METABOLIC EFFECTS OF CATECHOLAMINES IN SHEEP

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Summary

Intravenous infusion of 1·5 mg adrenaline over 30 min into adult Merino wethers (50 kg body weight), increased glucose, lactate, and free fatty acid (FFA) concentrations in plasma much more than did a single rapid intravenous injection of the same amount. There was no increase in plasma insulin concentration during adrenaline infusion or after adrenaline injection.

There was a logarithmic relationship between the rate of adrenaline infusion and the increment in plasma concentrations of glucose and lactate during the first 30 min of infusion. Infusion of adrenaline at either 0·0125, 0·025, 0·125, or 0·25 μmole/min caused very large increases in FFA concentrations and prevented any increase in the plasma insulin concentration. Cessation of infusion was followed by a rapid increase in plasma insulin.

Infusion of noradrenaline (0·025 μmole/min) caused a substantial, but smaller, increase in FFA than the same dose of adrenaline and almost no change in glucose or lactate concentrations. Noradrenaline prevented any increase in insulin concentration when glucose was infused at the same time.

Isoprenaline (0·025 μmole/min) caused greater increases in FFA but similar increases in lactate and much smaller increases in glucose than did adrenaline. In constrast to adrenaline and noradrenaline, isoprenaline greatly increased the plasma insulin concentration. This increase in insulin was greatly reduced when noradrenaline was infused with isoprenaline.

The adrenergic blocking agent phentolamine completely prevented the inhibitory effect of adrenaline infused at a rate of 0·025 μmole/min on insulin secretion, but only partly prevented it when adrenaline was infused at a rate of 0·125 μmole/min. Phentolamine itself significantly decreased plasma glucose and increased plasma FFA. Neither phenoxybenzamine nor propranolol blocked the inhibitory effect of adrenaline on insulin secretion. Propranolol, but not phentolamine, inhibited the stimulation of insulin secretion by isoprenaline. Phentolamine, phenoxybenzamine, and propranolol all decreased the response of FFA to adrenaline infusion, but only phentolamine blocked its effect on plasma glucose. Propranolol blocked the increase in lactate caused by adrenaline.

FFA mobilization and insulin secretion appear to be more sensitive to effects of the catecholamines than are glucose and lactate concentrations in sheep.

The observations indicate that the effects of the catecholamines on insulin secretion in the sheep are similar to those in man and indicate that these inhibitory effects on the insulin-secretory mechanism occur with small physiological amounts of the hormones.

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I. Introduction

The importance of the sympathetic nervous system and the hormones noradrenaline and adrenaline in the regulation of normal mammalian metabolism is well known (see review of Himms-Hagen 1967). While the major metabolic effects of the catecholamines are generally agreed on, there has been great variation between species in the relative potencies of adrenaline, noradrenaline, and other analogues such as isopropylnoradrenaline (isoprenaline) as well as in the results obtained with different methods of administration (Himms-Hagen 1967).

In sheep, adrenaline has been shown to cause marked hyperglycaemia (Setchell and McClymont 1955), to increase free fatty acid (FFA) concentrations (Lindsay 1961), and, more recently, to inhibit the insulin secretory response to several stimuli (Hertelendy, Machlin, and Kipnis 1969). Both noradrenaline and adrenaline have also been shown to increase plasma glucose, lactic acid, and FFA in lambs (Alexander, Mills, and Scott 1968). However, it has been claimed (Radloff and Schultz 1966) that ruminants may be less sensitive to these hormones than are other species.

The studies reported here were begun primarily in an attempt to assess the importance of the inhibitory action of adrenaline on insulin secretion (Coore and Randle 1964) in relation to its other metabolic actions in sheep. In addition, however, the studies were designed to assess the sensitivity of sheep to catecholamines and to examine the nature of the receptor mechanisms involved.

II. Materials and Methods

(*a*) *Animals*

Twelve adult Merino wethers with a medium-length fleece were housed individually in pens and received a daily ration of 1000 g of a 1 : 1 mixture of lucerne chaff and oats, which maintained them at a mean body weight of approximately 50 kg during the experimental period. The experiments were carried out at normal ambient temperatures; temperatures in the animal house (57–79°F) were not controlled.

(*b*) *Experimental*

All infusions of hormones and drugs were given intravenously to conscious animals via polyethylene cannulae placed in the left external jugular vein on the day prior to the experiment. A multi-channel peristaltic pump, which allowed six animals to be infused simultaneously, was used. Infusion solutions were made up in a 0·9% NaCl solution in glass-distilled deionized water. The following drugs were used: adrenaline as the hydrochloride (Parke Davis) or bitartrate (British Drug Houses); noradrenaline bitartrate (British Drug Houses); isoprenaline hydrochloride (Sigma); phenoxybenzamine (Dibenyline, Smith, Kline, and French Ltd.); phentolamine (Regitine, Ciba); propranolol (Inderal, I.C.I. Ltd.). Solutions were made up freshly before infusion. Catecholamine solutions contained 0·3% ascorbic acid as a preservative.

