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THE EFFECTS OF INTRA-ARTERIAL ADRENALINE ON CARBOHYDRATE METABOLISM IN MAN

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Adrenaline given intravenously or subcutaneously to normal human subjects effects an increase in blood-sugar and blood-lactic acid (Cori & Buchwald, 1930; Loeb, Reeves & Glasier, 1931), and a fall in serum potassium (Castleden, 1938; Keys, 1938). In animals intravenous adrenaline causes a fall in muscle glycogen (Cori, 1931). This also occurs in man (Hildes, Sherlock & Walshe, 1949).

In their studies on muscle-blood flow, Allen, Barcroft & Edholm (1946) described a technique for infusing adrenaline intra-arterially in man. It seemed to us that adrenaline given by this route might produce an even greater depletion of muscle glycogen in the infused leg than when given intravenously, although when given intra-arterially it does not have its usual systemic effects on the cardiovascular system.

MATERIAL AND METHODS

Material. Clinical notes on the twelve patients used in this investigation are given in the Appendix. They were all males ranging in years from 27 to 67, and when the observations were made they were, on the whole, free of symptoms and on a full hospital diet. None had any known defect of carbohydrate metabolism. The observations were made after a simple explanation of the procedure to the patient.

Experimental procedure. All observations were made in the morning after a 12 hr. fast in bed. 200 mg. sodium amytal was given about 1 hr. before the observations began. In three cases this mild sedative was omitted (Table 1). Adrenaline was infused into one femoral artery for a period of ½–¾ hr. This was preceded and followed by control periods of about 45 min. During the preliminary control period, in all but three cases, the femoral vein on the same side was catheterized for sampling. Frequent measurements of the blood pressure and pulse rate were made throughout the experiment, and changes in colour of the feet were noted.

Samples of capillary, brachial venous and femoral venous blood were taken at 10–15 min. intervals. Glucose was estimated in all samples, lactate and serum potassium in the venous samples. In most cases the glycogen content of the gastrocnemius muscle on the side of the infusion was

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estimated before, during and after the infusion. The methods used are described in more detail in view of some of the difficulties encountered.

Intra-arterial infusion. The femoral artery was chosen in preference to the brachial artery because of the ease of gastrocnemius muscle biopsy. The site selected for arterial puncture was 1–2 in. below the inguinal ligament. With the patient supine, the skin and subcutaneous tissues were anaesthetized with 2% procaine solution. A fine-bore needle (gauge 24) could then be introduced into the artery without difficulty and without discomfort to the patient. The infusion was maintained at a constant rate, using a motor-driven 50 c.c. syringe. This apparatus was modified from the model used by Allen *et al.* (1946). This delivers, against arterial pressure, at a constant rate ranging from 1 to 5 c.c. a minute. The rate of the infusion can be accurately and finely adjusted.

The arterial needle was fixed by dental wax to one end of a convenient length of transparent plastic tubing (Telcothene), which was connected through a 3-way tap to the nozzle of the syringe. The whole was filled with the diluted adrenaline solution and the syringe placed in position. The needle was then introduced into the femoral artery, held in place by adhesive strapping and the motor started. The patency of the needle could be checked at any time by momentarily turning the tap when arterial blood appeared in the end of the transparent tubing. By this arrangement it was possible to maintain an infusion for 45 min. without recharging the syringe. This prevents a needle of this bore blocking, as it tends to do when introduced into the artery attached to a small syringe in the usual way and then connected to rubber transfusion tubing.

In two cases, after about 10 min. of infusion, when the local anaesthesia had diminished, the patients complained of a numb burning sensation in the distribution of the medial cutaneous branch of the femoral nerve. In these cases the experiment was discontinued and the pain disappeared in about 15 min.

Femoral vein sampling. A small incision was made through local anaesthesia 1½ in. below and lateral to the pubic spine and the saphenous vein located. Through this vein a short length of sterile plastic tubing was introduced approximately 6 in. into the femoral vein for sampling. Between samples the tubing was kept patent by a slow saline infusion.

Muscle-glycogen estimation. Muscle samples of 20–100 mg. in weight were taken by biopsy of the ipsilateral gastrocnemius under local anaesthesia (Hildes, Sherlock & Walshe, 1949). Samples were taken immediately before the infusion, just before its termination and ½–1 hr. after the infusion ended. Duplicate, and in some cases, triplicate samples were analysed for glycogen content (Hildes *et al.* 1949).

