Insulin Sensitivity in the Hereditary Hypopituitary Dwarf Mouse.* (20234)

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Snell(1) described in a strain of mice an hereditary dwarfism which behaved as a true Mendelian recessive. Since then many investigations have been carried out on the dwarf which have shown interesting morphological and metabolic anomalies(2,3). Russell (4) reported that hypophysectomized or adrenalectomized animals exhibit a greatly increased sensitivity to the hypoglycemic effect of insulin as compared to normal intact animals.

Since the hereditary dwarf is deficient in anterior-pituitary and adrenocortical secretions, it was of interest to test insulin effects on this naturally occurring form.

Materials and methods. The animals used in this study were hereditary hypopituitary dwarf mice of the Bar Harbor strain (Subline, Syracuse); for controls and comparative purposes, normal mice of the same strain were utilized. All dwarfs used were 9 to 12 months old, ranging in weight between 9 and 14 g. Normal mice between 35 and 42 days old were used as controls because their weights at this time were similar to those of the dwarfs; moreover, at this age the normals are developmentally similar to the dwarfs at 9 to 12 months. The animals were fed Purina Laboratory Chow and water *ad lib.* The temperature of the animal room was carefully maintained at 75°F. Insulin (Illetin-Lilly) was administered subcutaneously.

Results. Insulin sensitivity. The dwarfs are remarkably more sensitive to insulin than normal mice, for it takes only 3% of the dose of insulin given to normal mice (2 units per kilo) to cause a similar convulsive effect. For instance, a single dose of 0.06 unit of insulin injected after the 24th hour of fasting is sufficient to cause in 1 hour a marked decrease of 45% in the blood sugar level. The same dosage of insulin causes a slight but significant drop in the blood sugar of normal mice (Table I). When dwarfs are fasted for 18 hours, allowed food for 6 hours, and then injected immediately with 0.06 unit of insulin per kilo, the blood sugar level drops 23% in an hour, or about half as much as was observed above following a 24-hour fast. In contrast, normal mice under similar experimental conditions of dosage and fasting exhibit a decrease of 9% (Table I). Further evidence of this marked insulin sensitivity of the dwarf is provided by the observations that higher insulin dosages of 0.125, 0.250, and 0.500 unit of insulin per kilo cause hypoglycemic coma and death in the dwarfs but produce no observable symptoms such as hypoglycemic cramps in the normal controls. When after 24 hours of fasting, adrenalectomized mice of normal size are given 0.5 unit of insulin per kilo, cramps and hypoglycemia result in 1 hour; but the animals do not succumb. If the dosage is raised to 2 units per kilo, the adrenalectomized animal enters a hypoglycemic coma which is followed by death.

Anti-insulin tests. In Table II the effects of various hormones acting as anti-insulin agents are indicated. Adrenocorticotrophin, cortisone, and adrenocortical extract all exhibit a marked capacity to prevent convulsions. Cortisone exerts the most marked anti-insulin response in both normal and dwarf mice. In normal intact animals cortisone, ACTH, and adrenocortical extract counteract the effects of insulin to such an extent that 5, 4, and 3 times the dose of insulin respectively are necessary to produce approximately the same percentage of convulsions that occurs in nonprotected normal controls receiving 2 units of insulin per kilo. If normal mice are adrenal-

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TABLE I. Effect of 0.06 Unit of Insulin per Kilo on Blood Sugars in Fasted Dwarf (dd) and Normal (N) Mice.

	Treatment	No. animals	Mean blood sugar, mg % ± S.E.,* at hr fasted 24†	25	26	28	32	40	45
dd	Insulin (.06 ml)	10	96±2.1	53±1.8	72±2.2	75±3.0	89±0.9	94±1.0	90±1.3
N	Idem	11	128±3.2	114±2.0	117±1.0	127±1.7	124±1.3	119±1.2	121±2.8
	Data in lower half of table similar to above except that animals were fasted 18 hr, fed between 18th and 24th hr, and fasted again after 24th hr.								
dd	Insulin (.06 ml)	6	146±4.1	113±1.1		90±2.4			82±1.8
N	Idem	6	150±3.8	137±2.0	142±1.9	144±3.0	130±0.9	121±2.6	112±1.2

* S.E. = stand. error. † Insulin inj. subcut.

