DIABETOGENIC ACTION OF PITUITARY HORMONES ON ADRENALECTOMIZED HYPOPHYSECTOMIZED DOGS

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THE diabetogenic action of the anterior pituitary extracts was demonstrated in hypophysectomized-pancreatectomized toads by Houssay and Biasotti (1). This action was not obtained in pancreatectomized cats and rats in the absence of adrenals (2, 3). But the diabetogenic action of the anterior pituitary extract was obtained in other adrenalectomized animals: a) toads deprived of adrenals and pancreas (4); b) toads deprived of hypophysis, pancreas, kidney and adrenals (5): c) toads deprived of hypophysis, pancreas and adrenals (4, 6); in cases *b* and *c*, the diabetogenic action was diminished by the absence of the adrenals. The diabetogenic action of the pituitary was also observed in mammals deprived of the adrenals such as: d) dogs with reduction of the pancreatic mass, deprived of both adrenals and maintained with cortico-adrenal extract (7, 8) or with desoxycorticosterone (8); e) dogs with reduction of the pancreatic mass, deprived of the adrenals, maintained only with sodium chloride and not receiving adrenal hormones (8); some of these dogs were also deprived of the thyroid. All these experiments demonstrated that hypophyseal diabetes may be obtained without the presence or participation of the adrenals. In dogs deprived of pancreas and adrenals, somatotrophin administration increased the resistance to insulin and produced glucose tolerance curves of diabetic types (9, 10). Somatotrophin also increase the resistance to insulin in adrenalectomized dogs (11).

Prolactin had a diabetogenic effect: a) in hypophysectomized-pancreatectomized toads (12, 13); b) in dogs (13, 14, 15); and cats (13, 14) with large reduction of the pancreatic mass. This hormone had also a certain anti-insulinic effect in dogs deprived of hypophysis and adrenals (9, 10, 16).

The present paper reports that the diabetogenic effect of somatotrophin, prolactin, adrenocorticotrophin and hydrocortisone was found in dogs with pancreas reduced to 15–18% of its mass, deprived of hypophysis and adrenals and maintained only with sodium chloride.

PLAN AND METHODS

Experiments were carried out in dogs deprived in the first operation of 82 to 85% of the pancreatic mass, in the second operation of the right adrenal, in the third of the hypophysis and, finally, in the fourth of the left adrenal.

Received June 16, 1956.

They received at different times subcutaneous injections of growth hormone (Wilson, lot 95567), prolactin (Bates, sample 71713) and adrenocorticotrophin (Armour, 146RS3, potency 3.65 the standard) at the doses indicated in the table, in 1 ml. of 0.8% Na Cl solution, during 4 to 5 days. Glycemia was determined daily according to the Somogyi-Nelson technique collecting blood from cuts on the ear edge, after 16 hours of fasting. The diabetic response was considered positive when the fasting blood glucose level, after the injection rose from the normal level to 150 mg. per 100 ml. of blood. The next assay was carried out at least 8 days after glycemia had returned to normal. These dogs were also injected subcutaneously with cortisol.

The animals were fed fresh or cooked meat (250 to 300 g./day). After hypophysectomy and after the second adrenalectomy they received: the first three days, a daily dose of 1 mg. of desoxycorticosterone acetate. Cortisone acetate was also injected: 2 mg. twice a day during two days, 1 mg. twice a day during the following three days and then it was discontinued. After the second ardenalectomy, they were given the first days 200 ml. of saline solution twice a day and later on, the only treatment was sodium chloride (4 to 5 g./day) given mixed with boiled beef meat. These animals required a constant care in order to maintain them in good conditions.

When the animals became asthenic or depressed (most of the time with hypoglycemia) or when they lay on the floor, walking only with great difficulty, they were given 0.5 mg./kg. of cortisone acetate, during 2 days. With this treatment they recovered strength and the blood sugar level (48–60 mg./100 ml.) returned to normal.

RESULTS

The dates on which the 3 dogs were operated as well as the time of study are represented in Table 1. Dog 66 was a female and Dogs 77 and 78 were males.

General symptoms.—The animals with pancreatic mass reduced and deprived of the right adrenal, gained weight rapidly after hypophysectomy and showed a big appetite; in two months, the body weight increased in Dog 66 from 6 kg. to 9.5 kg. (+3.5); Dog 77 from 6 to 7.2 kg. (+1.2) and Dog 78 from 8.9 to 10.3 (+1.4); adiposity was remarkable.

In general, they walked and moved slowly, specially Dog 66. Dogs 77 and 78 barked in the presence of persons unknown to them or when seeing cats. Dog 66 was the most excited in the last case. Weakness of the posterior legs was often observed and sometimes Dog 66 was unable to climb a staircase. She was extremely tame and docile.

Table 2 shows the initial glycemia and the highest level reached during the 4 to 5 days of treatment. It can be observed that somatotrophin (1 mg./kg./day) produced a diabetic response in the 3 dogs deprived of hypophysis, adrenals and a large part of the pancreas.

Prolactin administration of 1 mg./kg./day, also produced a diabetic response in Dogs 66 and 77 and in doses of 2–10 mg./kg./day in dog 78. Adrenocorticotrophin had no diabetogenic effect in these adrenalectomized dogs at doses which were active in Dog 66 and others before being deprived of the adrenals.

