LATERAL MODULATION OF THE HYPOGLYCEMIC ACTION OF INSULIN

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Assemblies of neurons, organizing determining despatch stations, constitute the neurophysiological basis of several complex neuropsychopathological syndromes [1]. Disorganization of these determinant foci may perhaps lie at the basis of the therapeutic action of insulin coma therapy [2]. Meanwhile, destabilization of these systems by deliberate modification of interhemispheric interaction with the aid of lateral subsensory electrical stimulation, through the creation of antisystems in the opposite hemisphere, has been used as a therapeutic procedure in mental diseases [3, 4]. When a combination of insulin coma therapy and lateral electrical stimulation was used on the same patients, potentiation of the effect of the first of these agents was observed during right-hemispheric electrical stimulation for first time [5], but the mechanism of this phenomenon was not clear.

This paper gives the results of reproduction of this phenomenon experimentally, with a study of some the components of the complex mechanism of the hypoglycemic action of insulin. It must be recalled that previous attempts to potentiate the hypoglycemic action of insulin experimentally by bilateral transcerebral electrical stimulation were unsuccessful [6].

EXPERIMENTAL METHOD

Experiments were carried out on 15 mature male chinchilla rabbits weighing 2.8-3 kg, kept on a standard diet. The sensitivity of the intact rabbits to the hypoglycemic action of exogenous insulin and the rate of its elimination from the circulation were determined [7]. Blood sugar (by the Hagedorn–Jensen method) and insulin levels (by the double-antibody method of radioimmunoassay) [8], were studied. The tests were carried out 7 days before and 1 day after electrical stimulation. Stimulation was applied as a continuous series of negative square pulses of current with a strength of 1.2-1.8 times below the threshold for motor responses, with a frequency of 1 to 30 Hz, for 10 min. Needle electrodes were used and were inserted unilaterally into the skin: the cathode in the region of the forehead, the anode in the region of the mastoid process. The blood sugar and insulin levels were determined in the course of the insulin test (1 U/kg body weight, intravenously), before and after electrical stimulation, which was given on the right side to rabbits of group 1 and on the left side to those of group 2. Animals of group 3 served as the control. The results were subjected to statistical analysis by the Student–Fisher test.

EXPERIMENTAL RESULTS

The insulin test showed that injection of a standard dose of insulin caused a marked fall of the blood sugar in all animals, which was most marked after 15 min. In the control group the hypoglycemic effect lasted 120 and 60 min respectively in the first and second investigations. After right-sided stimulation of the rabbits, a lower blood sugar level was observed for 180 min. Very probably the lower blood sugar level in this group was due to some extent to the low initial blood sugar level, but at the same time, lengthening of the biological action of the injected insulin was evident.

Determination of the fasting blood sugar level in all the groups of animals tested (Table 1) revealed no significant changes, ruling out the possibility of a pancreatic mechanism of lowering of the basal blood sugar in animals after right-sided stimulation, but

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TABLE 1. Time Course of Blood Sugar (in mM) and Insulin (in pM) Levels during Insulin Test Preceded by Unilateral Transcerebral Electrical Stimulation

Group of animals	Time of determination	Parameter determined	Initial level	Blood sugar and IRI levels determined at below-mentioned times after injection of insulin				
				15 min	30 min	60 min	120 min	180 min
1	Before stimulation	Blood 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
		IRI	126,3±16,9	384±74,1	350,2±35,5	353,1±44,9	195,2±32,2	216,7±38,0
	After stimulation	Blood sugar	5,22±0,22	2,69±0,07	3,10±0,09	3,43±0,22	3,65±0,31	4,66±0,42
			$p<0,05$	$p<0,05$	$p<0,01$	$p<0,01$	$p<0,01$	$p<0,01$
			$p_1<0,01$	$p_1<0,05$	$p_1<0,05$	$p_1<0,01$	$p_1<0,05$	$p_1<0,05$
			$p_3<0,01$	$p_3<0,05$	$p_3<0,01$	$p_3<0,01$	$p_3<0,01$	$p_3<0,05$
		IRI	93,3±10,1	492,3±72	536,8±21,2	380,3±32,3	188,0±67,0	212,4±32,2
					$p<0,02$			
					$p_1<0,01$			
2	Before stimulation	Blood 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
		IRI	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	Blood sugar	6,70±0,23	6,80±0,34	4,83±0,21	5,33±0,12	5,81±0,08	6,50±0,16
						$p_2<0,05$	$p_2<0,01$	
		IRI	84,8±12,5	347,3±25,3	305,7±20,0	250,0±12,6	190,9±13,5	110,1±6,4
					$p_3<0,001$			
3	First investigation	Blood 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
		IRI	95,1±34,6	330,1±18,8	355,2±68,2	303,2±19,1	258,3±27,0	125,6±38,9
	Second investigation	Blood 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
		IRI	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) Probability of "null hypothesis" (no difference) on comparison of data obtained in each group, with level before stimulation; p_1) significance of differences after stimulation between 1st and 3rd groups; p_2) between 2nd and 3rd groups; p_3) between 1st and 2nd groups. IRI) Immunoreactive insulin.

suggests an extrapancreatic mechanism of realization of the hypoglycemic effect of insulin (potentiation of its biological effect at pre- and postreceptor levels). The character of the blood sugar curve after injection of exogenous insulin is evidence of a parallel trend of elimination of the hormone from the blood stream: after 15-30 min the blood sugar reached a peak, and remained elevated after 60 min, thereafter falling steadily for 120-180 min. A significant rise of the blood insulin level compared with that before electrical stimulation was observed in animals subjected to right-sided stimulation, 30 min after injection of insulin.

Analysis of the results shows that the lower blood sugar level during the insulin test in animals after right-sided stimulation can be attributed only partly to delayed elimination of exogenous insulin (after 30 min). Coincidence of the character of the blood insulin curve for 60-80 min with that observed in the same animals before stimulation, accompanied by lengthening and deepending of the hypoglycemic effect of insulin, rules out any participation of differences in the rate of insulin excretion in the genesis of this effect, and also substantiates an extrapancreatic mechanism of potentiation of the hypoglycemic effect of insulin in animals after right-sided transcerebral electrical stimulation.

Thus the hypoglycemic action of insulin can be potentiated by unilateral (right-sided) transcerebral electrical stimulation.

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