusions of glucagon at the lower, more physiological, dose (5·0 ng kg^{-1} min^{-1}) produced a slower rise in the concentration of the hormone in the peripheral plasma to a mean maximum incremental value of 162 ± 27 pg/ml. at 10 min (range 127–241 pg/ml.). This rise in plasma glucagon concentration was of the same order of magnitude as that observed in response to stimulation of the splanchnic nerves at 10·0 c/s in adrenalectomized dogs (Figs. 1 and 4) and caused a small but significant rise in mean plasma glucose concentration (Fig. 4). It may therefore be concluded that release of glucagon contributes to the hyperglycaemia which occurs in adrenalectomized dogs in response to stimulation of the splanchnic nerves. The liver was found to contain abundant glycogen in each of these infusion experiments, yet the extent of the rise in plasma glucose concentration (32·5 ± 9·4 mg/199 ml.) was substantially less than that which occurred in response to splanchnic nerve stimulation at 10·0 c/s (103·6 ± 36·2 mg/100 ml.). It therefore seems unlikely that hyperglycaemia under the latter condition can be attributed entirely to release of glucagon.

Responses to splanchnic nerve stimulation of adrenalectomized dogs during induced hyperglycaemia

The rise in plasma glucose concentration which occurs in response to stimulation of the peripheral ends of the splanchnic nerves might itself modify the direct effects of nerve stimulation on the pancreatic islets. It is well known that glucose stimulates insulin release and inhibits that of glucagon. However, the extent to which hyperglycaemia might modify the responses of the pancreatic islets to adrenergic stimulation within the physiological range has not previously been assessed.

For this purpose it is necessary to minimize individual variations in the extent of the hyperglycaemia, which are determined by the availability of liver glycogen. This was achieved in the present experiments by administering exogenous glucose (0·375 g/kg) by rapid intravenous injection shortly after stimulation was initiated. Comparison of the changes in plasma glucose concentration in a group of control dogs, with those in dogs in which the splanchnic nerves were stimulated at either 2·0 or 10·0 c/s, shows that the tolerance to glucose is reduced by splanchnic nerve stimulation (Fig. 5).

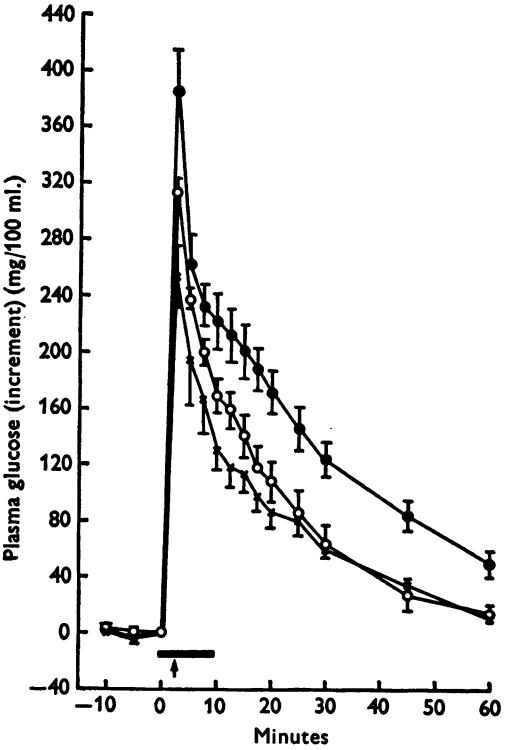

Fig. 5. The effect of stimulation of the peripheral ends of both splanchnic nerves for 10 min on the tolerance of adrenalectomized dogs to glucose. ×, glucose alone (n = 4). ○, 2·0 c/s + glucose (n = 4); ●, 10·0 c/s + glucose (n = 6). Glucose (0·375 g/kg) was injected I.V. at the arrow. Horizontal bar, duration of stimulus; vertical bars, S.E. of each mean value.

