INTEROCEPTIVE REFLEXES OF DOGS DURING HYPOGLYCEMIA AND SUBSEQUENT RESTORATION OF THE BLOOD SUGAR LEVEL

T. V. Popova

From the Laboratory of Pathological Physiology (Chief-Prof. V. S. Galkin) of the I. P. Pavlov Institute of Physiology (Director-Academician K. M. Bykov) Acad. Sci. USSR, Leningrad

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In short experiments on cats we have shown [7] that, as hypoglycemia progressively develops, it is constantly accompanied by phasic alterations in the pressor interoceptive reflexes.

The present research was undertaken to confirm the changes taking place in the absence of narcosis as well as to exclude the initial hyperglycemic stage inevitable in a short experiment.

EXPERIMENTAL METHODS

Six dogs were used in our experiments (3 females and 3 males). All the animals had gastric fistulae and in three one carotid artery was exteriorized. Blood pressure changes were followed as the mechanical receptors of the stomach were stimulated as well as those in rectum by use of methods we described previously [9], all this being followed by observing the sino-carotid pressor reflex. This last was induced by compressing with a finger for 30 seconds the carotid artery lying in the skin tag.

Insulin was given intravenously in increasing dosage in the experiments as they were repeated.

To terminate the hypoglycemic state intravenous glucose was employed as well as subcutaneous or intravenous adrenalin.

Blood sugar was determined by the Hagedorn-Jansen method.

Altogether there were 48 experiments: 34 to investigate the interoceptive reflexes under condition of hypoglycemia, 9 control and 5 for method.

Five hundred and sixty blood sugar determinations were made.

The general experimental conditions, insulin dosage and the degree of hypoglycemia attained are presented in the table.

EXPERIMENTAL RESULTS

As in our preceding short experiments on cats, in the first phase of hypoglycemia we observed heightening of the pressor interoceptive reflexes with a lowering of reactive threshold (Fig. 1, tracings 4-6). Later the reflexes became depressed or disappeared entirely (Fig. 1, tracings 7-9), while in an entire series of experiments, instead of pressor reflexes, a depressor reaction appeared.

As the animal emerged from the hypoglycemic state, the interoceptive reflexes were restored going, in many instances, through a phase of heightened pressor responses (Fig. 1, tracings 10, 11) which confirms the fact of the two phasic changes undergone by the interoceptive reflexes when the blood sugar level is reduced.

TABLE

Dogs	Wt (in kgs.)	No. experiments	Amount 40% Glucose before Insulin (in cc)	Quantity insulin		Blood sugar (in mg %)					Length of observation after giving insulin
				Units per kg.	cc.	Base	Record of "background"	Minimal level after insulin "	Decrease (in mg %) from base level	Decrease (in mg %) from maximum after glucose	
Basic experiments											
Grad	17.9—21 6	8	—	2—8	0.9—4.0	98—113	96—120	58—38	53—68		1 hour 29 min. —3 hour
Druzhok . . .	12.8—14.9	7	—	2—11	0.7—3.9	85—105	83—113	56—38	40—60		2 hour 07 " —3 " 33 min.
Zhuchka . . .	15.5—16.3	5	—	1.5—12	0.6—4.9	95—98	93—107	53—41	52—62		1 hour —3 " 25 "
Dirka	22.6—24.6	4	—	2—9	1.2—3.4	83—94	85—94	49—41	38—45		1 hour 26 min —3 " 49 "
Duglas	31.5—32.1	3	—	1.5—5	1.2—4.0	101	98—106	52—43	46—58		2 hour 14 " —3 " 53 "
Dzhanka . . .	19.9—20.9	3	—	2—4	1.0—2.0	89—97	82—114	50—48	34—66		1 hour 26 " —2 " 37 "
Experiments with preliminary glucose											
Grad	21.0	1	60	12	6.3	95	193—348	54	67	294	2 hours 54 min
Druzhok . . .	14 1	1	58	16	5.0	92	194—454	37	59	395	3 " 07 "
Dzhanka . . .	20.0—20.9	2	40—56	8—10	4.0—5.2	95—101	212—358	50—41	53—62	298—308	2 " 29 " —3 hours

In this manner the present studies confirm the results we obtained in our short experiments investigating the character of the changes undergone by the interoceptive reflexes under hypoglycemic conditions.