Blocking agents were usually infused over a period of 45–60 min and the infusion of catecholamines began 60 min after the end of this infusion.

Glucose was infused at the rate of 120 mg/min.

Blood samples were obtained by venipuncture from the right jugular vein with minimal disturbance to the animals. The samples were cooled immediately in iced water and plasma was separated by centrifuging at 4°C as soon as possible.

(*c*) *Analytical Methods*

Plasma glucose was determined by the glucose oxidase method of Huggett and Nixon (1957); plasma lactate was measured using lactate dehydrogenase (Lundholm, Mohme-Lundholm, and Vamos 1963). Plasma FFA were estimated by the method of Dole (1956) as modified by

Annison (1960), and plasma insulin was measured by the double-antibody radio-immunoassay method of Hales and Randle (1963) as modified by Bassett and Wallace (1966).

The statistical significance of the results was estimated by means of the conventional *t*-test.

III. Results

(*a*) *Effects of Intravenous Adrenaline*

Rapid intravenous injection of 1·5 mg adrenaline caused a marked increase in the glucose, lactic acid, and FFA concentration in the plasma of six wether sheep (Table 1). Maximum concentrations were reached within the first 15 min after the injection (Table 1). Despite the marked hyperglycaemia, the plasma insulin concentration increased slowly during the 120 min following adrenaline injection (Fig. 1), a result which might explain the very slow rate at which plasma glucose declined between 15 and 120 min after the injection (Table 1).

Table 1

Effects of adrenaline on plasma glucose, lactic acid, and free fatty acid concentrations in sheep

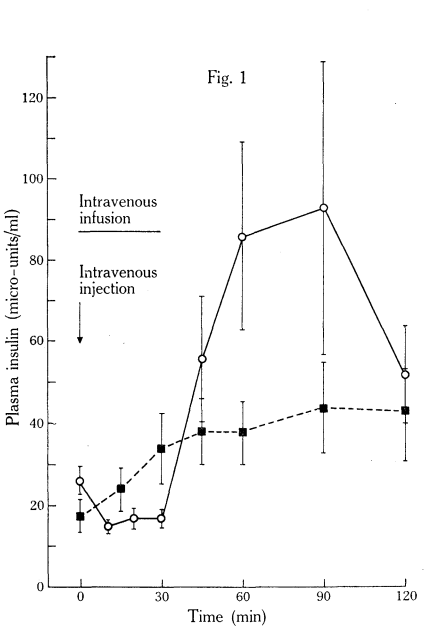
Adrenaline was given either as a single intravenous injection of 1·5 mg, or as a continuous intravenous infusion of 50 μg/min for 30 min. Values are means±standard error

Method of Administration	Time after Injection (min)								
	0	10	15	20	30	45	60	90	120
				Glucose (mg/100 ml)					
Injection	56	—	113	—	111	113	108	99	88
	±1·0		±2·4		±1·7	±2·2	±2·0	±2·5	±3·6
Infusion	58	108	—	154	195	188	183	182	174
	±2·5	±2·3		±7·1	±9·4	±1·5	±2·4	±5·4	±4·3
				Lactic acid (mg/100 ml)					
Injection	5·3	—	33·7	—	33·8	27·9	21·8	14·2	9·5
	±1·3		±1·7		±2·5	±3·0	±2·4	±2·3	±1·7
Infusion	6·4	19·8	—	31·8	42·4	55·9	54·4	42·4	32·0
	±0·9	±0·8		±1·7	±3·6	±3·4	±2·6	±3·4	±3·5
				Free fatty acids (μ-equiv/l)					
Injection	270	—	710	—	570	450	360	250	220
	±30		±70		±100	±90	±70	±40	±20
Infusion	460	1610	—	2490	2800	2660	2330	1573	947
	±81	±254		±288	±252	±142	±153	±159	±91

When the same amount of adrenaline (1·5 mg) was infused intravenously over 30 min (50 μg/min or 0·25 μmole/min) rather different results were obtained (Table 1; Fig. 1). The plasma glucose, lactic acid, and FFA concentrations all increased rapidly and the magnitude of the change in all three, especially that in FFA, was substantially greater than that following the single injection. Adrenaline infusion completely suppressed secretion of insulin in response to the hyperglycaemia, but as soon as the infusion was terminated the plasma insulin concentration increased rapidly to high levels (Fig. 1).