Hydrocortisone was active in these dogs deprived of the hypophysis and the adrenals and with large partial pancreatectomy, provoking a

TABLE 1. DATES OF OPERATION, AMOUNT OF PANCREAS REMOVED AND DURATION OF OBSERVATION

No. of dog	Pancreas removed %	Pancrea-tectomy	Removal of right adrenal	Hypophy-sectomy	Removal of left adrenal	Duration of obser-vation, days
66	82	29 April	18 Dec.	28 Nov.	7 March	375
77	85	13 Oct.	7 Dec.	15 Dec.	22 Feb.	180
78	85	13 Oct.	6 Dec.	14 Dec.	29 March	201

rise in the blood sugar level from 110 to 190 mg./100 ml. in Dog 66; from 98 to 185 mg./100 ml. in Dog 77 and from 76 to 170 mg./100 ml. in Dog 78.

The effect of 5 mg. of Prolactin was reinforced by the addition of 2 mg. of adrenocorticotrophin given to Dog 66 before removing hypophysis and adrenals, as glycemia rose from 89 to 209 mg./100 ml. No change was observed with the separate administration of these substances.

Although the diabetes was, in most cases, of the temporary type, there were cases of 9 and 11 days duration, after 4 days of treatment in Dog 66, before and after removing the adrenals and the hypophysis. Dog 77 showed permanent diabetes after receiving 2 mg./kg./day of hydrocortisone during

TABLE 2. DIABETOGENIC ACTION OF PITUITARY HORMONES IN DOGS WITH PARTIAL PANCREATECTOMY (PART. PANC.), HYPOPHYSECTOMIZED (HYP.), DEPRIVED OF THE RIGHT ADRENAL (UNIL. ADR.) OR BOTH ADRENALS (BIL. ADR.). INITIAL AND MAXIMAL GLYCEMIA DUE TO DAILY ADMINISTRATION OF HORMONES DURING 4 TO 5 DAYS

Dog	Somatotrophin		Prolactin		Adrenocorticotrophin	
	Mg./kg./ day	Gly-cemia	Mg./kg./ day	Gly-cemia	Mg./kg./ day	Gly-cemia
Female No. 66						
Part. panc., 82%	1	100–257	2	84–125	2	82–102
	1	75–211	5	95–107	3	80–152
			10	90–153		
Part. panc., Hyp.	1	76–116	—	—	—	—
Unil. adr.	2	95–335	—	—	—	—
Part. panc., Hyp.,						
Bil. adr.	1	86–200	1	92–268	3	92–75
			5	104–195	—	—
Male No. 77						
Part. panc.	1	94–104	—	—	—	—
	2	95–165	—	—	—	—
Part. panc., Hyp.,						
Bil. adr.	1	102–248	1	92–166	3	83–88
Male No. 78						
Part. panc.	1	91–203	—	—	—	—
Part. panc., Hyp.,						
Bil. adr.	1	92–206	1	84–115	3	67–79
	—	—	2	89–250	—	—
	—	—	10	81–260	—	—

4 days. In the other cases, glycemia returned to normal levels one to three days after discontinuing the treatments.

DISCUSSION

Adrenalectomized-hypophysectomized dogs can survive a long time when fed meat and sodium chloride.

It was demonstrated once more, that the adrenals and their hormones are not essential for the production of the diabetogenic effect of somatotrophin and prolactin. Thus diabetes was obtained in dogs deprived of adrenals and hypophysis, with pancreas previously reduced to 15–18% of its mass. This diminution of the pancreatic mass made the animals markedly sensitive to the mentioned hormones, thus allowing diabetes to develop using lower and nontoxic doses.

Former investigations on pancreatectomized-hypophysectomized toads, demonstrated that the diabetogenic action of the hypophysis was less intense in those animals deprived of the adrenals. Reciprocally the diabetogenic action of somatotrophin was increased in the dog by corticoid administration (17).

Somatotrophin was more active than prolactin, as in the previous experiments. The prolactin used did not contain somatotrophin (no increase of body weight after injection in hypophysectomized rats, 10 mg. in 10 days). The action of somatotrophin and prolactin may be an intrinsic property of the hormones themselves or of any component or impurity not essential for their specific effect. Their action is not due to adrenocorticotrophin as these hormones had diabetogenic cation and adrenocorticotrophin had no diabetogenic action in the dogs studied deprived of adrenals and hypophysis.

The marked adiposity observed in the dogs deprived of a large part of the pancreas, hypophysis and one adrenal was associated with hyperphagia. The possible metabolic changes were not studied. This adiposity decreased during the periods of hyperglycemia or diabetes.

Quietness and a tendency to sit or lie on the floor was evident in these animals. The slow movements of the posterior legs seem to be due to asthenia or muscular weakness, but no signs of articular alterations were observed.

These dogs maintained their normal behavior such as barking in the presence of unknown people or cats.

CONCLUSION

The pituitary hormones, somatotrophin and prolactin, had a diabetogenic effect in dogs deprived of hypophysis and adrenals and with pancreas surgically reduced to 15–18% of its mass. These facts demonstrate that the hypophysis and the adrenals are not essential for the production of the diabetogenic effect of these hormones.

Adrenocorticotrophin had no action on the glycemia of these adrenalectomized dogs.

Some of the animals showed moderate symptoms of asthenia in others these were marked. The animals recovered rapidly when injected with cortisone or hydrocortisone.

Hydrocortisone, at a dose of 3 mg./kg./day, produced in a short time, a diabetic hyperglycemia.

The dogs with reduced pancreas and deprived of one adrenal and the hypophysis developed a marked adiposity.

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