THE EFFECT OF CHLOR-ISO-PROPAMIDE ON EXPERIMENTALLY INDUCED RESISTANCE TO INSULIN

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The treatment of sugar diabetes with insulin is often associated with major difficulties, caused by surplus formation in the organism, or injection into the organism, of ACTH, glucocorticoids, and hormones of the thyroid gland. In these cases, the patient must be injected with a large amount of insulin.

In the search for agents capable of increasing the sensitivity of the organism to insulin, the perorally acting, sugar-lowering sulfamides have also been studied. In a series of investigations, it was shown that butamide, cyclamide, and chlor-propamide are capable of intensifying and prolonging the insulin effect. This action can be demonstrated in healthy rabbits and dogs, and in alloxan-diabetic animals, but it is especially clear in completely depancreatized animals receiving insulin [1]. Using sulfamides, we attempted to decrease the insulin resistance of patients with acromegaly, the Itsenko-Cushing syndrome, and patients that, in connection with other diseases, had received ACTH, glucocorticoids, and other of their preparations (prednisone, prednisolone, etc.). However, at the same time that the sulfamides showed a favorable influence on the sugar diabetes of some of the patients with acromegaly or the Itsenko-Cushing syndrome, on other patients suffering from these same diseases they had no effect.

As we demonstrated [1, 3], the potentiating effect of the sulfamides appears only at a certain dosage. Several authors who obtained negative results did not take this fact into consideration.

In this work we investigated the action of the sulfamides on insulin resistance, experimentally induced in completely depancreatized dogs that received a known amount of insulin and contrainsulin hormones, during a fixed alimentary regime.

EXPERIMENTAL METHOD

The experiments were performed on 5 dogs, deprived of their pancreases, but receiving it daily in dry form with their food, in a dose of 150 grams. Thus, we ensured access of its digestive enzymes and lipocaic substance into the organism. The food of the animal consisted of 1.5 kg of soup, 300 grams of bread, 25-30 grams of bone, 25 grams of vegetable oil, polyvitamins, and unlimited but measured amounts of water. The dogs were kept in metabolism cages. Daily calculation of the amount of ingested food and the amount of sugar excreted in the urine made it possible to determine the degree of utilization of carbohydrates by the dogs. Insulin was injected in a dose that had ensured the assimilation of almost all the food, maintenance of the animals' weights at established levels, and lowering of their glucosuria to a minimum. For approximately 2 weeks, at this insulin dose, we determined the glucosuria, glycemia, and carbohydrate balance. Then the animals were injected with thyroidin (0.2 grams/kg) or ACTH (24-50 units/day), or adresone or cortisone (50-133 mg/day), or prednisone (10 mg/day), over a period of 6-9 days. Thus, we induced a more or less significant increase in the demand for insulin. Against the setting of this induced insulin resistance, we injected chlor-iso-propamide (100 mg/kg), synthesized in our institute (T. F. Sysoeva and N. I. Makhenko), over the course of 5-7 days, and in the period of thyroidin injection – over a course of 16 days. Subsequently, we first stopped the injection of sulfamide, and then the injection of the contrainsulin hormones. The last series of experiments was carried out with insulin alone. As indices of the diabetic condition, we used the height of the glycemia, the magnitude of the glucosuria, the carbohydrate balance, and the weight of the animals. These indices (except the glycemia) were determined daily, the glycemia – every 1-2 days.

EXPERIMENTAL RESULTS

The data obtained are presented in Tables 1, 2, and 3.

As can be seen from Table 1, under the influence of thyroidin, administered perorally for 6 days, the hyperglycemia and the 24-h glucosuria increased. Despite this, the depancreatized dogs that received thyroidin assimilated a large amount of the carbohydrates. In the course of the following 16 days, the animals continued to receive insulin and thyroidin and were also injected with chlor-iso-propamide. In this case, in 2 dogs the glycemia and glucosuria decreased significantly; correspondingly, the utilization of carbohydrates also increased. After the injection of chlor-iso-propamide was stopped, in Astra and Pchelka the glucosuria, hyperglycemia and carbohydrate utilization again increased, while in Sokol the increase occurred in the hyperglycemia and utilization of carbohydrates. After the injection of thryoidin was stopped, the hyperglycemia diminished in Pchelka and approximated the level of the control experiments in the other 2 dogs, the glucosuria in Astra decreased, and in Sokol and Pchelka approximated the starting level.