In view of the pronounced effects of slow infusions of adrenaline, all subsequent studies were carried out using slow intravenous infusions lasting 60 min.

Since infusion of adrenaline at a rate of 0·25 μmole/min caused very marked changes in all the parameters measured, the effects of lower infusion rates were examined to establish dose–response relationships. Infusions at rates of 0·0125, 0·025, and 0·125 μmole/min for 60 min caused changes in glucose, lactic acid, FFA, and insulin plasma concentrations similar in pattern to those observed during the infusion of 0·25 μmole/min for 30 min (Table 1). For comparison of the various infusion rates the increments in the concentration of glucose, lactic acid, and FFA during the first 30 min have been used. There was a good log dose–response relationship between infusion rate and the increment in plasma glucose over the range of infusion rates used, and some evidence of a similar relationship for the increment in lactic acid concentration (Fig. 2). All infusion rates of adrenaline increased the



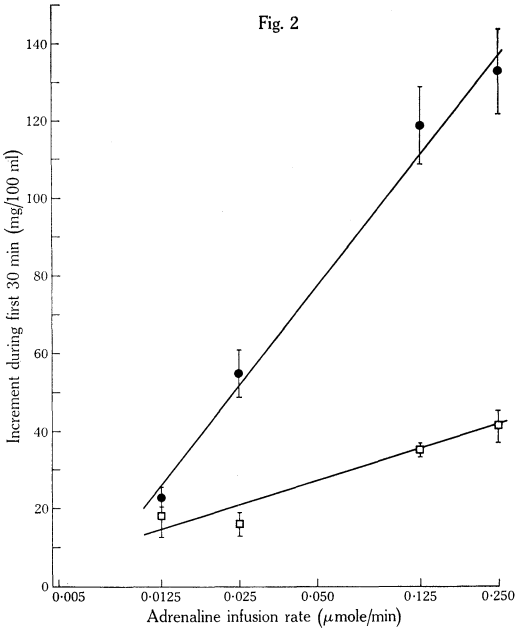
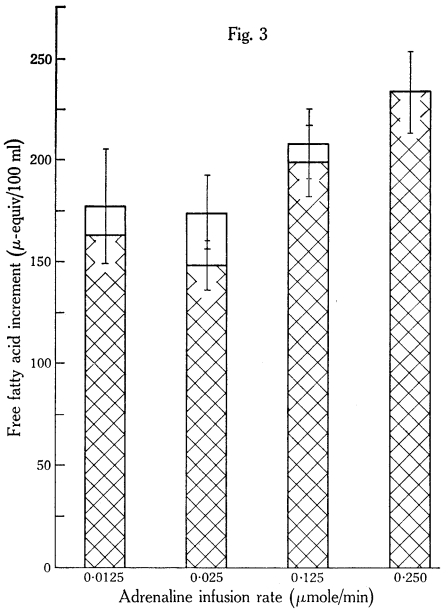


Fig. 1.—Changes in the plasma insulin concentration of sheep given adrenaline as a single intravenous injection of 1·5 mg (■) or as a continuous intravenous infusion at a rate of 50 μg/min for 30 min (○). In Figures 1–5 and 7–9 vertical lines indicate standard error.

Fig. 2.—Relationship of increases in plasma glucose (●) and lactic acid (□) concentrations of sheep, during the first 30 min of an intravenous infusion, to the dose of adrenaline used.

plasma FFA concentration greatly during the first 30 min of infusion and there was little further increase during the second 30 min of infusion (Fig. 3). The increase tended to be greater with the larger doses but differences between the infusion rates were not statistically significant. There was no increase in the plasma insulin concentration during infusion of adrenaline, at all infusion rates, but there was a rapid increase during the first 15 min after cessation of the infusion (Fig. 4).



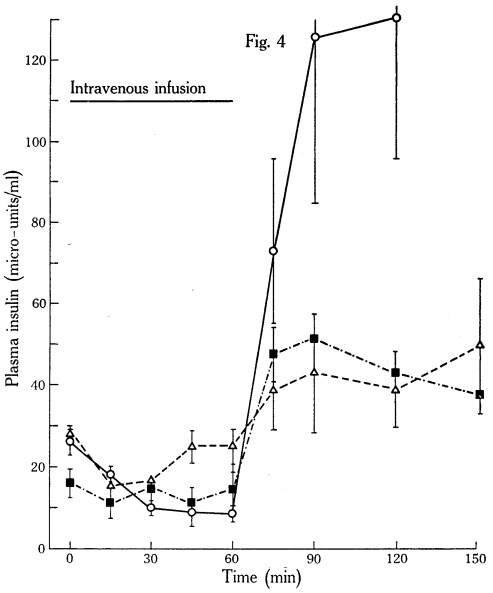


Fig. 3.—Changes in the mean plasma free fatty acid concentration of sheep given intravenous infusions of adrenaline for 60 min at four different rates. Increment in first 30 min, hatched bar; first 60 min, hatched + open bar.