The difference between the control group and that in which the nerves were stimulated at low frequency (2·0 c/s) was found to be comparatively small. However, stimulation at 10·0 c/s resulted in a significantly greater initial rise in glucose than in the control group (10·0 c/s: 386 ± 28 mg/

100 ml.; control: 254 ± 22 mg/100 ml.; $P < 0{\cdot}01$) and consistently higher values persisted throughout the remainder of the experiment. Thus effects due to glucose alone would presumably be greatest in the groups stimulated at the higher frequency and least in the control animals. An exception to this was the abrupt change in haematocrit observed in the control group. Mean haematocrit fell immediately after administration of glucose from $41{\cdot}51 \pm 3{\cdot}5$ to $34{\cdot}0 \pm 1{\cdot}1$ % and rose sluggishly towards the initial value thereafter. If this initial fall in haematocrit were due entirely to the osmotic effects of the increase in plasma glucose concentration it would be equivalent to an increase in plasma volume of 12·8 %. The changes in various cardiovascular parameters were consistent with the view that plasma volume is indeed expanded under these conditions. Results from one of these four animals are presented in Fig. 6 and it can be seen that there is a pronounced rise in central venous pressure together with a small increase in aortic pressure (15 mmHg); this latter effect was accounted for almost entirely by a rise in systolic pressure (35 mmHg).

In the other two groups the rise in mean aortic pressure was slightly greater and that in haematocrit smaller than in animals, tested in the same way but without administration of exogenous glucose.

The changes in plasma glucagon concentration which occurred in these three groups of animals were compared with those obtained previously in response to splanchnic nerve stimulation alone (Fig. 7*A*, *B*). In the control group mean plasma glucagon concentration declined steadily throughout the experimental period and administration of exogenous glucose was without noticeable effect (Fig. 7*C*). Stimulation of the peripheral ends of both splanchnic nerves at either 2·0 or 10·0 c/s produced closely similar changes in plasma glucagon concentration in the presence or absence of exogenous glucose (Fig. 7*A*, *B*). It is therefore concluded that the response of the α cells to stimulation via the sympathetic innervation at frequencies within the physiological range is immune to inhibition by hyperglycaemia.

The changes in mean plasma insulin concentration which occurred in adrenalectomized dogs in the absence of exogenous glucose suggested that the secretion of insulin was inhibited by splanchnic nerve stimulation. Thus, plasma insulin rose sluggishly in response to hyperglycaemia after stimulation was discontinued in animals tested at 2·0 c/s (Fig. 3). In contrast, no rise in mean plasma insulin concentration occurred in dogs tested at high frequency (10·0 c/s) even though there was a greater rise in mean plasma glucose concentration in these animals (Figs. 2 and 8*B*). This inhibitory effect of splanchnic nerve stimulation was clearly revealed in dogs given exogenous glucose (Fig. 8A). In the control group mean

plasma insulin concentration rose abruptly, in response to I.V. glucose, to a maximum incremental value of $38{\cdot}4 \pm 9{\cdot}5$ μu/ml. at $7\frac{1}{2}$ min and elevated levels persisted for 60 min. Both the rate and extent of this rise was reduced by stimulation at 2·0 c/s, even though the hyperglycaemic stimulus to insulin release was more intense (Fig. 5). In the group stimulated at 10·0 c/s mean plasma glucose concentration rose to even higher values and fell more slowly (Fig. 5) but no significant increase in mean plasma insulin concentration occurred until 10 min after stimulation was discontinued. It therefore appears that the insulin-

