NOTES AND COMMENTS

DIABETOGENIC ACTION OF DIFFERENT PREPARATIONS OF GROWTH HORMONE[1]

The diabetogenic action of the anterior pituitary growth hormone in dogs and cats which had been subjected to subtotal pancreatectomy was observed by Houssay and Anderson (1949 a and b). The dogs received growth hormone in dosages of 50 mg/kg/day and the cats, 25 mg/kg/day. The purpose of that study was to find out the diabetogenic action, if any, of somatotrophin, adrenocorticotrophin and prolactin. The minimal effective doses were not investigated.

In the present study, experiments were carried out a) to determine the minimal diabetogenic dose in subtotally depancreatized dogs, and b) to compare the diabetogenic action of three growth hormone preparations.[2]

METHODS

Twenty-five dogs with a subtotal pancreatectomy (77–87% of the original mass of the gland removed) were used. All showed a normoglycemia. Seven of these dogs subsequently underwent thyroidectomy 1–3 months after pancreatectomy whereas 3 dogs were thyroidectomized prior to the pancreatectomy.

Thyroidectomized dogs were used to eliminate any possible diabetogenic action of the thyroid hormone following stimulation of the thyroid gland by the TSH content in the growth hormone preparations.

The hormones were administered subcutaneously, in 1–2 ml. saline, for 4–5 days. If the postabsorptive blood sugar (18–20 hours fasted) exceeded 150 mg%, the diabetogenic action was considered positive. Most frequently the blood sugar level rose above 200 mg%, and in some cases to 300 mg%. After discontinuation of the growth hormone administration, no animal was used until a 7–10 day period of normoglycemia was observed. Only then did the dogs receive another regimen of a different growth hormone preparation.

RESULTS

Before pancreatectomy, the growth hormone did not produce diabetes when administered in dosages of 1 mg/kg/day for 4 days. When given in dosages of 5 mg/kg/day again during a 4 day period, the growth hormone produced an intense diabetic response in 25% of the dogs.

After subtotal pancreatectomy, the dogs became more sensitive to all three growth hormone preparations. Each dog received a constant dose of a growth hormone preparation which was administered subcutaneously daily for 4 days. After a period of 7–10 days, during which time the animal became normoglycemic, another dosage was tried. By this means, the animals were tested with 1.0 mg, 0.5 mg, 0.2 mg, 0.1 mg and 0.05

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[2] 1)Armour preparation GH3 prepared by the Wilhelmi-Fishman-Russell method, 2) Armour preparation PGH-163.208A prepared by the Raben-Astwood technique, and 3) a growth hormone preparation kindly supplied by Dr. M. Raben himself. The Armour preparations were supplied by Dr. Irby Bunding.

mg/kg. until the non-diabetogenic doses were found. Sometimes the smallest diabetogenic dose was used again.

The diabetogenic actions obtained with different doses of Wilhelmi-Fishman-Russell (Armour) and Raben (Armour) preparations are summarized in Table 1. The diabetogenic action of these two growth hormone preparations was observed in subtotally depancreatized dogs, whether or not the thyroid gland had been removed.

The preparations supplied by Dr. M. Raben produced diabetic responses in five dogs with subtotal pancreatectomy. The minimal effective doses varied between 0.2–1.0 mg/kg/day when administered for 4 days, according to the sensitivity of the animals.

In the most sensitive subtotally depancreatized dogs, the minimal effective dose was 0.05 mg/kg/day, but 0.01 mg/kg/day had no diabetogenic effect.

The growth promoting action of these preparations was compared by daily subcutaneous injection in hypophysectomized rats (3 lots of 10 animals). The untreated rats

TABLE 1. DIABETOGENIC EFFECTS OF VARIOUS DOSAGE REGIMENS OF GROWTH HORMONE (WILHELMI-FISHMAN-RUSSELL, ARMOUR) COMPARED WITH THE EFFECTS OF COMPARABLE DOSAGES OF GROWTH HORMONE (RABEN-ASTWOOD, ARMOUR)