Fig. 4.—Changes in the mean plasma insulin concentration of sheep infused with adrenaline for 60 min at rates of 0·0125 μmole/min (△), 0·025 μmole/min (■), or 0·125 μmole/min (○).

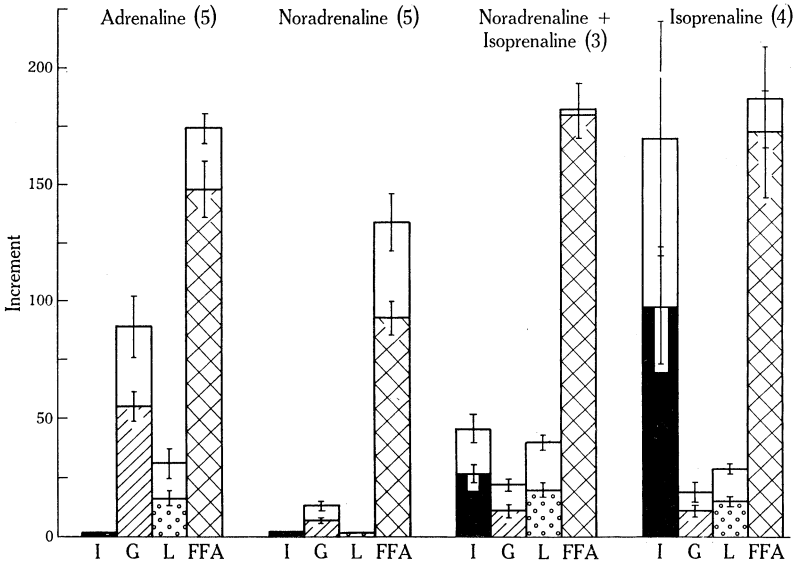


Fig. 5.—Increments in plasma insulin (I, in micro-units/ml), glucose (G, in mg/100 ml), lactic acid (L, in mg/100 ml), and free fatty acids (FFA, in μ-equiv/100 ml) during a 60-min infusion of noradrenaline, isoprenaline, or both, at rates of 0·025 μmole/min, compared to those during infusion of adrenaline at the same rate. Hatched area indicates changes during first 30 min. Numbers in parenthesis are the number of sheep receiving each treatment.

(*b*) *Effects of Noradrenaline and Isoprenaline*

Noradrenaline and isoprenaline were infused singly and together at rates of 0·025 μmole/min for 60 min. The results obtained are compared with those obtained during infusion of equimolar amounts of adrenaline.

Noradenaline infusion had very little effect on plasma glucose, insulin, or lactic acid concentrations, but caused a large increase in the FFA concentration, though this was significantly less than that occurring during infusion of adrenaline at the same rate, $P < 0{\cdot}01$ (Fig. 5).

During the first 30 min of infusion, isoprenaline increased the FFA concentration more than noradrenaline ($P < 0{\cdot}001$) and slightly, but not significantly, more than adrenaline. The effect of isoprenaline on glucose, though greater than that of noradrenaline ($P < 0{\cdot}05$), was less than that of adrenaline ($P < 0{\cdot}01$). Isoprenaline and adrenaline both increased the plasma lactic acid concentration to the same extent. When noradrenaline and isoprenaline were given together the effects on glucose, lactic acid, and FFA were similar to those of isoprenaline, and there was no indication of an additive or synergistic action of the two, except possibly on the lactic acid increase.

Isoprenaline, unlike adrenaline or noradrenaline, caused a substantial increase in the plasma insulin concentration (Fig. 5), even though it caused only a small increase in the plasma glucose. While there was no change in insulin during infusion of noradrenaline, any suppressive effect of this hormone on insulin secretion would not have been detected by these infusions because of the very small changes in plasma glucose. However, when glucose was infused (120 mg/min) with noradrenaline (0·025 μmole/min) into two sheep there was still no increase in plasma insulin until the termination of the noradrenaline infusion, when a rapid increase in the insulin concentration of both sheep occurred; the markedly smaller increase in insulin concentration during the infusion of both noradrenaline and isoprenaline than during that of isoprenaline alone (Fig. 5) is also indicative of a suppressive effect of noradrenaline on insulin secretion.

