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MODULATION OF THE HYPOGLYCEMIC ACTION OF INSULIN BY LATERALIZED TRANSCEREBRAL ELECTRICAL STIMULATION

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The neurophysiological basis of some complex neuropsychopathological syndromes consists of assemblies of neurons which organize determinant dispatch stations [1]. On empirical grounds disorganization of these determinant foci is considered to lie at the basis of the therapeutic action of insulin coma therapy [2]. Meanwhile, destabilization of these systems by the oriented modulation of interhemispheric interaction by means of lateralized subsensory electrical stimulation has been used as a method of treatment of mental disorders, through the creation of antisystems in the opposite hemisphere [4, 6]. With a combination of insulin coma therapy and lateralized electrical stimulation in the same patients, potentiation of the action of the former by right-hemispheric electrical stimulation was found for the first time [5], although the mechanism of this phenomenon was not clear.

This phenomenon was reproduced experimentally in the present investigation in order to study some components of the complex mechanisms of the hypoglycemic action of insulin. It will be recalled that previous attempts to potentiate the hypoglycemic action of insulin experimentally by bilateral transcerebral electrical stimulation proved unsuccessful [3].

EXPERIMENTAL METHOD

Experiments were carried out on 30 mature male chinchilla rabbits weighing 2.8-3 kg, kept on the standard diet. The sensitivity of the rabbits to the hypoglycemic action of exogenous insulin and the rate of clearance of insulin from the blood stream [8] were studied. Blood levels of sugar (by the Hagedorn–Jensen method) and insulin (double-antibody radioimmunoassay) were determined [7]. The investigations were carried out 7 days before and again 1 day after electrical stimulation. A continuous series of negative square pulses with a strength of 1.2-1.8 times below the threshold of motor responses, with a frequency of 1 to 30 Hz was applied for 10 min. Needle electrodes were inserted intradermally, unilaterally: the cathode in the frontal region, the anode in the region of the mastoid process. There were two series of experiments, in each of which three groups (with five rabbits in each group) took part. In series I the blood sugar level was measured before and after

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TABLE 1. Time Course of Blood Sugar Level (in mmoles/liter) Following Unilateral Transcerebral Electrical Stimulation (M ± m)

Group of animals	Experimental conditions	Initial level	Duration of fasting state				
			1 h	2 h	3 h	4 h	5 h
1	Before stimulation	5.88±0,06	5,67±0,16*	5,14±0,16	6,11±0,22*	5,17±0,47	4,83±0,26
	After stimulation	5,55±0,25***	5,23±0,13*4	5,27±0,11***	5,12±0,15***	5,05±0,12*4	4,85±0,09***
2	Before stimulation	5,35±0,37*	5,17±0,35*	5,75±0,39	4,72±0,17**	5,15±0,12**	4,83±0,20*
	After stimulation	6,65±0,10	6,48±0,10	6,33±0,19	6,01±0,06	5,99±0,06	5,81±0,10
3	Before stimulation	5,67±0,28	5,27±0,13	5,39±0,14	5,80±0,20	4,94±0,27**	4,41±0,39**
	After stimulation	6,42±0,18	6,23±0,08	6,06±0,17	5,99±0,17	5,90±0,09	5,75±0,39

Legend. *p < 0.05, **p < 0.01 compared with level after stimulation, ***p < 0.05, ****p < 0.01 between groups 1 and 2 and groups 1 and 3 after stimulation.

TABLE 2. Time Course of Blood Sugar (in mmoles/liter) and Insulin (in pmoles/liter) Levels during Insulin Test Following Unilateral Transcerebral Electrical Stimulation (M ± m)