TABLE 1. The Effect of Chlor-Iso-Propamide on Insulin Resistance Induced by Thyroidin (Mean Data)

Experimental conditions	Date of the experiment (1961)	Number of determinations	Carbohydrate utilization (in g)	Glucosuria (in g)	Number of determinations	Glycemia (in mg %)
			Dog Astra			
Insulin (4 units)	4-7/III	4	215	18	2	258
Insulin and thyroidin (1.5 g)	8-13/III	6	196	25	2	321
Insulin, thyroidin and chlor-iso-propamide (0.7 g)	14-29/III	16	240	10	7	204
Insulin and thyroidin	30/III-9/IV	11	249	17	5	237
Insulin	10-20/IV	11	201	8	5	279
			Dog Sokol			
Insulin (14 units)	3-7/III	5	212	30	3	349
Insulin and thyroidin (2.1 g)	8-13/III	6	163	94	2	379
Insulin, thyroidin and chlor-iso-propamide (1 g)	14-29/III	16	199	30	7	234
Insulin and thyroidin	30/III-13/IV	15	259	3	7	255
Insulin	14-24/IV	11	218	24	4	332
			Dog Pchelka			
Insulin (8 units)	3-7/III	5	183	56	3	443
Insulin and thyroidin (2.7 g)	8-13/III	6	192	70	2	456
Insulin, thyroidin, and chlor-iso-propamide (1.3 g)	14-29/III	16	185	33	7	331
Insulin and thyroidin	30/III-9/IV	11	208	48	5	395
Insulin	10-20/IV	11	226	67	5	302

As evidenced by the data in Table 2, under the influence of 50 units of ACTH, injected in equal portions twice a day (Astra and Pchelka were injected with an additional 24 units prior to this), the hyperglycemia and glucosuria increased (the latter remained unchanged only in Sokol), the utilization of carbohydrates remained generally unchanged, and in certain cases even increased, possibly due to their increased intake of food.

Against the setting of continued injection of insulin and ACTH, the chlor-iso-propamide markedly lowered the hyperglycemia and glucosuria. Under its influence, the utilization of carbohydrates decreased in Astra, Pchelka, and Mushka, and remained unchanged in Sokol and Laska.

As can be seen from Table 3, under the influence of adresone the glycemia increased considerably in Astra and fell somewhat in Sokol and Pchelka. The urine sugar concentration for Astra did not change, while in Sokol and Pchelka it increased. In this case, carbohydrate utilization barely changed in Astra and Sokol, but decreased in Pchelka.

TABLE 2. The Effect of Chlor-Iso-Propamide on Insulin Resistance Induced by ACTH (Mean Data)

Experimental conditions	Date of the experiment (1961-1962)	Number of determinations	Carbohydrate utilization (in g)	Glucosuria (in g)	Number of determinations	Glycemia (in mg %)
			Dog Astra			
Insulin (4 units)	1-8/V	8	186	0	3	217
Insulin and ACTH (24 units)	9-13/V	5	147	5	2	192
Insulin and ACTH (50 units)	14-19/V	6	189	22	3	301
Insulin, ACTH and chlor-iso-propamide (0.6 g)	20-25/V	6	160	0	3	95
Insulin and ACTH (40 units)	26/V-5/VI	11	207	0	4	123
Insulin	6-20/VI	15	207	0	7	261
			Dog Sokol			
Insulin (10 units)	14-19/V	6	242	20	3	260
Insulin and ACTH (50 units)	20-25/V	6	232	19	3	309
Insulin, ACTH and chlor-iso-propamide (0.8 units)	26/V-1/VI	7	230	10	3	165
Insulin and ACTH (40 units)	2-11/VI	10	243	0	4	228
Insulin	12-20/VI	9	252	3	4	247
			Dog Pchelka			
Insulin (8 units)	29/IV-8/V	10	213	0	4	299
Insulin and ACTH (24 units)	9-13/V	5	200	0	2	244
Insulin and ACTH (50 units)	14-19/V	6	227	17	3	340
Insulin, ACTH and chlor-iso-propamide (1.1 g)	20-25/V	6	180	0	3	151
Insulin and ACTH (40-50 units)	26/V-5/VI	11	176	9	4	307
Insulin	6-20/VI	15	241	1	7	331
Insulin (12 units)	1-7/I	7	239	5	4	300
Insulin and ACTH (50 units)	8-12/I	5	245	9	3	360
Insulin, ACTH and chlor-iso-propamide	13-18/I	6	225	0	3	190
Insulin and ACTH	19-25/I	7	168	33	3	321
Insulin	26/I-1/II	7	192	46	3	376
			Dog Laska			
Insulin (32 units)	1-7/I	7	219	12	3	314
Insulin and ACTH (50 units)	8-12/I	5	227	30	3	368
Insulin, ACTH and chlor-iso-propamide (1.3 g)	13-18/I	6	228	9	3	267
Insulin and ACTH	19-25/I	7	217	25	3	417
Insulin	26/I-1/II	7	166	55	3	344
			Dog Mushka			
Insulin (12 units)	1-7/I	7	155	2	3	228
Insulin and ACTH (50 units)	8-12/I	5	184	5	3	262
Insulin, ACTH and chlor-iso-propamide (0.9 g)	13-18/I	6	125	0	3	180
Insulin and ACTH	19-25/I	7	115	16	3	309
Insulin	26/I-1/II	7	179	8	3	250