(*c*) *Effect of Adrenergic Blocking Agents on the Actions of Adrenaline*

To elucidate whether the adrenergic mechanisms involved in the regulation of insulin secretion were consistent with the existence of α- and β-receptor sites (Ahlquist 1948) on the insulin-secreting cells of the pancreas, the α-receptor blocking drugs phenoxybenzamine and phentolamine, and the β-receptor blocking drug propranolol were administered to a number of sheep before infusion of adrenaline.

The effects of prior intravenous infusion of these blocking agents on the response of plasma insulin, glucose, lactate, and FFA concentrations to infusion of adrenaline (0·025 μmole/min) are shown in Figure 6.

Two sheep were given 1·0 mg/kg of phenoxybenzamine and two other sheep were given 5·0 mg/kg over 60 min, but the response of all four sheep to the subsequent infusion of adrenaline was essentially the same. Phenoxybenzamine did not alter the effect of adrenaline on plasma glucose or lactate concentrations and did not block the inhibitory action of the hormone on insulin secretion. Phenoxybenzamine blockade did, however, significantly decrease the response of plasma FFA concentration to adrenaline ($P < 0{\cdot}01$).

Phentolamine was given to four sheep over 60 min at a dose of 1·0 mg/kg. Adrenergic blockade with this drug resulted in marked decreases in the responses of

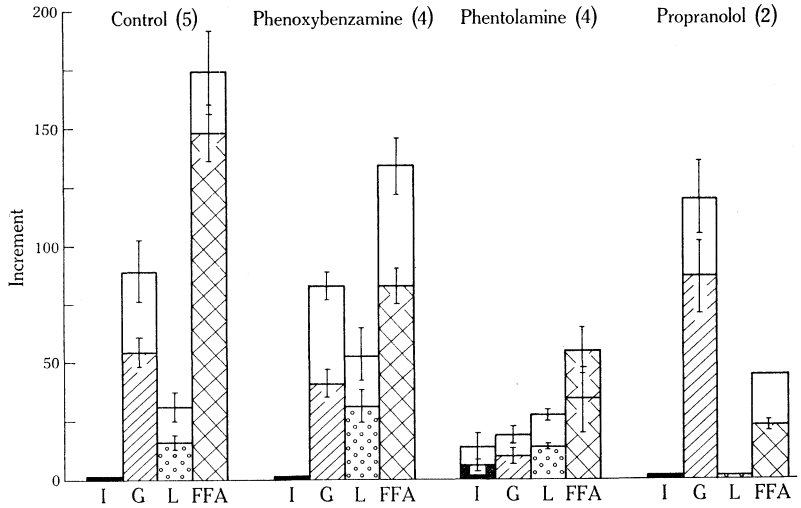


Fig. 6.—Effects of adrenergic blocking agents on the mean increments in plasma insulin (I, in micro-units/ml), glucose (G, in mg/100 ml), lactic acid (L, in mg/100 ml), and free fatty acids (FFA, in μ-equiv/100 ml) during a 60-min intravenous infusion of adrenaline at 0·025 μmole/min. Hatched areas indicate changes during first 30 min of infusion. Vertical lines indicate standard error except for propranolol, where they indicate values in the two individuals. Numbers in parenthesis are the number of sheep receiving each treatment.

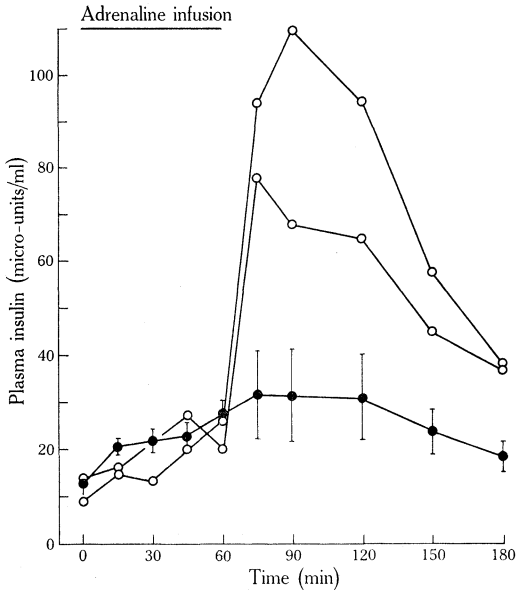


Fig. 7.—Changes in the mean plasma insulin concentration of four sheep during intravenous infusion of adrenaline at 0·025 μmole/min (●) and in two sheep during adrenaline infusion at 0·125 μmole/min (○) after prior infusion of phentolamine into all six animals.

glucose ($P < 0·001$) and FFA ($P < 0·001$) to subsequent adrenaline infusion, but did not alter the increase in plasma lactate concentration. Phentolamine apparently

blocked the effect of adrenaline on insulin secretion, since plasma insulin increased significantly during subsequent adrenaline infusion. Further experiments on two phentolamine-blocked sheep showed that infusion of larger amounts of adrenaline (0·125 μmole/min) could still partially block the insulin-secretory response to hyperglycaemia. In this experiment (Fig. 7) there was a very rapid increase in the insulin concentration after termination of the adrenaline infusion, even though it had increased during the infusion of adrenaline.

