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## DIABETOGENIC ACTION OF PURIFIED ANTERIOR PITUITARY HORMONES

This communication deals with the diabetogenic action of three of the anterior pituitary hormones, namely growth hormone, adrenocorticotrophic hormone (ACTH) and prolactin. Previous work has indicated that purified growth hormone is diabetogenic (Marx *et al.*, 1943; Houssay, 1945).

The growth hormone, which had been prepared by Armour and Co.[1] (lots #8KR32 and #3PKR3) exhibited a purity, as judged by the electrophoretic diagram, of approximately 84 per cent of a single component which had a mobility comparable to that of purified growth hormone. Assay of the material in a 60–70 gram hypophysectomized rat showed that a 50 gamma dose per day caused a body increment of 1.0 gram per day. The ACTH, which was also supplied by the Armour Laboratories (lot #45-A-4), had been prepared by a modification of the Sayers method. Biological assay on hypophysectomized rats, making use of the ascorbic acid depletion method of Sayers *et al.* (1948), showed a potency of 96 per cent. The amounts of contaminating hormones such as prolactin, growth, thyrotrophic and gonadotrophic hormones, were negligible. The preparation exhibited 0.4 units per mg. of posterior pituitary activity. The prolactin, which was supplied by E. R. Squibb and Sons[2] (lot #71713), showed a potency of 24.2 units per mg. The preparation did not contain an amount of growth hormone sufficient to increase the body weight of 4 hypophysectomized rats which were injected with 5 mg. daily (80 mg. total) over a period of 17 days; nor of 2 hypophysectomized rats which received 10 mg. daily (110 mg. total) for 11 days. It did contain ACTH since the average weight of the adrenal glands in the group which received the 80 mg. total dose was 28 mg.; the rats which received the 110 mg. amounts had 31 mg. adrenals, while the uninjected controls had 20 mg. adrenals. By the Sayers assay method this lot of prolactin was found to contain 10–30% ACTH. According to the rooster blood pressure method, 1 mg. of the preparation contained 0.008 international units of posterior pituitary activity. The gonadotrophic and thyrotrophic hormones were present in negligible amounts.

Partial pancreatectomy was performed on dogs, cats and rats. It has been found that a decrease in the mass of pancreatic tissue greatly increases the sensitivity of the diabetogenic action of the pituitary. In the dogs 83–87% of the pancreas was removed, in the cats 73–75%, and in the rats 95%. Batrachians were also used; in these the pancreas and the anterior pituitary were removed in their entirety. All of the mammals showed a

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[2] We wish to thank Dr. Robert Bates of E. R. Squibb and Sons for supplying us with the prolactin.

normal blood sugar before the injections were started. The dogs were given 50 mg. of hormone per kg. per day for 4 days, the cats 25 mg. per kg. per day for 3 days, and the rats 25 mg. per kg. per day for 3 days. These injections were made by the intra-peritoneal route. Fasting blood sugar determinations were made daily during this period. The batrachians received 1.0 mg. per day. The injection was given subcutaneously immediately after the anterior pituitary and the pancreas had been removed. The blood sugar was determined 24 hours later.

TABLE 1. DIABETOGENIC ACTION OF PURIFIED ANTERIOR PITUITARY HORMONES

| Animal No. | Highest fasting blood sugar during injection period* | | |
|---|---|---|---|
| | Growth hormone | Prolactin | ACTH |
| | mg. % | mg. % | mg. % |
| Dog #30 | 336 | 168 | 140 |
| Dog #2 | 296 | 147 | 86 |
| Dog #5 | 185 | 134 | 89 |
| Dog #10 | 90 | 133 | 84 |
| Cat #1 | 304 | 97 | |
| Cat #3 | 278 | 221 | |
| Cat #6 | | 203 | |
| Cat #7 | | 167 | |
| Cat #9 | | 221 | |
| Rat #1204 | 158 | | |
| Rat #1206 | 134 | | |
| *Rana pipiens* | | | |
| Injected (av. 10) | 144 | 70 | 163 |
| Control (av. 10) | 78 | | |
| *Bufo arenarum* | | | |
| Injected (av. 30) | 130 | 108 | 121 |
| Control (av. 30) | 81 | | |

* Fasting blood sugar before injections was normal in every case.

The results of this study are shown in Table 1. The growth hormone produced hyperglycemia, glycosuria and polyuria in 3 of the 4 dogs, in both of the cats so treated, and in all 40 batrachians used.

In dog #30 a permanent diabetes developed as a result of the injections. In addition to the 3 courses of injections as indicated in Table 1, on 3/30/49 and 3/31/49 the injections of growth hormone were repeated. On 4/1/49 its fasting blood sugar was 336 mg.% and from then on until it was sacrificed (9/1/49) its fasting blood sugar averaged 200 mg.%. Clinical evidence of diabetes was apparent. Body weight fell from 20 lbs. at the time of the first injections (2/12/40) to 12 lbs., when the animal was sacrificed. A glucose tolerance test on 8/17/49 in which 50 cc. of 20% glucose were administered orally showed the following: fasting blood sugar, 361 mg.%; ½ hour, 432 mg.%; 1 hour, 576 mg.%; 2 hour, 440 mg.%; 3 hour, 348 mg.%; 4 hour, 327 mg.%; 5 hour, 328 mg.%. During the last month 8 units of protamine zinc insulin were given daily.

Prolactin produced an elevated fasting blood sugar in all 4 dogs injected, in 4 of the 5 cats, and in 60% of the batrachians. In the dogs and cats there was glycosuria and polyuria in addition to the high blood sugar.

ACTH produced hyperglycemia in only one dog of the 4 injected, and in 83 per cent of the batrachians. The experiments with dogs had to be interrupted because of insufficient ACTH.

The diabetogenic action of prolactin could be due to the ACTH since this preparation contained 10–30 per cent of ACTH. But the prolactin effect was more intense than that of the purified ACTH, which had a potency of 96 per cent. It is possible that the hyperglycemic action of the prolactin could be due to a potentiation of ACTH action by prolactin. Another interpretation may be that the effect of the two hormones was additive. The possibility that another diabetogenic agent was present in the prolactin preparation could not be ruled out.

## CONCLUSIONS

These experiments indicate that the growth hormone has a diabetogenic action on dogs, cats and batrachians.

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