Blood-sugar estimations were carried out in duplicate, by the method of Haslewood & Strookman (1939), using 0·05 ml. samples in the case of capillary blood and 0·2 ml. samples for venous blood.

Blood-lactic acid was estimated by the method of Long (1946).

Serum potassium was estimated by the method of King, Haslewood, Delory & Beall (1942).

Dosage and preparation of adrenaline. Ampoules of 1:1000 adrenaline (Allen and Hanbury) were suitably diluted in normal saline containing 50 mg. ascorbic acid per 100 ml. (Cori, Fisher & Cori, 1935). The infusion was at a constant rate, but the dosage in the twelve subjects ranged between 0·032 and 0·12 μg./kg. body wt./min. (Table 1). This covers the range of intravenous dosage used by other workers (Cori & Buchwald, 1930; Loeb *et al.* 1931, and others) and approximates to the intra-arterial dose used by Allen *et al.* (1946). These workers infused adrenaline for only 10–12 min. The maximal effect of intravenous adrenaline on muscle glycogen in man probably occurs at 30 min. (Hildes *et al.* 1949), and we decided to infuse for approximately this time.

RESULTS

The results of ten experiments are summarized in Table 1, and the details of one of the experiments are shown in Table 2.

Effects on the cardiovascular system. Blood pressure and pulse rate were taken at frequent intervals during the experiment (Table 1). In one case blood-pressure readings were omitted because of difficulty in venous sampling from

TABLE 1. Effects of intra-arterial adrenaline in ten cases

Case no.	Adrenaline (μg./kg./min.)	Time of infusion (min.)	Systolic B.P. (max. rise mm. Hg)	Pulse rate (max. rise beats/min.)	Maximum change in blood sugar (mg./100 ml.)*			Maximum change in blood lactic acid (mg./100 ml.)*		Muscle glycogen (g./100 g.)		
					Capillary	Brachial venous	Femoral venous	Brachial venous	Femoral venous	Control	Change‡ affected adrenaline	30 min. after infusion
1	0·110	46	4	0	+16	+8	—	−0·2	—	—	—	—
4†	0·084	45	4	4	−6	−8	−3	−2·0	+0·5	—	—	—
5†	0·032	38	4	0	+8	—	—	—	—	1·98	−0·14	1·78
6†	0·066	35	0	0	—	−1	+15	+1·3	+1·4	—	—	—
7	0·070	28	12	12	+25	—	—	—	—	1·77	+0·11	1·79
8†	0·100	24	8	0	0	—	+4	−0·3	+7·5	3·03	−0·02	3·07
9†	0·100	23	2	8	+7	+1	+4	+1·3	+1·6	—	—	—
10†	0·120	24	8	12	+7	+7	+10	+1·0	+2·1	1·54	+0·06	1·50
11†	0·100	40	—	4	+2	+8	+2	+0·9	+0·9	1·32	+0·05	1·35
12†	0·096	42	10	20	+9	+14	—	+5·2	—	1·67	−0·05	1·68
Means	0·088	34	5	6	+8	+4	+6	+0·9	+2·3	1·89	+0·005	1·86
Mean values for intravenous adrenaline in 20 subjects (Hildes, Sherlock & Walshe, 1949)												
	0·081	60	32	20	+48	—	—	+8·7	—	—	−0·60	—

* Maximum change recorded during the infusion compared with the mean control value.
† Sodium amytal 200 mg. orally 1 hr. prior to observation.
‡ Change in muscle glycogen at end of the infusion compared with the control value. In case 5 a sample 15 min. after starting the adrenaline contained 1·95 g. glycogen per 100 g.

that arm. In no case was there any noteworthy change in blood pressure or pulse rate except in case 12 where the pulse increased 20 beats per min.

No measurements were made of skin temperature or muscle-blood flow, but alterations in skin vessel tone were assessed by comparing the skin colour of the feet. Blanching of the foot on the operated side was evident within 2½ min. of starting the infusion and was maintained throughout. When the infusion was stopped, there was a hyperaemic flush which came on slowly, and at first unevenly, to reach maximal intensity within 5 min. and then subsided to normal colour within 10 min.