Propranolol, a β-receptor blocking agent, was given to two sheep at a dose of 0·5 mg/kg. This did not alter the effects of adrenaline on plasma insulin or glucose concentrations (Fig. 6), but virtually abolished its effects on plasma lactic acid and FFA concentrations.

TABLE 2

EFFECTS OF α- AND β-ADRENERGIC BLOCKING DRUGS ON PLASMA GLUCOSE, INSULIN, AND FREE FATTY ACID CONCENTRATIONS IN SHEEP

Blood samples were obtained at the start of infusion of blocking agent, the end of infusion 45–60 min later, and then 1 hr after this and prior to catecholamine infusion. Values are given as mean±standard error. Significance of difference from value at start of infusion as follows: * $P < 0·05$; ** $P < 0·01$

Time of Sampling	No. of Readings	Glucose (mg/100 ml)	Insulin (micro-units/ml)	Free Fatty Acids (μ-equiv/l)
		Phenoxybenzamine		
Start of infusion	5	56·2±1·5	12·7±1·8†	250±10
End of infusion	5	53·7±1·4	6·0±1·7†	248±15
End of infusion+60 min	5	53·0±1·1	14·0±3·1	368±22**
		Phentolamine		
Start of infusion	10	52·2±1·7	15·4±2·6	482±62
End of infusion	8	43·9±2·8*	36·0±11·6	851±112**
End of infusion+60 min	10	43·6±1·7**	23·0±4·2	1084±152**
		Propranolol		
Start of infusion	8	53·9±1·8	19·6±3·7	545±55
End of infusion	0	—	—	—
End of infusion+60 min	8	54·9±1·9	26·4±5·6	652±54

† Three readings only.

Phentolamine, therefore, was the only blocking agent able to alter the inhibitory effect of adrenaline on insulin secretion. However, blood samples collected at the termination of phentolamine administration in a total of eight experiments showed that this drug itself decreased plasma glucose. At the same time, phentolamine increased FFA and probably insulin concentrations, though because of great variability the effect on insulin was not statistically significant (Table 2). Neither phenoxybenzamine nor propranolol appeared to exert similar effects.

(*d*) *Effects of Adrenergic Blocking Agents on the Actions of Isoprenaline*

The effects of phentolamine (1·0 mg/kg) and propranolol (0·5 mg/kg) blockade on the responses to isoprenaline infusion are shown in Figure 8. Isoprenaline was infused at two rates (0·025 and 0·125 μmole/min), but after phentolamine

blockade the response to both infusion rates was similar and the results for the four animals are considered together. After propranolol, however, the subsequent response to isoprenaline was dependent on the infusion rate used.

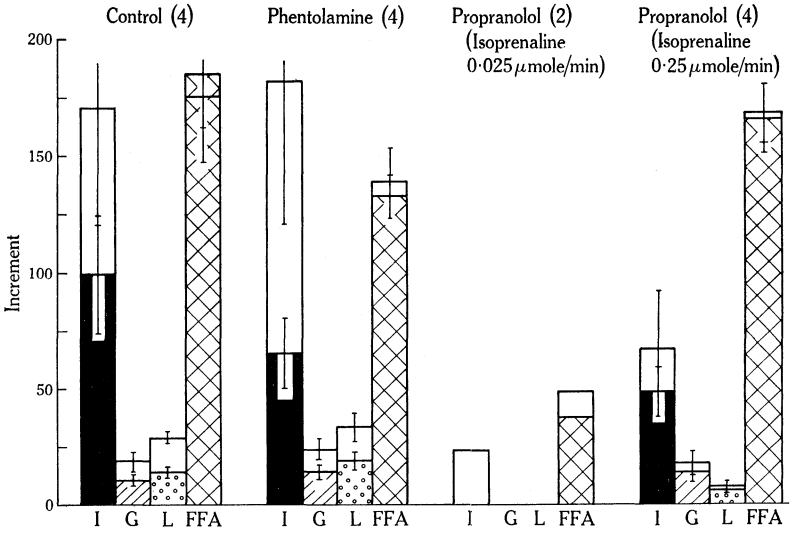


Fig. 8.—Effect of adrenergic blocking agents on the mean increments in plasma insulin (I, in micro-units/ml), glucose (G, in mg/100 ml), lactic acid (L, in mg/100 ml), and free fatty acids (FFA, in μ-equiv/100 ml) during a 60-min infusion of isoprenaline at a rate of 0·025 or 0·25 μmole/min. Hatched areas indicate changes during first 30 min of infusion. Numbers in parentheses are the number of sheep receiving each treatment.