TABLE II. Anti-Insulin Tests in Normal Intact and Adrenalectomized Mice and Intact Dwarfs Fasted 24 Hr.

Treatment	Amt inj.	Insulin dose/kilo mouse	Total No. animals	Convulsions, %
Intact normal mice				
Controls	—	2	39	90
ACTH	.5 mg	2	14	14
		8	10	80
Cortisone	.2 "	2	18	0
		10	10	70
ACE	.7 ml	2	22	14
		6	10	90
DCA	.2 mg	2	19	84
	2.0 "	2	10	100
Testosterone propionate	2.5 "	2	21	100
Adrenalectomized normal mice*				
Controls	—	.5	9	100
ACTH	.5 mg	.5	8	88
		2.0	5	70
Cortisone	.2 "	.5	10	0
		2.0	5	80
ACE	.7 ml	.5	10	10
		2.0	5	100
Intact dwarf mice				
Controls	—	.06	12	100
ACTH	.5 mg	.06	6	17
		.25	5	80
Cortisone	.2 "	.06	10	10
		.30	5	60
ACE	.7 ml	.06	12	17
		.25	5	80
DCA	.2 mg	.06	12	100
	2.0 "	.06	12	100
Testosterone propionate	2.5 "	.06	12	100

* Adrenalectomized animals maintained on daily subcut. inj. of 0.1 mg of DCA in 0.1 ml of peanut oil and 0.9% sodium chloride in drinking water.

ectomized and primed with cortisone and ACE, 2 units per kilo instead of 0.5 unit per kilo are required to cause convulsions. Dwarf mice receiving ACTH, cortisone, and ACE convulse with 4, 5, and 4 times the dose of insulin respectively in contrast to nontreated control dwarfs receiving 0.06 unit of insulin per kilo.

The results of these experiments (Table II) also serve to emphasize the ineffectiveness of DCA as an anti-insulin agent in both normal and dwarf mice, since dosages from .2 to 2

mg proved incapable of preventing convulsions. This observation is of interest since it has been generally considered by Wang and Verzar(5) that DCA is capable of affecting carbohydrate metabolism. With a tenfold increase in the dosage, it appears that sufficient DCA absorption should occur to reveal any possible anti-insulin effect. Nevertheless, none was obtained.

In all experiments reported here, testosterone propionate exhibited no anti-insulin effect (Table II).

Discussion. Although this study has shown that the hypopituitary dwarf mouse is extremely sensitive to insulin as compared with controls, the mechanism to explain the increased sensitivity of the dwarf is not definitely understood. On theoretical grounds, any or all of the following factors may be responsible for this phenomenon: a) A decreased rate of inactivation of insulin by the blood and tissues. b) Inadequate counterregulatory responses (*i.e.*, glycogenolysis and gluconeogenesis) to hypoglycemia by the liver. c) Hypophyseal and adrenocortical deficiencies, perhaps rendering the dwarf incapable (especially under the stress of fasting) of producing an anti-insulin factor or factors such as ACTH and adrenocortical hormones oxygenated at C-11 and 17.

Identification of insulin-antagonistic factors is of interest. The present study shows that ACTH, cortisone, and ACE are antagonistic to the blood-sugar lowering action of insulin, *i.e.*, they increase the tolerance of the dwarf to a given dose of insulin. Preliminary experiments (unpublished data) have shown that growth hormone is also anti-insulin. Insulin sensitivity and anti-insulin action under these conditions perhaps are associated with a pituitary deficiency *per se* as well as with the deficiencies of the pituitary-adrenal axis. The above findings are consistent with what is known in other experimental and clinical situations(6-8).

Summary. Under the experimental conditions employed in these studies, findings may be summarized as follows: a) The insulin-hypersensitive hereditary hypopituitary dwarf mouse can tolerate only 3% of the dose of insulin that produces comparable symptoms in normal mice (2 units of insulin/kg of mouse). Higher dosages cause severe hypoglycemia followed by death. b) ACTH, adrenocortical extract (ACE), and cortisone act as anti-insulin agents as shown by their ability to increase blood-glucose levels and to reduce hypoglycemic convulsions. Desoxycorticosterone acetate and testosterone propionate exhibit no anti-insulin action. c) Factors that may be responsible for the hypersensitivity to insulin are discussed.

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