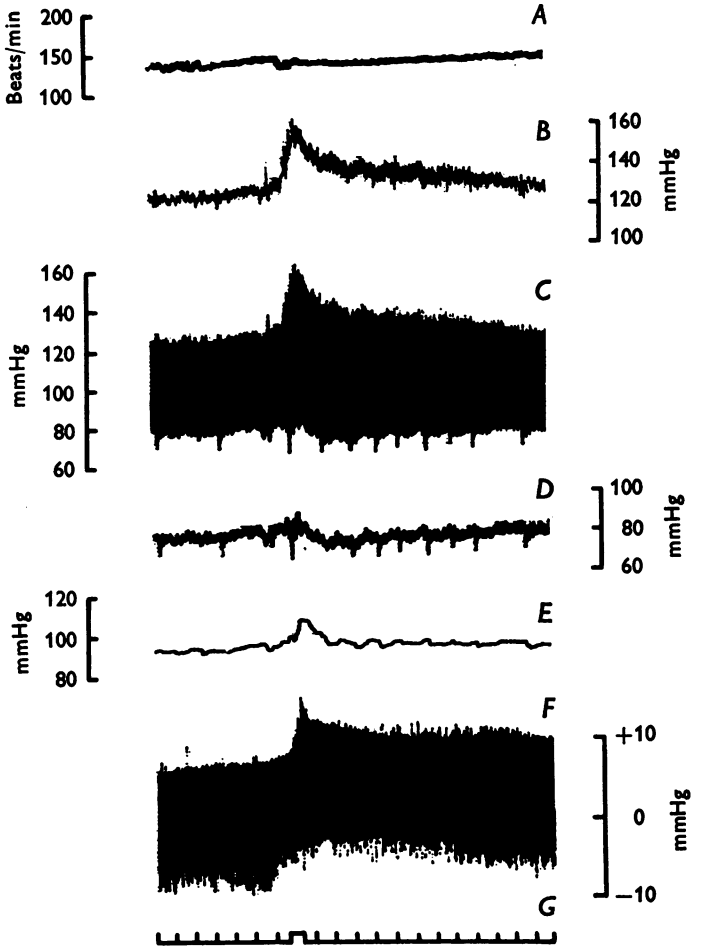

Fig. 6. Cardiovascular responses to exogenous glucose (0·375 gm/kg) in an adrenalectomized dog with cut splanchnic nerves under barbiturate anaesthesia. *A*, heart rate; *B*, systolic aortic pressure; *C*, phasic aortic pressure, *D*, diastolic aortic pressure; *E*, mean aortic pressure; *F*, central venous pressure; *G*, event and 2 min time marker.

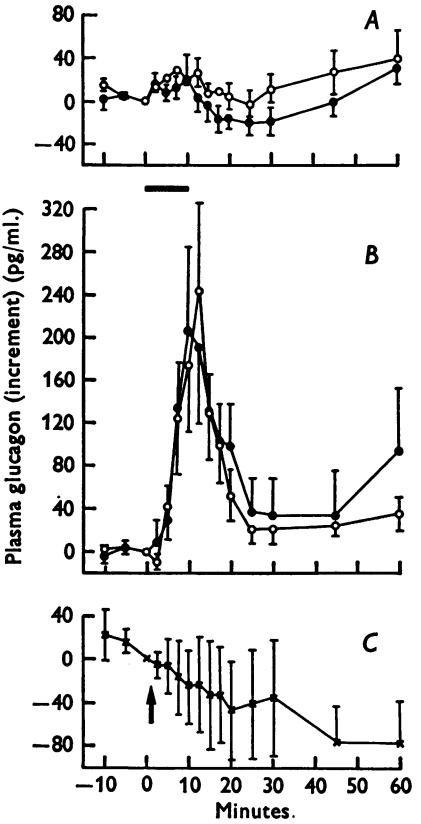

Fig. 7. Comparison of changes in mean plasma glucagon concentration of adrenalectomized dogs in response to stimulation of the peripheral ends of the splanchnic nerves for 10 min in the presence (●) or absence (○) of exogenous glucose (0·375 g/kg). *A*, 2·0 c/s (n = 5, no glucose; n = 4+glucose); *B*, 10·0 c/s (n = 5, no glucose; n = 6+glucose); *C*, glucose alone (×, n = 4). Horizontal bar, duration of stimulus; vertical bars; S.E. of each mean value. Glucose (0·375 g/kg) was injected I.V. at the arrow.

release mechanism is extremely sensitive to inhibition via the sympathetic innervation in this species.

Responses to splanchnic nerve stimulation of adrenalectomized cats

Responses to splanchnic nerve stimulation were examined in three adrenalectomized cats under the same conditions as those for dogs, except that a stimulus frequency of 4·0 c/s was employed. This frequency was chosen on the assumption that it represented a submaximal stimulus which should, nevertheless, produce unequivocal effects if the splanchnic

innervation to the pancreas plays an important part in controlling the rates at which glucagon and insulin are released from the pancreas under physiological conditions.

In each experiment splanchnic nerve stimulation elicited a prompt rise in both plasma glucose and glucagon concentration without significant change in plasma insulin concentration. It is concluded that the cat resembles the dog, in that the glucagon release mechanism is sensitive to stimulation via the sympathetic innervation. The results also suggest that stimulation of the splanchnic sympathetic innervation may inhibit insulin release in the cat as in the dog, since no rise in plasma insulin occurred, even though plasma glucose concentration increased by between 92 and 121 mg/100 ml. in each of these three animals.