TABLE 3. The Effect of Chlor-Iso-Propamide on Insulin Resistance Induced by Adresone and Prednisone (Mean Data)

Experimental conditions	Date of the experiment (1961-1962)	Number of determinations	Carbohydrate utilization (in g)	Glucosuria (in g)	Number of determinations	Glycemia (in mg %)
			Dog Astra			
Insulin (4 units)	28/VI-4/VII	7	189	0	3	95
Insulin and adresone (50-133 mg)	5-11/VII	7	199	0	3	171
Insulin, adresone and chlor-iso-propamide (0.5 g)	12-18/VII	7	165	1	3	148
			Dog Sokol			
Insulin (10 units)	15-20/VI	6	246	3	3	267
Insulin and adresone (75-133 mg)	5-11/VII	7	238	9	3	201
Insulin, adresone (83-100 mg) and chlor-iso-propamide (0.8 g)	12-18/VII	7	241	0	3	153
Insulin and adresone	19-26/VII	8	237	0	3	71
			Dog Pchelka			
Insulin (8 units)	15-20/VI	6	249	0	3	319
Insulin and adresone (75-133 mg)	5-11/VII	7	178	12	3	293
Insulin, adresone (83-100 mg) and chlor-iso-propamide (1 g)	12-18/VII	7	206	4	3	220
Insulin and adresone	19-27/VII	9	208	8	4	356
Insulin	28/VII-4/VIII	8	217	0	3	265
Insulin (8 units)	20-26/XI	7	224	28	4	300
Insulin and prednisone (10 mg)	27-30/XI	4	126	75	3	406
Insulin, prednisone and chlor-iso-propamide (0.9 g)	1-5/XII	5	151	34	3	425
Insulin and prednisone	6-11/XII	6	126	24	3	450
Insulin	12-17/XII	6	152	35	3	405
			Dog Laska			
Insulin (32 units)	20-26/XI	7	139	36	4	338
Insulin and prednisone (10 mg)	27-30/XI	4	138	56	3	377
Insulin, prednisone and chlor-iso-propamide (1.2 g)	1-5/XII	5	196	5	3	259
Insulin and prednisone	6-11/XII	6	203	3	3	311
Insulin	12-17/XII	6	251	2	3	205
			Dog Mushka			
Insulin (12 units)	20-26/XI	7	151	15	4	303
Insulin and prednisone (10 mg)	27-30/XI	4	140	16	3	335
Insulin, prednisone and chlor-iso-propamide (0.9 g)	1-5/XII	5	98	4	3	289
Insulin and prednisone	6-11/XII	6	116	5	3	356
Insulin	12-17/XII	6	130	9	3	304

Under the influence of prednisone, the glycemia and 24 hour-glucosuria increased in all the dogs. Carbohydrate utilization remained unchanged in Laska and Mushka subsequent to the action of prednisone, but decreased in Pchelka. During the period of injection of chlor-iso-propamide, used in both series of experiments, the hyperglycemia markedly decreased in all 5 dogs, and the glucosuria in 4 dogs; only in Astra, following aglucosuria, did sugar appear in the urine (1 g in 24 h).

Thus, thyroidin, ACTH, adresone, and prednisone, injected in established doses, appreciably elevate the requirement for insulin, while chlor-iso-propamide significantly decreases it. Increase in the insulin requirement by thyroidin occurs as a result of an increase in glycogenolysis, protein and fat breakdown, gluconeogenesis, and the utilization of glucose by the tissues, and is also due to the breakdown of insulin itself, as a protein substance. ACTH, adresone, and prednisone increase the resistance to insulin by means of an increase in gluconeogenesis from proteins and fats, and by decreasing carbohydrate utilization by the tissues. Despite the difference in the mechanisms for increasing insulin resistance, chlor-iso-propamide showed the same action.

Our investigations show that instead of increasing the dose of insulin, it is possible to increase its effect by the injection of chlor-iso-propamide. By itself, chlor-iso-propamide, as well as other sulfamides, does not show any effect on carbohydrate metabolism in depancreatized animals. It is still difficult to say what type of mechanism lies behind the potentiation of the insulin effect by the sulfamides.

SUMMARY

A study was made of the effect produced by sulfanilamides on the insulin resistance, experimentally induced in depancreatized dogs. Experimental animals with extirpated pancreases received 150 grams of raw pancreas with food (daily), a certain dose of insulin, and contrainsular hormones with an always definite food regimen. As established, thyroidin, ACTH, adresone, and prednisone given in definite doses considerably increased the insulin requirement, whereas chlor-iso-propamide considerably decreased this requirement. Investigations demonstrated that, instead of increasing the insulin dose, one may intensify its effect by chlor-iso-propamide administration.

LITERATURE CITED

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