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Inhibition by Cortin of the Blood Sugar Changes Caused by Adrenalin and Insulin.

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It has been shown by previous investigators that cortin and crystalline cortin-like compounds when given in excess to normal animals have no hyperglycemic or diabetogenic action,[1] while in the partially pancreatectomized animal, these substances are strongly diabetogenic.[2, 3] These observations have been considered to prove that normally, insulin produced by the animal's own pancreas inhibits the inherent sugar-mobilizing action of cortin, a mechanism which is disturbed after partial pancreatectomy. The action of crude cortical extracts on adrenalin hyperglycemia has been examined in the rabbit by Oda[4] who claimed that such extracts may inhibit adrenalin hyperglycemia. On the other hand, in the cat Britton and Silvette[5] and in the rabbit Sabatucci[6] obtained negative results. Oda[4] claimed, furthermore, that cortical extracts increase the hypoglycemic effect of insulin, an observation which would appear to be in contradiction with the above mentioned findings on the partially pancreatectomized animals. The following experiments have been performed to clarify these questions.

In all experiments reported in this communication, adult "hooded" male rats weighing between 160 and 249 g have been used. The animals were distributed in such a manner as to make the average weight of each experimental group approximately 200 g. The rats were fasted during the 24 hours preceding the beginning of the experiment. In our first experiment, 6 rats received a subcutaneous injection of 0.2 cc of a 1:1000 solution of adrenalin. They were sacrificed for blood sugar determination (Shaffer, Hartmann and Somogyi's method) 30 minutes later. Another group of 6 rats received 1 cc of Wilson's cortical extract*) 15 minutes prior to the

1 Grollman, Arthur, *Am. J. Physiol.*, 1938, **122**, 460.

2 Kendall, E. C., *XVI Internat. Physiol. Cong.*, Zurich, August, 1938.

3 Long, C. N. H., Fry, E. G., and Thompson, K. W., *Proc. Am. Physiol. Soc.*, Baltimore, 1938.

4 Oda, Y., *Fol. endocrin. jap.*, 1928, **4**, 53.

5 Britton, S. W., and Silvette, Herbert, *Science* (N.Y.), 1931, **1**, 373.

6 Sabatucci, Nicoletta, *Boll. Soc. ital. Biol. sper.*, 1934, **9**, 655.

* We are greatly indebted to Dr. David Klein of the Wilson Laboratories for supplying us with the cortical extract.

injection of the same amount of adrenalin as was used in the first group. 0.03 cc of this cortical extract contained 1 unit of cortin as defined by Selye and Schenker.[7] The average blood sugar in the group receiving adrenalin alone was *191* mg % with variations between 170 and 228 mg % while in the group pretreated with cortin, the average blood sugar was *145* mg % and the extreme variations, 126 to 170 mg %. We repeated this experiment on another group of rats under identical conditions except that the animals were killed 1 hour after the adrenalin injection. In this experiment, the group receiving adrenalin alone had an average blood sugar of *240* (range: 224-256), while that pretreated with cortin had an average blood sugar of *206* mg % (range:178-219).

These experiments showed that the hyperglycemic response to adrenalin is decreased in animals pretreated with cortin but we felt that blood sugar curves would be necessary to determine whether the inhibition is real or merely apparent and due to a delay of the maximum response. For this purpose, we repeated the experiment on another group of 12 rats, 6 of them receiving adrenalin alone, and 6 in combination with cortin in the same manner as in the previous experiments. Blood was taken at intervals from the heart for sugar determinations. Table I summarizes our results which indicate that the inhibition was real, inasmuch as the blood sugar in the group receiving cortin was not only inhibited at a certain time but actually never reached as high a level as after adrenalin alone. Since the maximum blood sugar level is not necessarily attained at the same time in each case, the peak values have been italicized in the tables and it was found that the average of all these peak values is 184 in the case of the first group as compared with 151 in the second group which received both hormone preparations.

In order to establish how adrenalin influences insulin hypoglycemia, we performed another experiment on 12 fasted rats giving 2 units of Toronto insulin subcutaneously to all animals. This injection was preceded in 6 rats by the subcutaneous administration of 1 cc of cortin, 15 minutes before the insulin. Since these animals were fasted for 20 hours only, the initial blood sugar was not as low as it usually is at the beginning of these experiments. These results have been summarized in Table II from which it is evident that the hypoglycemia produced by insulin has also been inhibited by cortin to some extent. The average of the italicized numbers, which represent the maximum hypoglycemia of each animal, is *39*

[7] Selye, Hans, and Schenker, Victor, PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 518.

