THE ORIGIN OF THE GLUCOSE IN THE HYPERGLYCÆMIA INDUCED BY PITUITRIN.

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The injection of extracts of the posterior lobe of the pituitary either intravenously or subcutaneously into a normal animal produces usually an increase in blood-sugar which may last from one to two hours or, in some cases, longer, depending on dosage, and the type and condition of animal; occasionally the hyperglycæmia is negligible and in a few instances the blood-sugar has been found to fall (1, 2). While it is accepted that the usual action of pituitrin[1] is to produce hyperglycæmia, there is no satisfactory evidence to show how the effect is brought about. Moehlig and Ainslie (3), however, have suggested that the source of the additional sugar is the muscle glycogen, which they believe may be liberated in an indirect manner by the action of pituitrin on the suprarenals. If pituitrin can set free glycogen from the muscles in this way, it appeared that the decerebrated, eviscerated animal was a suitable preparation in which to investigate the problem.

The preparations were made from cats according to the method described by Burn and Dale (4) and the continuous glucose infusion apparatus of these authors was used to maintain as nearly as possible a constant blood-sugar level prior to the injection of pituitrin; glucose infusion was continued throughout the experiment at the same rate. The concentration of the solution was 1·5 p.c. and the rate of infusion required varied in different animals from 1 c.c. in 2·9 mins. to 1 c.c. in 4 mins. The temperature of the preparation was maintained by means of an electrically heated table, hot water bottles and suitable felt wrappings which formed a tent over the animal and contained a warming bulb. Blood for sugar estimations was withdrawn from one femoral vein and pituitrin injections were made into the femoral vein of the opposite limb. The dose of pituitrin was in every case 1 c.c.

[1] The pituitrin used and referred to throughout the paper is the preparation issued under that name by Parke, Davis and Co.

From Table I it is seen that in no experiment was the sugar level raised by pituitrin but, on the contrary, a very definite fall was produced. This fall was not evident till the second half-hour in some cases while in others it was apparent during the first half-hour after pituitrin. Control experiments in which no pituitrin was given showed no such abrupt changes in sugar level over the same period of time (Exps. 7 and 8).

TABLE I.

		Before pituitrin			After pituitrin		
Exp.	Hours ...	1	½	0	½	1	1½
1		·330	·320	·310	·266	·231	—
2		·242	·238	·230	·219	·206	·194
3		·294	·291	·288	·288	·259	—
4		·250	·253	·254	·250	·206	·197
5		·204	·210	·218	·223	·210	·200
6		·418	·419	·426	·412	·346	·325
7 (control)		·326	·321	·314	·311	·305	·296
8 (control)		·262	·265	·265	·267	·264	·270

In every case except Exp. 5 the suprarenals and their blood-supply were left intact; in Exp. 5 the glands were excluded from the circulation by a pedicle ligature, without in any way altering the subsequent response to pituitrin. The sudden increase in the rate of fall of glucose concentration in this series of experiments may be explained by (*a*) dilution of the blood, (*b*) increased oxidation of glucose, or (*c*) building up or decreased breaking down of muscle glycogen.

In support of the first of these possible explanations there are the observations of Craig(5) on human beings and of Underhill and Pack(6) on dogs that the administration of pituitary extract in conjunction with the exhibition of large quantities of water does cause a diminution in hæmoglobin content of the blood, while Partos and Katz-Klein(7) obtained a definite dilution of the blood in rabbits as a result of the injection of pituitary extract and showed that this dilution may mask the hyperglycæmia usually seen in the intact animal. In the present series of experiments the hæmoglobin content of the blood was determined at intervals before and after pituitrin in three preparations and in two of them blood-sugar estimations were made at the same time. The results are shown in Table II.

It is obvious that in Exp. 4 blood dilution cannot account for the observed fall in blood-sugar and that in Exp. 9 the 5 p.c. dilution following the injection of pituitrin would be insufficient to account for the fall of sugar concentration in any of the experiments in Table I. In Exp. 6 where the concentrations of both sugar and hæmoglobin are seen to fall after the dose of pituitrin it is necessary to examine the changes

TABLE II.

