コイの背こけ病III

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Sekoke Disease, Spontaneous Diabetes in Carp Found in Fish Farms—III. Response to Mammalian Insulin*

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Previous papers[1,2] have described diabetic syndrome in Sekoke carp. In recent diabetes research, there has been a tendency to place great importance on the pancreatic and serum insulin activities, and the response of animals or their tissues to exogenous insulin. Hyperinsulinemia and unresponsiveness to insulin have often been reported in diabetic animals, especially in diabetic rodents.[3–10] These findings have offerred invaluable suggestion for the pathogenesis of the disease. In this connection, it is of particular interest to know response of the diseased carp to insulin.

The present work deals with effects of mammalian insulin to the glycemic levels in Sekoke and normal carp. As the results of the study, it was made clear that normal carp exhibited a marked hypoglycemia by the intramuscular administration of 10 IU/kg body weight of mammalian insulin, while Sekoke carp were less responsive to the same hormonal dosage.

Materials and Methods

Animals: Sekoke and normal carp were collected from fish farms in Gumma Prefecture in May, 1965, and fed carp pellet prepared by Nihon Haigo Shiryo Co., for about 6 months in a concrete tank ($1.2\times4.5\times0.8$ m) of our Laboratory. Among them, 93 Sekoke carp and 143 normal controls, weighing 42 g and 41 g on the average respectively, were selected for the study. Several days before the experiment, they were transferred to aquariums, $24\times34\times45$ cm, each provided with 20–22°C running water.

Insulin: Crystalline insulin, a potency of 23.6 IU/mg, guaranteed by National Institute of Hygienic Sciences, Ministry of Health and Welfare, was dissolved in distilled water. The preparation was administered intramuscularly to 24-hour fasted carp.

Determination of blood glucose: The fish were anesthetized by quinaldine and carefully bled from the bulbus arteriosus by a heparinized syringe. Blood sugar was analyzed on 0.1 ml of blood by a modified Folin-Malmros' method.[11] Hypoglycemic effect of insulin was studied by single determinations of blood sugar from different individuals at various observation times because of the reason described in the previous paper.[2]

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Results

Hypoglycemic effect of insulin on normal carp: 1) 5 IU/kg body weight. Since appropriate insulin-dose to the tolerance test for carp was unknown, this dosage was tested first. During the time of 5–16 hours after the treatment, several carp developed hypoglycemia. As a whole, however, hypoglycemic effect of this hormonal dose was inconspicuous (Fig. 1). 2) 10 IU/kg body weight. As shown in Fig. 2, 10 IU/kg of insulin produced a marked reduction of blood sugar 5 hours after insulin injection with a return to near normal levels by 20–24 hours (Fig. 2).

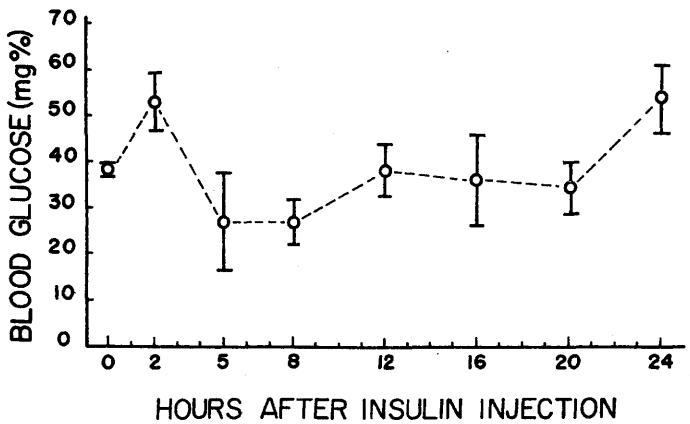

Fig. 1. Effect of intramuscularly injected insulin (5 IU/kg) on the glycemic levels of normal carp. Each dot with a vertical line expresses mean ± standard error of the mean (n=8–10).

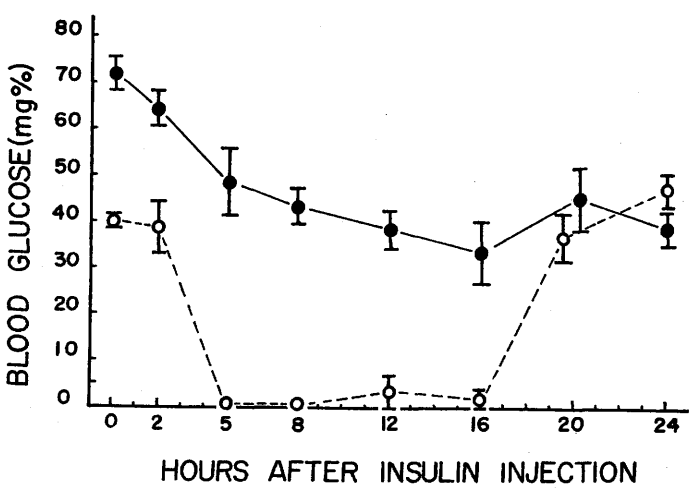

Fig. 2. Effects of intramuscularly injected insulin (10 IU/kg) on the glycemic levels of Sekoke and normal carp. Each dot (●...Sekoke carp, ○...normal controls) with a vertical line expresses mean ± standard error of the mean (n=8–18.)

