THE EFFECT OF CHLORPROPAMIDE ON THE TRANSFER OF SUGAR FROM THE BLOOD TO THE TISSUES OF THE BRAIN AND POSTERIOR EXTREMITIES

S. G. Genes and P. M. Charnaya

Division of Pathophysiology (Head – Honored Scientist Professor S. G. Genes),
Ukrainian Institute of Experimental Endocrinology (Director – Cand. Med. Sci. S. V. Maksimov)
(Presented by Active Member AMN SSSR V. V. Parin)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny,
Vol. 54, No. 8, pp. 53-56, August, 1962
Original article submitted August 2, 1961

We showed in a previous communication [1] that chlorpropamide, one of the most potent antidiabetic preparations, which has been synthesized in the Ukrainian Institute of Experimental Endocrinology (by T. F. Sysoeva and N. I. Makhnenko), intensively lowers the blood sugar level in dogs anesthetized with amytal. This is due to the rapid decrease in the secretion of sugar into the blood stream by the liver, and to the weakening of the homeostatic property of the liver of reacting by an increase in the secretion of sugar to a reduced influx of sugar, and in some dogs, in addition, to an increased transfer of sugar into the organs of the portal system.

In the present paper we describe experiments to investigate the influence of chlorpropamide on the transfer of sugar from the blood to the tissues of the brain and the posterior extremities.

This problem is interesting from two points of view. First, most writers claim that the principal point of action of insulin is the skeletal muscles and the organs of the portal system, whereas the antidiabetic sulfonamides have their main action on the liver, where they decrease its secretion of sugar. We have attempted to verify whether, in fact, chlorpropamide has some effect on the transfer of sugar from the blood into the tissues of the posterior extremities. Secondly, in the explanation of the hypoglycemic action of insulin and the sulfonamides, the role of the brain tissue is not usually taken into consideration. We know, however, that the brain functions almost exclusively at the expense of the energy of oxidation of glucose. The human brain utilizes 80 mg of glucose per minute [7], and, consequently, 115 g of glucose is utilized in the 24 hours. The aerobic utilization of glucose by the human brain accounts for almost 20% of all the oxygen consumed by the body [6]. We have tried to discover whether chlorpropamide affects the transfer of sugar from the blood to the brain tissue.

It was shown in a previous communication [3] that sodium amytal, in narcotic but nontoxic doses, has no effect on the normal blood sugar level and on its normal transfer to the tissues of the posterior extremities and of the brain for a period of 24 h. The present experiments were therefore conducted under deep amytal narcosis.

EXPERIMENTAL METHOD

Experiments were carried out on healthy dogs. Sodium amytal was injected repeatedly in the course of the experiment in the form of a 2.5% solution: the first time subcutaneously and thereafter intravenously, as required. After the animal had fallen soundly asleep (disappearance of the corneal reflex), a burr-hole was made in the skull in the region of the longitudinal venous sinus of the brain, the femoral artery and vein were exposed, and laparotomy was performed (to study the reaction of the liver). The blood sugar level was determined by the Hagedorn–Jensen method: before administration of chlorpropamide 5 times at intervals of 3 min, and after introduction of the compound (100 mg/kg) into the intestine – hourly for up to 12 h. Blood for the sugar estimations was taken simultaneously from the femoral artery, the femoral vein, and the venous sinus of the brain. The dogs were specially warmed to maintain their body temperature.

EXPERIMENTAL RESULTS

The results of the investigations are shown in Tables 1 and 2. It is clear from these tables that chlorpropamide considerably lowered the blood sugar. Under these circumstances the brain extracted sugar from the blood of one dog (Tobik) to a slightly lesser degree, and in 4 dogs to a much greater degree than before administration of the drug, while in the 6th dog (Polkan) the brain extracted the normal amount of sugar during the 6 hours of the experiment.

TABLE 1. Effect of Chlorpropamide (100 mg/kg) on the Transfer of Sugar from the Blood to the Tissues of the Brain and Posterior Extremities

Dogs	Index	Time after administration (min)					Time after administration (hours)												
		0	3	6	9	12	½	1	2	3	4	5	6	7	8	9	10	11	12
Burka	A	72	72	65	72	66	59	50	42	40	43	45	41	45	—	54	45	—	—
	B	2	6	4	11	5	11	11	5	4	14	15	18	13	—	16	8	—	—
	C	4	1	+1	6	0	2	3	4	2	2	11	6	6	—	7	+3	—	—
Ryzhik	A	75	83	75	78	77	63	59	66	59	55	59	48	49	47	61	50	54	52
	B	10	18	9	12	7	7	5	16	11	12	20	16	22	16	30	20	29	18
	C	5	3	3	6	5	+2	+6	9	3	+1	3	5	3	1	7	+1	4	4
Malysh	A	89	83	84	90	92	—	67	56	56	42	52	53	52	45	49	56	—	—
	B	10	+5	0	11	11	—	7	+2	11	9	25	17	19	15	18	25	—	—
	C	8	1	+3	3	8	—	6	+12	2	+3	9	13	7	3	13	11	—	—
Tobik	A	79	79	75	76	75	—	60	49	42	34	28	31	33	29	34	38	29	34
	B	10	8	12	13	11	—	6	4	7	5	8	11	13	8	13	18	+5	15
	C	7	5	5	5	6	—	11	8	13	0	+4	2	6	1	13	4	2	6

Notes: A – Sugar concentration (mg%) in arterial blood;
B – Transfer of sugar (mg%) to the brain;
C – To the tissue of the posterior extremities;
+ – Excretion of sugar by the tissues of the brain and posterior extremities.