Exp.	Hours ...	Before pituitrin 1	½	0	After pituitrin ½	1	1½
4	Hæmogl. p.c.	68	70	69	68	67	64
	Glucose	·250	·253	·254	·250	·206	·197
6	Hæmogl. p.c.	88	87	85	82	75	73
	Glucose	·418	·419	·426	·412	·346	·325
9	Hæmogl. p.c.	—	60	57	56	54	54
	Glucose	—	—	—	—	—	—

more closely. If curves are drawn to show the percentage change in the initial concentrations throughout the experiment (Fig. 1) it is seen that before pituitrin was injected the sugar concentration was rising slightly and the hæmoglobin falling, both changes clearly the result of the infusion of sugar solution. After pituitrin had been injected the sugar concentration fell more rapidly than that of the hæmoglobin[1]. It is difficult to see how dilution of the blood by tissue fluid could account for this. The fluid in the tissue spaces would contain no hæmoglobin, but at any rate some sugar, an amount of sugar, in fact, determined by the amount in the blood. Unless, therefore, the capillaries can take up

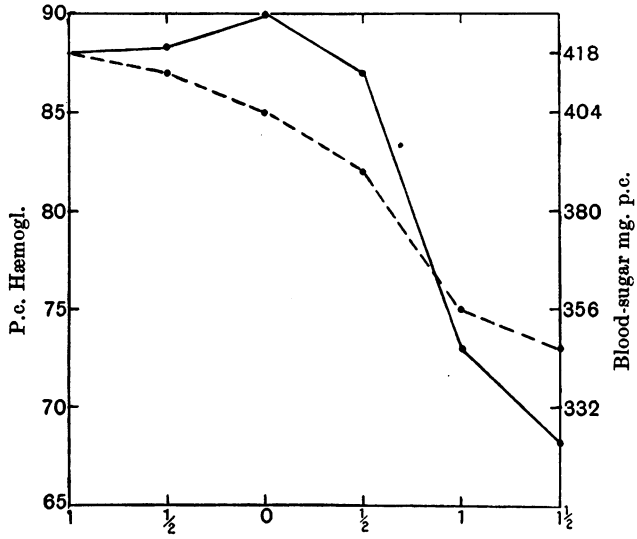

Fig. 1.

fluid from the tissue spaces in such a way as to exclude the sugar which that fluid contains, a supposition for which no evidence exists and which

[1] I am indebted to Mr A. Spencer for carrying out hæmoglobin estimations.

it is very difficult to allow, the dilution of the blood by tissue fluid must lower the concentration of hæmoglobin more than that of the sugar. The figures in this experiment and the curves in Fig. 1 show that, on the contrary, the concentration of sugar after pituitrin even in this experiment is lowered more than that of the hæmoglobin. The fall of blood-sugar therefore cannot be accounted for by blood dilution. Whatever be the cause of the disappearance of glucose from the blood in eviscerated animals following the injection of pituitrin, it is obvious that the muscles are not the source of the additional sugar in pituitrin hyperglycæmia. Whether pituitrin has any specific action on carbohydrate metabolism in muscle is not known, but the experiments of Ahlgren(8) suggest the possibility. Using Thunberg's methylene blue method for measuring tissue oxidation, he showed that some samples of hypophyseal extract definitely increased the oxidation processes in muscle; with other samples he found a decrease.

The results so far described are of interest in view of the findings of Tingle and Imrie(9) that pituitrin temporarily lowers the blood-sugar in diabetics. Moreover, in two of the cases reported by these authors there is a further similarity in that the fall was not evident till the second half-hour.

Further confirmation of the view that pituitrin cannot liberate glucose from the muscles was obtained in three experiments on the decerebrated and eviscerated cat in an attempt to demonstrate the antagonism between pituitrin and insulin. 1 c.c. of pituitrin was injected intravenously half an hour after the administration of 7 clinical units of insulin. It is evident from Table III that in no case is the rate of fall of blood-sugar retarded by the pituitrin.

TABLE III.