TABLE I.
Effect of Cortin on Adrenalin Hyperglycemia.

No. of animals	1	2	3	4	5	6	Avg
			Adrenalin.				
Fasting blood sugar	96	87	96	79	96	71	88
Time after adrenalin injected							
0 hr 30 min	145	136	143	136	145	132	140
1 " 30 "	174	170	163	*182*	166	*178*	*172*
2 " 30 "	*211*	*198*	*163*	178	*170*	170	183
7 "	96	92	104	111	119	79	100
			Adrenalin + Cortin.				
Fasting blood sugar	79	87	100	75	96	96	90
Time after adrenalin + cortin injected							
0 hr 30 min	79	87	104	107	100	119	99
1 " 30 "	119	124	145	128	128	*141*	*130*
2 " 30 "	*128*	*145*	*186*	*170*	*136*	sample lost	153
7 "	87	92	128	96	75	79	89

in the case of treatment with insulin alone and *60* in the case of insulin and cortin. A repetition of this experiment on rats fasted for 24 hours and receiving only 1 unit of insulin gives similar results. Thus 2 hours after the insulin injection, the average blood sugar was *38* mg % (range: 23-58) while in the group receiving insulin and cortin, it was *60* mg % (range: 54-67). The average of the maximum hypoglycemia values was *28* in the former and *42* in the latter group. The fact that these values are lower than in the group summarized in Table II is due to the longer fasting period which led to a lower initial blood sugar value (average 82 mg %) in this experiment. In both groups, however, the inhibition of the hypoglycemic effect of insulin appears to be quite obvious. The fact that cortin in the dosage employed has no significant effect on the blood

TABLE II.
Effect of Cortin on Insulin Hypoglycemia.

No. of animals	1	2	3	4	5	6	Avg
			Insulin.				
Fasting blood sugar	111	107	100	92	111	100	103
Time after insulin injected							
1 hr	67	*54*	43	*39*	63	33	49
2 "	*31*	58	*31*	43	*47*	*31*	*40*
4 "	54	63	71	87	71	87	72
6 "	79	92	71	87	75	87	82
			Insulin + Cortin.				
Fasting blood sugar	107	92	111	103	107	96	102
Time after insulin + cortin injected							
1 hr	75	67	75	96	87	*43*	74
2 "	*71*	*54*	67	*67*	*67*	71	*66*
4 "	92	71	*58*	75	92	71	76
6 "	96	79	71	87	79	83	82

sugar by itself, was shown in another group of 6 rats in whom the blood sugar after 24 hours fasting was 89 mg % on the average (range: 83-92). One hour after subcutaneous injection of 1 cc of cortin, it was 89 mg % (range: 87-92) and one hour after that 92 mg % (range: 76-105).

Summary. Experiments on the fasted rat indicate that both the hyperglycemia caused by adrenalin and the hypoglycemia following insulin administration may be inhibited, though not completely suppressed, by cortin. It appears that cortin exerts a stabilizing effect on the blood sugar not unlike that obtainable by certain pituitary extracts as described by Neufeld and Collip.[8]

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Effect of Methylcholanthrene on Latent Period of Breast Tumors in Dilute Brown Mice.*

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The production of breast tumors in non-susceptible female mice of strains IF, CBA, JK, and NH by subcutaneous injection of methylcholanthrene was reported almost simultaneously in England[1] and in this country.[2] Observations in this laboratory also indicate that methylcholanthrene may affect the production of mammary carcinoma in a strain of mice that is known to develop the tumors spontaneously.

Breeding female dilute brown (Little dba) mice have a high incidence of spontaneous mammary carcinoma.[3] Subline 212, on which our experiments were performed, has a lower incidence of breast tumors than other members of the strain. Forty-two identified breeding female mice of this line have been observed for at least one year. Fourteen of them developed one or more spontaneous breast tumors when 250 to 475 days old. The average latent period was 371.0 days.

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8 Neufeld, A. H., and Collip, J. B., *Endocrinol.*, 1938, **23**, 735.

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1 Bonser, G. M., and Orr, J. W., *J. Path. and Bacteriol.*, 1939, **49**, 171.

2 Strong, L. C., and Smith, G. M., *Yale J. Biol. and Med.*, 1939, **11**, 589.

3 Murray, W. S., *Am. J. Cancer*, 1934, **20**, 573.