TABLE 2. Effect of Chlorpropamide (100 mg/kg) on the Transfer of Sugar from the Blood to the Tissues of the Brain and Posterior Extremities (Mean Data)

Dogs	Before administration				After administration			
	No. of investigations	blood sugar level in fem. artery	amount of sugar retained		No. of investigations	blood sugar level in fem. artery	amount of sugar retained	
			by the brain	by tissues of posterior extrem.			by the brain	by tissues of posterior extrem.
		in mg%				in mg%		
Burka	5	69	5.6	2.0	10	46	11.5	4.0
Ryzhik	5	78	11.2	4.4	13	56	17.1	2.2
Malysh	5	88	5.4	3.4	10	53	14.4	4.5
Sharik	5	70	5.6	2.0	7	36	11.4	3.6
Tobik	5	77	10.8	5.6	12	37	8.6	5.2
Polkan	4	71	5.0	6.0	6	66	5.0	5
Laska	4	81	–	3.3	13	63	–	3.9

Chlorpropamide caused only a slight increase in the transfer of sugar from the blood into the tissues of the posterior extremities of 4 dogs, and caused a decrease in the remaining 3. The transfer of sugar from the blood into the brain took place much more intensively than into the tissues of the posterior extremities, both before administration of chlorpropamide and, especially, after administration.

These results show that the extraction of sugar from the blood by the tissues of the posterior extremities was very slightly increased under the influence of chlorpropamide (3.8 and 4.1 mg%), while extraction of sugar by the brain tissues was considerably increased (7.3 and 11.3 mg%).

As we pointed out above, chlorpropamide lowers the blood sugar level by decreasing its secretion by the liver and by weakening the property of the liver of reacting to a diminished inflow of sugar by a diminished secretion of sugar. The present investigation showed that chlorpropamide also stimulates the transfer of sugar from the blood to the tissues of the posterior extremities and, in particular, of the brain. This was shown by the absolute values of the sugar transferred from the blood, but it was still more conspicuous from the relative values. It appeared that sugar passes from the blood to the tissues of the posterior extremities and the brain to a lesser degree the lower the level of its concentration in the blood [1, 4, 5]. Under the influence of chlorpropamide, and despite the considerable fall in the blood sugar (in our experiments, from 76 to 51 mg% on the average), it passed into the tissues of the brain and the posterior extremities in larger amounts than before administration of the compound.

This action of chlorpropamide on the tissues is very similar to the action of insulin, which increases the permeability of the muscle and brain tissue to glucose [4].

Our results support the view that the hypoglycemic action of the sulfonamides is mainly an insulin action. Sulfonamides and, in particular, chlorpropamide, stimulate the secretion of insulin by the β-cells of the islet apparatus and potentiate its action [2].

SUMMARY

Administration of chlorpropamide (synthesized at the Ukrainian Institute of Experimental Endocrinology) intensively decreased the blood sugar level in amytal-anesthetized dogs for a period up to 12 h. This reduction of the blood sugar level depended (as shown in the previous communication) not only on the decrease of its discharge into the blood by the liver. The present investigation revealed that chlorpropamide also increased the transition of the blood sugar into the tissues of posterior extremities, and much more intensively into the tissues of the brain. Such action of chlorpropamide on the tissues is similar to the action of insulin, which increases the permeability of muscular and brain tissue to glucose. The data obtained favors the view that the hypoglycemic action of sulfamides is mainly due to insulin. Sulfamides, and, particularly chlorpropamide, intensify the secretion of insulin by the β-cells and potentiate its action.

LITERATURE CITED

1. S. G. Genes, The Pathogenesis and Treatment of Diabetes Mellitus [in Russian] (Khar'kov, 1944); Collection: Functional Interrelationships between the Various Systems of the Organism in Normal and Pathological States [in Russian] (1962).
2. S. G. Genes, Probl. Endokrinol., No. 5, 3 (1958).

3. S. G. Genes and P. M. Charnaya, Byull. éksper. biol., No. 1, 54 (1960).
4. S. G. Genes, Uspekhi Sovr. Biol., No. 2, 188 (1961).
5. P. M. Rapoport-Charnaya, The Effect of Insulin on Some Aspects of Carbohydrate Metabolism in the Brain. Author's abstract of candidate's dissertation [in Russian] (Khar'kov, 1952).
6. N. A. Lassen, Physiol. Rev., 39, 183 (1959).
7. L. Sokoloff, S. Perlin, C. Kornetsky et al., Ann. N. Y. Acad. Sci., 66, 468 (1957).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