Dose of hormone	Subtotally depancreatized dogs		Subtotally depancreatized-thyroidectomized dogs	
mg./kg./day for 4 days	Wilhelmi-Fishman-Russell prep. (Armour lot No. GH3)	Raben-Astwood prep. (Armour No. PGH-163.208A)	Wilhelmi-Fishman-Russell prep. (Armour lot No. GH3)	Raben Astwood prep. (Armour No. PGH-163.208A)
0.05	*4/8†	—	2/3	—
0.20	5/10	2/4	2/4	2/4
1.00	9/11	3/5	5/6	3/6
5.00	—	3/3	—	3/3

* Figures in numerators of the fractions indicate number of dogs that showed fasting blood sugar levels above 150 mg%, i.e., a positive diabetogenic response.

† Figures in denominators represent the total number of dogs given the specific dosage of growth hormone indicated in the first column.

lost 7 gm/100 gm of body weight during a 7 day control period. The growth hormone preparation prepared by the Wilhelmi-Fishman-Russell method produced a weight increase of 16 gm/100 gm of body weight when administered subcutaneously daily for 7 days to the hypophysectomized rats in dosages of 1 mg/day. With the same dosages and duration of administration, the Raben preparation (Armour No. PGH-163.208A) produced a weight increase of 9 gm per 100 gm of body weight. The claim of Raben and Westermeyer, namely, that their preparation was growth promoting and not diabetogenic, could not be confirmed.

On many occasions, most of the dogs developed a transitory diabetes after growth hormone administration. Some dogs remained with a permanent diabetes after the last regimen lasting 4 days. This was true for 4 dogs given the Wilhelmi-Fishman-Russell preparation and 2 dogs given the Raben (Armour No. PGH-163.208A) preparation. In all the animals exhibiting permanent diabetes (for 18, 18, 29 and 29 days, respectively), an hydropic vacuolization of the β cells of the islets of Langerhans filled with glycogen was found constantly. In the animals sacrificed with normoglycemia, only a few β cells had vacuolization and they showed a slight to almost total degranulation.

CONCLUSIONS

1) Dogs became very sensitive to the diabetogenic action of three growth hormone

preparations following subtotal pancreatectomy (77–87% of the pancreatic mass resected).

2) Two preparations obtained by the Raben method also showed a definite diabetogenic action.

3) The Armour preparation of growth hormone obtained by the Wilhelmi-Fishman-Russell method had more growth promoting and more diabetogenic activity than the Armour preparation of growth hormone obtained by the Raben method.

4) The diabetogenic action of the growth hormone preparations was observed in the absence of the thyroid gland.

5) Both types of growth hormone preparations may produce permanent diabetes with hydropic degeneration (glycogen infiltration) of the β cells of the islets of Langerhans.

B. A. HOUSSAY AND R. R. RODRIGUEZ

Instituto de Biologia of Medicina Experimental
Costa Rica, 4185 Buenos Aires

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THE INFLUENCE OF DDD ON THE COURSE OF ALLOXAN DIABETES IN THE ADULT RAT[1,2,3]

INTRODUCTION

It has been established over the course of many years that the drug alloxan produces the symptoms of typical diabetes mellitus in the rat. Rats treated with this material rapidly develop high blood sugar, ketonuria, polyuria and rapid weight loss. Houssay, some twenty years ago, demonstrated that the symptoms of diabetes could be relieved by adrenalectomizing dogs suffering from the disease. It was postulated that this action removed an inhibition from the carbohydrate utilization system and permitted the animal to utilize glucose. This was substantiated when it was shown that injection of adrenal extract or anterior pituitary extract into the pancreatectomized-adrenalectomized dogs would produce a rapid return of the diabetes.

Nichols and Gardner (1951) demonstrated that animals fed DDD (2,2 bis-(parachlorophenyl)-1, 1-dichloroethane) developed adrenal cortical atrophy and became insulin sensitive. Nichols and Sheehan (1952) also demonstrated that dogs pretreated with DDD did not develop as severe hyperglycemia when alloxan was given intravenously as did controls.

Because Nichols, *et al.*, had investigated the action of DDD and alloxan over a period

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[3] DDD is 2, 2 bis(parachlorophenyl)-1,1-(dichloroethane).