		Before insulin			After insulin		
Exp.	Hours ...	1	½	0	½	1	1½
10		·213	·204	·196	·174	·133	·109
11		·275	·284	·292	·254	·222	·204
12		·305	·321	·341	·274	·248	—

The abrupt rise in sugar level following the injection of pituitrin in the normal animal suggests a sudden glycogenolysis rather than a temporary suppression of the normal rate of utilisation of glucose. It was natural therefore to consider the liver as the possible seat of action. For this investigation cats under amytal anæsthesia were used, the liver was excluded from the circulation by anastomosing the portal vein with the

central end of one renal vein, in one experiment by means of a suitably shaped paraffined glass cannula and in two others by glass cannulæ connected by tubing after injecting hirudin intravenously[1]. All other structures in the hepatic pedicle were cut between ligatures. In all three cases the animals lived for two hours after operation. The blood-sugar of the cat without hirudin was high and fell rapidly, that of the two where hirudin had been given was low and fell less rapidly. The rate of fall was determined in the latter by two, and in the former by three estimations at intervals of half an hour. 1 c.c. pituitrin was then injected intravenously and sugar estimations continued. In no case was any great change in the rate of fall of blood-sugar produced (Table IV), although in Exp. 13 the rate appeared to be accelerated.

TABLE IV.

		Before pituitrin			After pituitrin	
Exp.	Hours ...	1	½	0	½	1
13		·245	·222	·181	·127	·103
14		—	·108	·097	·078	·063
15		—	·104	·080	·065	·041

Although the short duration of these experiments was unsatisfactory it appeared that the production of pituitrin hyperglycæmia was not possible in the absence of the liver, and the two following experiments suggest that the degree of hyperglycæmia is governed by the amount of available glycogen in this organ. The normal response of a rabbit on a full diet to 1 c.c. pituitrin was determined (Exp. A) and then the animal's diet was reduced and repeated injections of strychnine given over a period of three days, when the reaction of the blood-sugar to the same dose of pituitrin was investigated (Exp. B). In the second case a less degree of hyperglycæmia was found.

Exp.	Hours ...	0	½	1	1½	2	2½	3
A		·101	·161	·141	··113	·109	·103	—
B		·109	·135	·103	·117	·113	·107	·106

The question of how pituitrin liberates liver glycogen has not so far been capable of definite answer, but it is apparent that the sympathetic nervous system plays no important part in the action because, in several experiments in rabbits which had previously received a dose of ergotamine tartrate sufficient to prevent adrenaline hyperglycæmia, pituitrin still produced an increase in blood-sugar comparable in degree to that

[1] I am indebted to Dr Trevan for a supply of hirudin.

produced in the absence of ergotamine (10). Moreover, in Table V are given the hyperglycæmic responses to pituitrin in cats, under amytal anæsthesia, after operative procedures which eliminate sympathetic action on the liver. In Exp. 17 both suprarenal glands were removed by incising the peritoneum, raising the glands and tying a ligature round the pedicle prior to injecting pituitrin. The same operation was done in Exp. 18, but in addition all nervous connections of the liver in the hepatic pedicle were cut. In both cases pituitrin produced hyperglycæmia greater, rather than less, than that observed in a control animal (Exp. 16). Exp. 19 shows the response to pituitrin in a cat under amytal in which the hepatic artery was tied, and here again the effect is not diminished.

TABLE V.

Exp.	Hours ...	0	½	1	1½	2	2½	3
16		·100	·176	·135	·098	·090	·091	—
17		·125	·165	·176	·122	·084	·074	·083
18		·113	·182	·140	·107	·103	·093	—
19		·118	·202	·159	·142	·111	·092	—

It thus appears that, although pituitrin acts on the liver glycogen reserves, its action does not depend on the sympathetic nervous system either directly or indirectly by way of the suprarenals; nor is the blood-supply from the hepatic artery an important factor. It may be, then, that pituitrin exerts its effect either (1) directly on the liver cells, (2) indirectly by the production of some substance which is carried to the liver in the portal blood, or (3) by so altering the blood-supply to the liver that glycogenolysis is temporarily increased. An investigation of these alternatives will form the subject of a further paper.

SUMMARY.

1. The intravenous injection of pituitrin into decapitated, eviscerated cats increases the rate of disappearance of sugar from the blood. The antagonism between insulin and pituitrin is not evident.

2. In cats under amytal anæsthesia, in which the liver is cut out of the circulation, pituitrin does not produce the hyperglycæmia seen in normal animals, nor does it diminish the rate of fall of blood-sugar.

3. From these observations it appears that the source of glucose in pituitrin hyperglycæmia is the liver glycogen.

4. Experiments are described which appear to exclude (*a*) the sympathetic nerve-supply to the liver, (*b*) the suprarenal glands, (*c*) the blood-supply to the liver by way of the hepatic artery, as intermediary factors in the production of pituitrin hyperglycæmia.

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