TABLE 2. Intra-arterial adrenaline infusion. Case No. 11

Time (min.)	Blood-sugar (mg./100 ml.)			Blood-lactic acid (mg./100 ml.)		Serum potassium (mg./100 ml.)		Muscle glycogen (g./100 g.)
	Capillary	Brachial venous	Femoral venous	Brachial venous	Femoral venous	Brachial venous	Femoral venous	
				Preliminary control period				
0	93	85	85	4·5	4·8	—	22·4	—
15	—	—	—	—	—	—	—	1·32
30	96	84	87	5·8	8·0	20·7	20·0	—
				Adrenaline infusion 0·100 μg./kg./min. for 40 min.				
70	93	87	88	6·1	7·3	20·0	20·4	—
85	97	91	87	5·1	4·5	20·7	—	—
110	—	93	89	4·2	5·1	19·2	20·7	1·37
				Control period				
120	104	—	102	—	7·0	—	20·0	—
140	97	94	95	4·5	10·1	20·0	20·0	—
160	87	95	92	7·7	8·6	—	20·0	1·35

Facial pallor was noted in some cases but this was never very marked and was delayed in onset. When the infusion was stopped, there was no marked flushing of the face, although in one or two cases a slight flush was noted. This is in marked contrast with the immediate and striking pallor of the face seen when adrenaline is given intravenously, and the marked facial flushing when intravenous adrenaline is stopped.

Effect on blood sugar. The maximum changes in blood sugar above the fasting level are shown in Table 1. The mean of these changes was +8 mg./100 ml. in the case of capillary blood, +4 mg./100 ml. in brachial venous blood and +6 mg./100 ml. in femoral venous blood. There is no statistically significant difference between the mean value of capillary blood sugar before and the mean value during the adrenaline infusion (difference between the means = 7·1 mg./100 ml., 2 × standard error of the difference = 9·6).

However, in four cases one or other blood sample did show a rise in blood sugar of 14 mg. or more per 100 ml., the highest being 25 mg./100 ml. above the fasting level (Table 1). It is interesting to note that the high blood-sugar level in each of these four cases was delayed, in one 20 min. and in the others 30 min. after the start of the adrenaline infusion. Three of the subjects had not

received sodium amytal. This substance given in a dose of about 50 mg./kg. body wt. is known to stabilize carbohydrate metabolism in animals. The dose of sodium amytal given to our cases was only of the order of 3·5 mg./kg. body wt. The slightly greater rise in blood-sugar of some patients that did not receive the drug is therefore considered fortuitous.

Effect on blood-lactic acid. Table 1 shows the changes in blood-lactic acid in both brachial and femoral venous blood. The values in the table show the maximum change that occurred in each case. The differences between the mean values before and during adrenaline infusion were 0·4 mg./100 ml. and 0·7 mg./100 ml. for brachial and femoral blood respectively. Neither of these differences is significant.

Effect on serum potassium. There was no significant change in serum potassium concentration either in brachial venous blood or femoral venous blood when adrenaline was infused into the femoral artery. In the case of brachial venous blood, the mean values before and during infusion were 20·5 and 20·1 mg./100 ml. respectively. The mean values for femoral blood were 19·2 and 18·3 mg./100 ml. before and during infusion.

Effect on muscle glycogen. Duplicate, and sometimes triplicate, samples were taken at each biopsy and analysed for glycogen (Good, Kramer & Somogyi, 1933; Hildes *et al.* 1949). Initially, some difficulty was encountered in obtaining accurate duplicate checks. With practice, in particular regard to muscle sampling, this difficulty was overcome to the extent that a deviation of the order of 16% from the fasting level could be regarded as significant ($P < 0·05$). Only the muscle glycogens estimated since accepting this standard of analysis have been included in Tables 1 and 2. The changes in muscle glycogen produced by intra-arterial adrenaline were studied in six cases. The mean values and standard deviation during and after the infusion, expressed as a percentage of the fasting level, were found to be 101% (S.D. 7·5) and 98·6% (S.D. 7·5) respectively.

DISCUSSION

Adrenaline given intravenously results in a breakdown of liver glycogen to glucose with a rise in blood-sugar values. There is also glycogenolysis in muscle with lactacidaemia. If adrenaline produces a direct effect on muscle glycogen, infusion into an artery should result in a very conspicuous fall in the muscle glycogen of the related limb with a subsequent rise in blood-lactic-acid values. However, the present experiments show that intra-arterial adrenaline does not result in any significant change in the glycogen content of the muscle of the limb infused. Moreover, the lactic-acid content of the venous blood from that limb is not increased. These observations suggest that adrenaline does not have a direct effect on muscle glycogen. Adrenaline is destroyed by tissues very rapidly and remains for only a short time in the blood stream (Weinstein & Manning, 1937; Richter & Tingey, 1939). If given into an artery it is probably

inactivated in the limb tissues and, provided the dose is not excessive, general effects should be minimal. This is borne out by the present results. Intra-arterial adrenaline produced little rise in the systemic blood sugar and in those cases in which a slight increase was noted it was delayed 20–30 min. after starting the infusion.