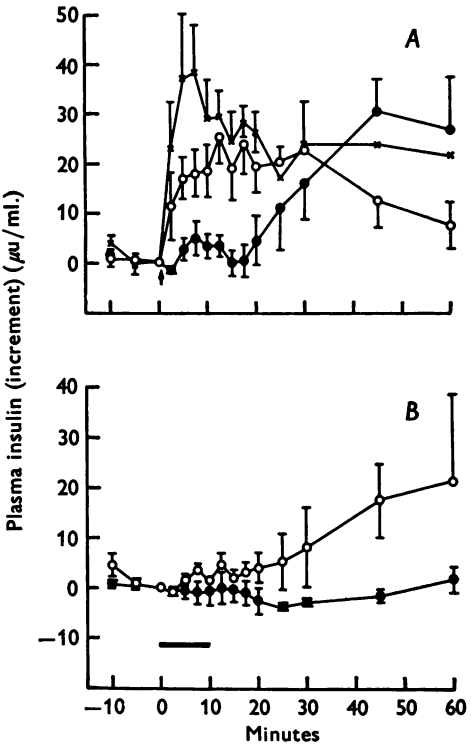

Fig. 8. Comparison of changes in mean plasma insulin concentration of adrenalectomized dogs in response to stimulation of the peripheral ends of the splanchnic nerves for 10 min in the presence or absence of exogenous glucose. *A*, glucose (0·375 g/kg) was injected I.V. at the arrow. ●, 10·0 c/s, $n = 6$; ○, 2·0 c/s, $n = 4$, ×, glucose alone, $n = 4$. *B*, no glucose injected. ○, 2·0 c/s, $n = 5$; ●, 10·0 c/s, $n = 5$. Horizontal bar, duration of stimulus; vertical bars, S.E. of each mean value.

Responses to splanchnic nerve stimulation of adrenalectomized sheep

The extent to which the sympathetic innervation to the pancreas is generally important in controlling release of pancreatic hormones was further investigated by examining the responses of adult sheep (this species was chosen, in spite of the technical difficulties engendered, because of the differences in metabolism and dietary habit).

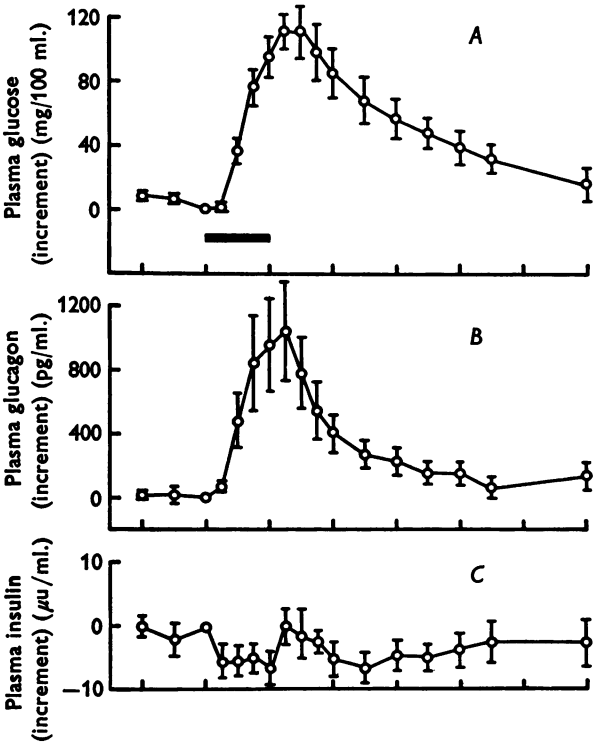

Fig. 9. Responses to stimulation of the peripheral end of the left splanchnic nerve at 10·0 c/s for 10 min in four adrenalectomized sheep. *A*, plasma glucose, *B*, plasma glucagon, *C*, plasma insulin. Horizontal bar, duration of stimulus; vertical bars, S.E. of each mean value.

Stimulation of the peripheral end of the left splanchnic nerve in four bilaterally adrenalectomized sheep, at 10·0 c/s for 10 min, produced a rapid and substantial rise in the concentration of both glucose and glucagon in the arterial plasma in each experiment. Comparatively little individual variation was encountered and the changes in the mean concentrations are shown in Fig. 9. In spite of the rise in plasma glucose

concentrations which occurred during these experiments, mean plasma insulin concentration fell during stimulation, indicating suppression of insulin release during the period of stimulation.

DISCUSSION

The observation that stimulation of the splanchnic innervation to the pancreas causes release of glucagon in both the cat and the dog is in accordance with the findings of other workers in these species (Esterhuizen & Howell, 1970; Marliss, Girardier, Seydaux, Kanazawa, Wollheim, Orci & Porte, 1972). Comparable responses occur in the calf (Bloom *et al.* 1973*b*) and the adult sheep, indicating that a wide variety of species respond in a similar fashion. The extent of the rise in plasma glucagon concentration during splanchnic nerve stimulation in all these species provides strong evidence that the associated suppression of insulin release can be attributed to direct inhibition of the β cell, rather than to vasoconstriction within the gland. The two responses are also complementary with respect to the combined effects of these hormones on hepatic metabolism, since insulin is known to inhibit hepatic glucogeogenesis (Park & Exton, 1972) and promote hepatic glycogenesis (de Duve, 1956).

