

Effect of Insulin on Partially Hypophysectomized Rats.

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Although much work has been done on the relation of the pituitary gland to the glucose regulatory system, the exact nature of the reaction is not yet clear. Early experiments showed an increased insulin sensitivity in hypophysectomized animals.^{1, 9, 5} This has been assumed to indicate the complete ablation of the hypophysis.⁷ Posterior lobe extracts have been shown to diminish or abolish this sensitivity and to neutralize the toxic effect of hypoglycemia.^{1, 8} Some workers have shown that the nature of the antagonism of posterior lobe extract to insulin-glucose mechanism is related to the peripheral utilization of blood glucose,² while others have sought to explain this antagonism, existing in over-activity of the pituitary, by changes in general carbohydrate metabolism within the animal organism.⁶

Sex hormone extract from the anterior lobe of the hypophysis has produced an increased blood glucose, while the growth hormone has been shown to produce little effect.³ Other investigators could demonstrate little or no effect of anterior lobe products on this insulin-glucose mechanism.⁸

Hypophysectomy has been believed to disturb the regulatory mechanism which tends to preserve glycogen during fasting.⁴ An accessory pancreatic factor has been postulated, since the complete ablation of the hypophysis in depancreatized dogs enables them to utilize carbohydrate.⁸ The magnitude of fall in blood glucose values after insulin has been shown to be increased from 14% to

¹ Burn, J. H., *J. Physiol.*, 1923, **57**, 318.

² Cohen, H., and Libman, B., *Quart. J. Med.*, 1937, **6**, 157.

³ Eidelsberg, J., *Proc. Soc. Exp. Biol. and Med.*, 1932, **29**, 959.

⁴ Fisher, R. E., and Pencharz, R. I., *Proc. Soc. Exp. Biol. and Med.*, 1936, **34**, 106.

⁵ Geiling, E. M. K., Campbell, D., and Ishikawa, Y., *J. Pharm. and Exp. Therap.*, 1927, **31**, 247.

⁶ Goetsch, E., Cushing, H., and Jacobson, C., *Bull. Johns Hopkins Hosp.*, 1911, **22**, 165.

⁷ Hartman, C., Firor, W. M., and Geiling, E. M. K., *Am. J. Physiol.*, 1930, **95**, 662.

⁸ Houssay, B. A., and Biasotti, A., *Endocrinology*, 1931, **15**, 511.

⁹ Houssay, B. A., and Magenta, M. A., *Compt. Rend. Soc. Biol.*, 1925, **92**, 822.

35% by complete hypophysectomy in monkeys, while incomplete hypophysectomy produced an almost insignificant change from normal.¹²

Experimental investigation in glandular physiology has been done largely on completely hypophysectomized animals. Therefore, it seemed desirable in this investigation to study the nature of insulin sensitivity of albino rats partially hypophysectomized.

Hypophysectomies were done according to a modification of Smith's¹¹ technic and blood sugars were determined by Miller-Van Slyke's¹⁰ microtitration procedure. The 47 strong, active rats used were allowed at least 2 weeks to recover from the hypophysectomy. Obviously, a standard dose of insulin was required to produce an appreciable hypoglycemia but not shock or convulsions. This, determined experimentally, was found to be $\frac{1}{4}$ clinical unit per 125 g body weight for normals, and $\frac{1}{16}$ clinical unit per 125 g body weight for hypophysectomized rats. A 0.2 cc blood sample was taken immediately before insulin injection and every 30 minutes afterwards for 2 hours, then at hourly intervals for the third and fourth hours, when the animals were sacrificed and autopsied immediately to determine the degree of completeness of the hypophysectomy. In doubtful cases the sella was sectioned serially and studied for pituitary fragments. Twenty-two animals showed complete hypophysectomy, and hypoglycemia with a general trend of the value downward. Twenty-five showed incomplete hypophysectomy, with a hyperglycemia in each reaching its height at $1\frac{1}{2}$ to 2 hours. No blood sugar fell as low in this group as in the former one.

It was observed that 5 of the 22 animals of the completely hypophysectomized group died before the termination of the experiment. These animals went into typical insulin shock with convulsions and died. No attempt was made to relieve the hypoglycemic condition. The blood glucose values in Table I are typical of both completely and partially hypophysectomized rats and give the results obtained on animals 27, 52, and 61, respectively. In 10 of the 25 animals which were incompletely hypophysectomized there was an initial fall in blood glucose 30 minutes after insulin injection. Fifteen showed an increase or remained at about the initial level. After reaching the peak at $\frac{1}{2}$ to 2 hours the value began to fall and either

¹⁰ Miller, Benjamin F., and Van Slyke, Donald D., *J. Biol. Chem.*, 1936, **114**, 583.

¹¹ Smith, P. E., *Am. J. Anat.*, 1930, **45**, 205.

¹² Smith, P. E., Tyndall, H. H., Dotti, L., and Engle, E. T., *Proc. Soc. Exp. Biol. and Med.*, 1936, **34**, 247.

returned to about the initial level or fell slightly below. Histological or gross findings proved all these animals to have some part of the gland present, the amount varying from fragments up to as much as 3 mg. Further investigations are now in progress in an effort to determine what portion of the gland produced this phenomenon.

TABLE I.
Blood Glucose in Completely and Partially Hypophysectomized Rats After Insulin Injection in mg per 100 cc of Blood.

	Animal No.	Normal Glucose	Minutes after injection of insulin					
			30	60	90	120	180	240
Completely hypophysectomized	27	125	100	73	71	74	56	65
Incompletely hypophysectomized	52	112	98	106	118	120	108	86
	61	112	128	134	140	164	136	118

The evidence here presented affords ample proof of a difference in insulin response of partially and completely hypophysectomized rats. Results confirm the recorded statements that removal of the entire hypophysis renders an animal hypersensitive to insulin.^{9, 5} They show that hyperglycemia is produced after insulin in partially hypophysectomized rats, and that the maximum fall in blood glucose, after the peak is reached, is never so great as in those completely hypophysectomized.

Smith, *et al.*,¹² demonstrated an initial fall in blood glucose in 3 partially hypophysectomized monkeys after a 30-minute interval following insulin. My results indicate that after 30 minutes 10 animals showed an initial fall, in agreement with their findings, while 15 showed an initial rise. It would be of interest to know what would have been the trend of blood glucose curves in their animals if the experiment had been continued over a longer period.

The results suggest that the pituitary fragments are stimulated in some manner so that they secrete a substance not only antagonistic to insulin but producing a mobilization of glucose in the blood stream following insulin injections. The exact biological nature of this mechanism cannot yet be elucidated. These results suggest a method which might prove beneficial clinically in determining pituitary deficiency and the degree of hypophysectomy in experimental animals.

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