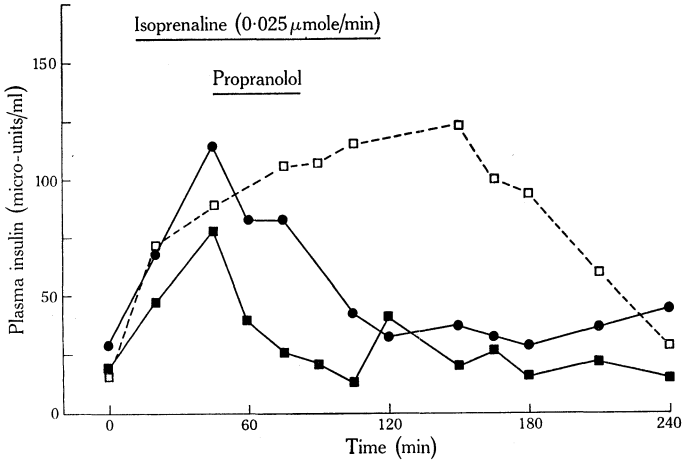


Fig. 9.—Changes in the plasma insulin concentration of two sheep given propranolol during an infusion of isoprenaline (———) and in one sheep given isoprenaline alone (– – – –) at the same rate (0·025 μmole/min).

Phentolamine did not alter the plasma glucose response to isoprenaline, but propranolol blockade prevented the response to infusion of 0·025 μmole/min of

isoprenaline. However, there was an increase in plasma glucose during infusion of isoprenaline at 0·125 μmole/min following propranolol blockade.

Phentolamine did not alter the increase in plasma insulin during isoprenaline infusion, but propranolol substantially blocked this increase. With the higher isoprenaline infusion rate the increase in insulin in the propranolol-blocked sheep was greater; it was not, however, as great as that occurring during control infusions of isoprenaline at 0·025 μmole/min.

The blocking actions of propranolol were also clearly seen when the drug was infused during the course of an isoprenaline infusion (Fig. 9). High plasma insulin concentrations declined sharply when propranolol infusion was begun, despite continued infusion of isoprenaline.

Phentolamine blockade did not alter the lactate response to isoprenaline, but propranolol completely prevented the increase in lactate during infusion of the smaller amount of isoprenaline. Phentolamine did not block the FFA-mobilizing action of isoprenaline, and propranolol only effectively blocked this action of isoprenaline at the lower infusion rate (Fig. 8).

IV. Discussion

The effects of intravenous infusion of catecholamines on the plasma insulin, glucose, lactate, and FFA concentrations observed in the present experiments are similar to those observed in sheep by Hertelendy, Machlin, and Kipnis (1966) and confirm that the sheep responds to these hormones in a similar way to man and a number of other species (Himms-Hagen 1967). Also the quantitative similarity of the changes observed in the sheep to those seen in man, when similar infusion rates of the hormones have been used (Porte *et al.* 1966; Porte and Williams 1966; Porte 1967*a*, 1967*b*), indicates that there are no important differences between these species in their sensitivity to the catecholamines. The statement of Radloff and Schultz (1966) that ruminants are less sensitive than other species to the FFA-mobilizing action of these hormones is not consistent with the present findings and is probably attributable to the single intravenous injection mode of catecholamine administration they used. This is exemplified by the present studies, where differences in the mode of administration of the hormone produced substantially different results.

The present results show adrenaline to be more active than noradrenaline in increasing plasma concentrations of both glucose and lactate in adult sheep when infused in equimolar amounts. On the other hand, Alexander, Mills, and Scott (1968) showed that both adrenaline and noradrenaline caused large increases in the plasma concentrations of glucose and lactate in young lambs. However, they used infusion rates some 10–100 times greater than those used in the present studies and it is unlikely that their experiments, which were designed to examine the maximum responses to these hormones, would distinguish clearly between the two.