Group of animals	Experimental conditions	Parameter	Initial level	Time after injection of insulin, min				
				15	30	60	120	180
4	Before stimulation	Sugar	6,73±0,30**	4,11±0,37**	5,02±0,28*	5,66±0,15*	6,42±0,28*	7,12±0,05*
		Insulin	126,3±16,9	384,6±74,1	350,2±35,5**	353,1±44,9	195,2±32,2	216,7±38,0
	After stimulation	Sugar	5,22±0,22 $P_1<0,01$ $P_3<0,01$	2,69±0,07 $P_1<0,05$ $P_3<0,05$	3,10±0,09 $P_1<0,05$ $P_3<0,01$	3,43±0,22 $P_1<0,01$ $P_3<0,01$	3,65±0,31 $P_1<0,05$ $P_3<0,01$	4,66±0,42 $P_1<0,05$ $P_3<0,05$
		Insulin	93,3±10,1	492,3±72	536,8±21,2 $P_1<0,01$	380,3±32,3	188,0±67,0	212,4±30,2
5	Before stimulation	Sugar	6,70±0,28	3,93±0,42	5,22±0,56	5,61±0,42	6,06±0,45	6,60±0,30
		Insulin	93,3±15,9	414,8±24,7	414,8±66,9	373,2±61,1	188,0±47,0	216,7±28,7
	After stimulation	Sugar	6,79±0,23	6,80±0,34	4,83±0,21	5,33±0,12 $P_2<0,05$	5,81±0,08 $P_2<0,01$	6,50±0,16
6	First test	Insulin	84,8±12,5	347,3±25,3	305,7±20,0 $P_3<0,001$	250,0±12,6	190,9±13,5	110,1±6,4
	Second test	Sugar	7,0±0,12	3,73±0,32	5,43±0,32	5,55±0,29	5,92±0,24	6,49±0,39
		Insulin	95,1±34,6	330,1±18,8	355,2±68,2	303,2±19,1	258,3±27,0	125,6±38,9
		Sugar	6,80±0,22	3,82±0,32	4,16±0,31	4,96±0,06	5,22±0,09	6,65±0,13
		Insulin	64,6±18,8	335,5±19,3	242,2±17,2	233,2±12,6	233,2±12,8	86,1±10,6

Legend. *p < 0.01, **p < 0.05 compared with level after stimulation. P_1, P_2, P_3) Significance of differences between groups 4 and 6, 5 and 6, and 4 and 5, respectively, after stimulation.

stimulation. Electrical stimulation of the animals of group 1 was given on the right side, in those of group 2 on the left side, and rabbits of group 3 served as the control. In the experiments of series II the blood sugar and insulin levels were measured in the course of the insulin test (1 U/kg intravenously), before and after electrical stimulation, which was given on the right side to rabbits of group 4 and on the left side to the rabbits of group 5. Animals of group 6 served as the control.

EXPERIMENTAL RESULTS

The time course of the blood sugar level before and after electrical stimulation studied for a period of 5 h, revealed elevation at individual times of measurement during the second investigation in the control animals and, in particular, after left-sided electrical stimulation (Table 1). In the animals subjected to right-sided stimulation the blood sugar curve did not rise, or it actually fell (after 1 and 3 h). These results are evidence of a lower blood sugar in animals after right-sided stimulation (Table 1).

As Table 2 shows, in animals of the control group the blood sugar level after left-sided stimulation was unchanged compared with that observed before stimulation. In animals subjected to right-sided stimulation the fasting blood sugar level fell.

The insulin test showed that injection of a standard dose of insulin caused a marked fall of the sugar concentration in all the animals, by the greatest degree after 15 min. In the control group the hypoglycemic effect lasted 120 and 60 min, respectively, at the 1st and 2nd test. After right-sided stimulation a lower blood sugar level was observed for 180 min (Table 2). Very likely the lower blood sugar level in the rabbits of this group could be attributed to some degree to the low initial value, but at the same time, lengthening of the biological action of the injected dose of insulin will be evident.

Determination of the fasting blood insulin level in all the animals tested (Table 2) revealed no significant changes, which rules out any possible pancreatic mechanism of the lowering of the basal blood sugar level in the animals after right-sided stimulation, but suggests an extrapancreatic mechanism of realization of the hypoglycemic effect of endogenous insulin: potentiation of its biological effect at the pre- and (or) postreceptor level. The character of the blood insulin curve after injection of exogenous insulin indicates a unidirectional trend of elimination of the hormone from the circulation: after 15-30 min the blood insulin level peaked, and thereafter it remained high until 60 min, after which it fell gradually after 120-180 min.

The fact that the insulin level was higher in the animals after right-sided stimulation, 30 min after injection of insulin, than before electrical stimulation is noteworthy.

As a result of analysis of these results the lower blood sugar level during the insulin test in animals after right-sided stimulation can be attributed only in part to delay in excretion of exogenous insulin (after 30 min). The coincident character of the blood insulin curve for 60-180 min with that observed in the same animals before stimulation, associated with lengthening and deepening of the hypoglycemic effect of insulin, rules out any involvement of differences in the rate of insulin elimination in the genesis of that effect, and also supports the suggestion of an extrapancreatic mechanism of potentiation of the hypoglycemic effect of insulin in animals after right-sided transcerebral electrical stimulation.

The results are thus evidence that the hypoglycemic action of insulin can be enhanced by unilateral right-sided transcerebral electrical stimulation.

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