Comparison of the present results in dogs, cats and sheep, with those obtained previously in calves under the same conditions (Bloom *et al.* 1973*b*), suggests that there are substantial species differences in the amount of glucagon which is released from the pancreas in response to splanchnic nerve stimulation. Thus, whereas stimulation at 10·0 c/s in dogs produced a maximal incremental rise in plasma glucagon concentration of only 244 ± 81 pg/ml., stimulation at the same frequency in 3–5 week old calves produced rises of between 2875 and 3660 pg/ml. In cats bilateral stimulation at 4·0 c/s raised plasma glucagon concentration by between 166 and 383 pg/ml., whereas the comparable mean value in calves was 1190 ± 139 pg/ml. (Bloom *et al.* 1973*b*). It therefore appears that stimulation of the sympathetic innervation to the pancreas produces a smaller increase in circulating glucagon in the cat and dog than in the young calf or adult sheep. The possibility that these species differences could be accounted for by different glucagon exit rates can be discounted since the hormone has been found to have a comparatively short half-life in the dog (*ca.* 5 min) and disappears from the plasma equally rapidly after splanchnic nerve stimulation in the calf (Bloom *et al.* 1973*b*).

The results obtained in dogs given exogenous glucose show that stimulation of the pancreatic α cell via the sympathetic innervation is not inhibited by hyperglycaemia, even when the plasma glucose concentration

is raised far in excess of the normal range (Fig. 7). It is noteworthy that the amount of glucose administered in these experiments apparently increased the osmolarity of the plasma sufficiently to cause significant increase of plasma volume. This finding is in complete accord with the observations of Järhult and his colleagues, who have suggested that the hyperglycaemia which occurs in response to haemorrhage, and is mediated by increased sympathetic activity, plays a part in maintaining the blood volume (Järhult, 1975; Järhult, Hillman & Mellander, 1975).

Assessment of the precise physiological role of the sympathetic innervation to the pancreatic islets is complicated by the fact that both α and β cells also appear to be susceptible to parasympathetic stimulation. Secretion of insulin in response to vagal stimulation is now well documented (see for instance Woods & Porte, 1974) and it is generally accepted that the β cell responds directly to cholinergic stimulation (Findlay, Gill, Lever, Randle & Spriggs, 1969; Porte, Girardier, Seydaux, Kanazawa & Pasternak, 1973). Studies with perfused pancreas preparations from dogs and rats have shown that glucagon is released in response to cholinergic stimulation (Iversen, 1973; Kaneto & Kosaka, 1974; Alric, Loubatières-Mariani, Loubatières & Puech, 1972) and the response is abolished by atropine in both species. Administration of atropine to calves with cut splanchnic nerves significantly reduces both the tolerance to insulin and the rise in plasma glucagon concentration during hypoglycaemia (Bloom, Edwards & Vaughan, 1974). Furthermore, stimulation of the peripheral ends of the vagus nerves produces a marked rise in plasma glucagon concentration in this species. All the available evidence suggests that the initial release of glucagon during moderate hypoglycaemia in the calf is mediated by the parasympathetic innervation to the pancreas, whereas the delayed release of glucagon which is observed during severe hypoglycaemia represents part of a generalized response to stress (Bloom *et al.* 1973*b*; 1974; Bloom, Edwards, Hardy, Malinowska & Silver, 1975*a*), such as that described in the baboon (Bloom, Daniel, Johnston, Ogawa & Pratt, 1973*a*).

Although the sympathetic system may be relatively insensitive to changes in plasma glucose concentration, the sensitivity of the glucagon release mechanism to splanchnic nerve stimulation in the calf is such that it may be concluded that tonic variations in sympathetic efferent activity modify the rate at which the hormone is normally released (Bloom *et al.* 1973*b*). The observations on stimulation at low frequency (2·0 c/s in dogs and 4·0 c/s in cats) and unilaterally (sheep) support the contention that this is also true in other species. Moreover, infusions of exogenous glucagon in dogs, which reproduce the comparatively small changes in plasma glucagon concentration which occur in this species

in response to splanchnic nerve stimulation, suffice to raise the plasma glucose concentration in these animals. It therefore appears that the sympathetic innervation to the pancreas normally contributes to the maintenance of plasma glucose concentration by stimulating the release of glucagon and inhibiting that of insulin.

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