In the present experiments near-maximal increases in plasma FFA concentration and virtually complete inhibition of any insulin-secretory response to hyperglycaemia were observed with all infusion rates of adrenaline, some of which caused only minor changes in the plasma glucose or lactate concentration. This indicates that both

FFA mobilization and insulin secretion are more sensitive indices of catecholamine action in sheep than are increases in either plasma glucose or lactate levels. Since rapid increases in plasma glucose are frequently seen in stressful situations where activation of the adrenal medulla probably occurs, the present results leave little doubt about the importance of the sympathetic nervous system and adrenal medulla in the control of insulin secretion and FFA mobilization in sheep.

In the absence of information on the blood levels of the catecholamines established by infusion, it is difficult to speculate on the sensitivity of the various metabolic processes to the effects of noradrenaline and isoprenaline relative to their sensitivity to adrenaline. However, a comparison of the effects of the three catecholamines and the effects of α- and β-adrenergic blocking agents on their action indicates that these metabolic actions cannot be described simply in terms of specific α- or β-receptor sites.

For example, neither noradrenaline (an α-receptor stimulator) nor isoprenaline (a β-receptor stimulator), nor a combination of the two, increases plasma glucose to an extent comparable to adrenaline, yet all are potent stimulators of FFA mobilization in sheep. Similarly, both phenoxybenzamine and phentolamine, α-receptor blocking agents, significantly reduce the rate of FFA mobilization, yet have different effects on the changes in plasma glucose, lactate, and insulin concentrations. All these effects of the catecholamines are complex and undoubtedly involve alterations in tissue blood flow as well as alterations in tissue metabolism, so it is possible that both α- and β-adrenergic effects are involved in all. However, the difficulties and contradictions involved in attempting to classify the metabolic actions of the catecholamines as α- or β-adrenergic effects have already been considered exhaustively by Himms-Hagen (1967) and it does not seem useful to attempt such a classification of the metabolic effects in the sheep.

The effects of catecholamines on the regulation of insulin secretion by the β-cells of the pancreatic islets in man have been interpreted as indicating the presence of inhibitory α-receptors (Porte 1967*a*) and stimulatory β-receptors (Porte 1967*b*). The present experiments and those of Hertelendy, Machlin, and Kipnis (1969) show that adrenaline and noradrenaline inhibit insulin secretion in sheep and that this action is blocked by phentolamine. The present experiments also show that insulin secretion in sheep is stimulated by isoprenaline and this action is blocked by propranolol, consistent with the findings in man (Porte *et al.* 1966; Porte 1967*a*, 1967*b*). However, the ability of noradrenaline to inhibit the isoprenaline-stimulated increase in plasma insulin almost completely, when the two are infused together in equimolar amounts, indicates that the inhibitory effect of noradrenaline on the insulin-secretory mechanism is dominant over the stimulatory effect of isoprenaline. Since these adrenergic effects are apparently mediated through alterations in the adenyl cyclase activity and rate of cyclic 3′,5′-adenosine monophosphate synthesis in the islet cells (Turtle, Littleton, and Kipnis 1967; Malaisse, Malaisse-Lagae, and Mayhew 1967), it would appear that the site of inhibition by adrenaline and noradrenaline may be at an earlier stage in the process of cyclic 3′,5′-adenosine monophosphate synthesis than the site of stimulation by isoprenaline. Alternatively, it may be that attachment of noradrenaline to a single receptor site inhibits competitively the attachment of isoprenaline to it.

The effects of phentolamine also suggest the possibility that a single receptor site may be involved, since this drug appears able to stimulate insulin secretion itself as well as block the inhibitory effect of adrenaline. On the other hand, its failure to block the stimulation of insulin secretion by isoprenaline is more consistent with the existence of separate receptor sites for stimulation and inhibition of insulin secretion. Hertelendy, Machlin, and Kipnis (1969) reported that insulin secretion was stimulated during adrenaline infusion when phentolamine was also given, and implied that blockade of α-receptors allowed a stimulatory effect of adrenaline on β-receptors to be demonstrated. However, the results of the present experiments suggest that the increased insulin secretion may have been caused by the phentolamine itself.

In conclusion, it is evident from the experiments reported here that the catecholamines adrenaline and noradrenaline may exert an important inhibitory influence on the pancreatic insulin secretory process in sheep, even at levels where their effects on plasma glucose are minimal. Since infusion of adrenaline at similar rates also significantly inhibits growth hormone secretion in sheep (Hertelendy, Machlin, and Kipnis 1969; Wallace and Bassett 1970), effects of the catecholamines on the secretion of other hormones must be taken into account in any interpretation of the effects of stressful stimuli on metabolism in this species.

V. Acknowledgment

The technical assistance of J. P. McCaffrey is gratefully acknowledged.

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