We have found no other experiments reported that bear directly on this point. Griffith, Lockwood & Loomis (1946), studying the effects of intra-arterial adrenaline on sugar retention by the leg tissues of anaesthetized cats, found that doses which cause vasodilatation may cause a twofold increase in lactate output. This implies an increased breakdown of muscle glycogen. However, muscle glycogen was not estimated. This data on lactate output was considered inconclusive, but the trend was in agreement with the findings of Cori *et al.* (1935). The findings of Cori and his collaborators are based on experiments with intravenous adrenaline. In a subsequent paper, Griffith, Omachi, Lockwood & Loomis (1947) found much higher lactate output using intravenous adrenaline. Borysiewicz (1930) injected adrenaline into the femoral artery of dogs and found a normal glycaemic response but no change in blood pressure. Baudouin, Bénard, Lewin & Sallet (1936), also in dogs, using the infusion technique, report that to produce the same glycaemic effect by intra-femoral arterial injection, twice to four times the intravenous dose is necessary. In neither of these papers were the blood-lactic acid and muscle-glycogen values recorded. A dose of adrenaline comparable with that used in the present work infused into the aorta of rats resulted in a fall in the glycogen content of the related muscle and a rise in blood-lactic acid (Sherlock, 1949). None of the above observations is readily comparable with the results of the present study—the species used, the type of anaesthesia and the technique of administration being very different.

Adrenaline is known to stimulate the anterior pituitary to release adreno-corticotropic hormone (Long, 1947). It might be postulated that the changes in muscle occurred secondarily to pituitary stimulation. However, adrenaline given intravenously to hypophysectomized animals produces all its usual effects on carbohydrate metabolism (Russell & Cori, 1937), so this does not seem to be the case. The mechanism by which adrenaline causes muscle glycogenolysis in man is still obscure.

Allen *et al.* (1946) injected half our dose of adrenaline intra-arterially into normal man during 5 or 24 min. Conspicuous changes occurred in muscle-blood flow in the limb infused but without significant change in heart rate or general blood pressure. The effect on muscle-blood flow in anaesthetized cats varies with the dose (Griffith *et al.* 1946; Griffith *et al.* 1947); small doses produce vasodilatation and larger doses vasoconstriction. In the present experiments, although the intra-arterial adrenaline did not disturb muscle glycogen there was pallor of the skin of the limb perfused. This indicates constriction of skin

vessels. Again there was no change in heart rate or blood pressure. Adrenaline therefore does appear to act directly on blood vessels, constricting those of the skin and dilating those of the muscle.

SUMMARY

1. Adrenaline was infused into the femoral arteries of ten normal men in an average dose of 0·088 μg./kg. body wt./min. Measurements of general blood pressure and pulse rate, skin colour, blood-sugar, blood-lactic acid serum potassium and muscle glycogen were made.

2. Blood pressure and pulse rate showed only trivial changes. Pallor of the skin of the infused limb was produced and this remained throughout the period of infusion.

3. Blood-sugar, blood-lactic acid and serum potassium showed no significant change either in a systemic vein or in the femoral vein of the limb perfused.

4. The muscle glycogen content of the gastrocnemius of the limb perfused did not change.

5. Adrenaline introduced intra-arterially in man apparently has no direct glycogenolytic effect on muscle. It is probably rapidly destroyed or changed in the limb tissues and produces no general effects on carbohydrate metabolism.

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APPENDIX

	Case	Age	Wt. (kg.)	Diagnosis
1.	E.N.	34	50	Bronchial asthma
2.	J.C.	69	60	Chronic bronchitis
3.	W.C.	54	47	Convalescent bronchopneumonia
4.	H.B.	58	64	Convalescent gastric ulcer
5.	A.T.	67	55	Convalescent gastric ulcer
6.	W.P.	63	54	Amytrophic lateral sclerosis
7.	J.G.	49	65	Convalescent duodenal ulcer
8.	J.H.	59	50	Convalescent gastric ulcer
9.	G.P.	50	58	Gastric ulcer and eczema of hands
10.	F.P.	27	55	Duodenal ulcer
11.	G.S.	67	67	Convalescent duodenal ulcer
12.	J.C.	46	58	Convalescent duodenal ulcer

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