Hypoglycemic effect of insulin on Sekoke carp: 1) 10 IU/kg body weight. The tolerance curve of the diseased fish shown in Fig. 2 apparently indicates a refractoriness of the fish to the hormone. The mode of the curve characterized by a decreased lowering rate, tardy fall, and delayed attainment to the lowest level is the same as those generally referred to as 'insulin-resistant' in mammals. 2) On Sekoke carp with lower intact glycemic levels. One might be inclined to think that higher blood sugar values in intact Sekoke carp may result in a seeming ineffectiveness of insulin, even if the reduction of blood sugar by the hormone is similar to that in normals. For this purpose, 6 Sekoke carp with lower intact glycemic levels, and 5 normal controls were treated with the same dose of insulin as before. Effects of insulin on the glycemic level was traced on the same individuals. The results, shown in Table 1, clearly indicate that ineffectiveness of the hormone in Sekoke carp was not related primarily to their intact glycemic levels.

Table 1. Hypoglycemic effects of 10 IU/kg body weight of insulin on Sekoke carp with lower intact glycemic levels, and on the normal controls.

	Blood sugar value (mg%)	
	Intact*	5 hours after injection
Normal carp		
1	58	0
2	31	0
3	42	0
4	57	0
5	26	0
Sekoke carp		
1	40	43
2	61	46
3	40	51
4	40	36
5	56	18
6	46	38

* Intact levels are those determined about 24 hours prior to insulin injection.
(0) in the normal carp means undetectable level.

Discussion

Hypoglycemic effect of mammalian insulin has been investigated on various fish species. In these studies, fishes are roughly classified into 3 types according to their responses to insulin. 1) Fishes readily showing hypoglycemia with convulsion by a fairly lower dose of the hormone. Brown trout,[21] scup,[12,13] menhaden,[12,13] common mackerel,[13] bull's eye mackerel,[13] skate,[15] and sea bass[15] fall under this type. 2) Fishes being resistant to insulin. Hypoglycemia and convulsion are undetected in this type even after a single

or repeated injection of a massive or tremendous dose of insulin. Daddy sculpin[16] belongs to this type. 3) Fishes developing hypoglycemia, but no convulsion, with relatively low or moderate dose of insulin. Puffer,[12,13] sea robin,[13] toadfish[13,17], tench,[14] and hagfish[18] belong to this type.

In the present study, carp is considered to come under the last type mentioned above. But, it should be emphasized that the diseased carp showed a refractoriness to mammalian insulin.

MAYER *et al.*[3] noted insulin-resistant diabetes in genetically obese mice. Groen *et al.*[4] reported a case of spontaneous diabetes in a dog which exhibited insulin resistance. More recently, hyperinsulinemia accompanying hyperglycemia and a concomitant unresponsiveness of one or more tissues to insulin has been reported in diabetic rodents by many workers.[5–10] Thus, these metabolic changes seem to be postulated as essential features for spontaneous diabetes in animals. Recent biochemistry and immunology have challenged these seemingly paradoxical phenomena and increasingly accumulated important knowledge associated with various aspects of insulin and related products.[19–22] Now a conception that diabetes is primarily related to an absolute deficiency of insulin seems to have been discarded by most workers. In this connection, insulin-resistance in Sekoke disease should be stressed. At the same time, it is to be pointed out that further studies are required regarding insulin activities in the pancreas, nonsuppressible insulin-like activity, and peripheral utilization of the hormone in Sekoke carp.

Summary

Responses of Sekoke, and normal carp to mammalian insulin were studied.

1) Hypoglycemic effect of 5 IU/kg body weight insulin was not distinct in normal carp.

2) A dose of 10 IU/kg body weight of insulin produced a marked hypoglycemia in normal carp 5 hours after the treatment. Blood sugar returned to near normal levels by 20–24 hours. During the period of the experiment, no convulsion was observed.

3) Sekoke carp were less responsive to 10 IU/kg body weight of insulin than normals.

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