Nevertheless, the comparison of the short experiments with the series brings out one clear difference: whereas in the acute experiments heightened pressor reflexes predominated, in the present series studies the phase of reflex depression or actual suppression was much the more pronounced.

An explanation of this difference can be sought in special experiments in which the dogs received a preliminary injection of glucose, this being done because in the acute cat experiments (under condition of narcosis) the insulin was being injected against a background of hyperglycemia (up to 354 mg%).

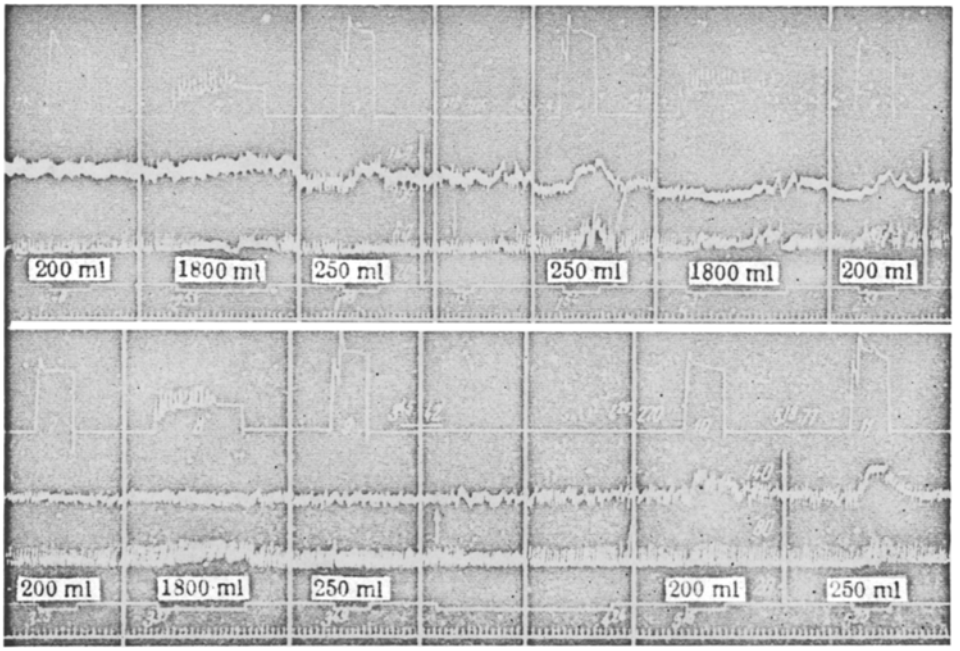

Fig. 1. Two phasic changes in the interoceptive reflexes and thresholds of stimulation as hypoglycemia developed from intravenous injection of insulin (2 units/kg) and then was followed by introduction of glucose. Dog Grad, experiment April 11, 1956. Reflexes from rectum—1, 3, 4, 6, 7, 9, 10, 11; reflexes from stomach— 2, 5, 8. Significance of tracings (from above down): Pressure within organ, blood pressure, respiration, stimulation marker, time signal (5 seconds). Insulin ↓, glucose ↑.

As can be seen from Fig. 2, when the dogs received preliminary doses of glucose sufficient to maintain for 53 minutes the blood sugar at levels of 200-339 mg %, there was observed a pronounced phase of heightened pressor reflexes which continued for three hours, this being something never observed when insulin was injected against a background of normal blood sugar levels.

In this experiment we never were able to obtain the phase of depressed pressor reflexes even when the lowest glycemic level was 42 mg% which is somewhat below that in the usual experiments (48 mg%).

The introduction of glucose after the insulin, "removed" in this experiment the heightened pressor reflexes and also normalized the general behavior of the animal.

Thus we believe that we can conclude that the differences in the first and second stages between the short and series experiments seen after the injection of insulin are explained by a difference in the basic glycemic level which, in turn, determines the length of time the blood sugar remains depressed initially.

A second reason for this difference lies in the different duration of the period of low glycemic levels.

Under narcosis there were no hypglycemic convulsions and the second hypoglycemic phase in the cats progressed rapidly to the death of the animal. In the dogs, the convulsions which developed led to an immediate rise of the blood sugar level, maintaining it at a low but safe level.

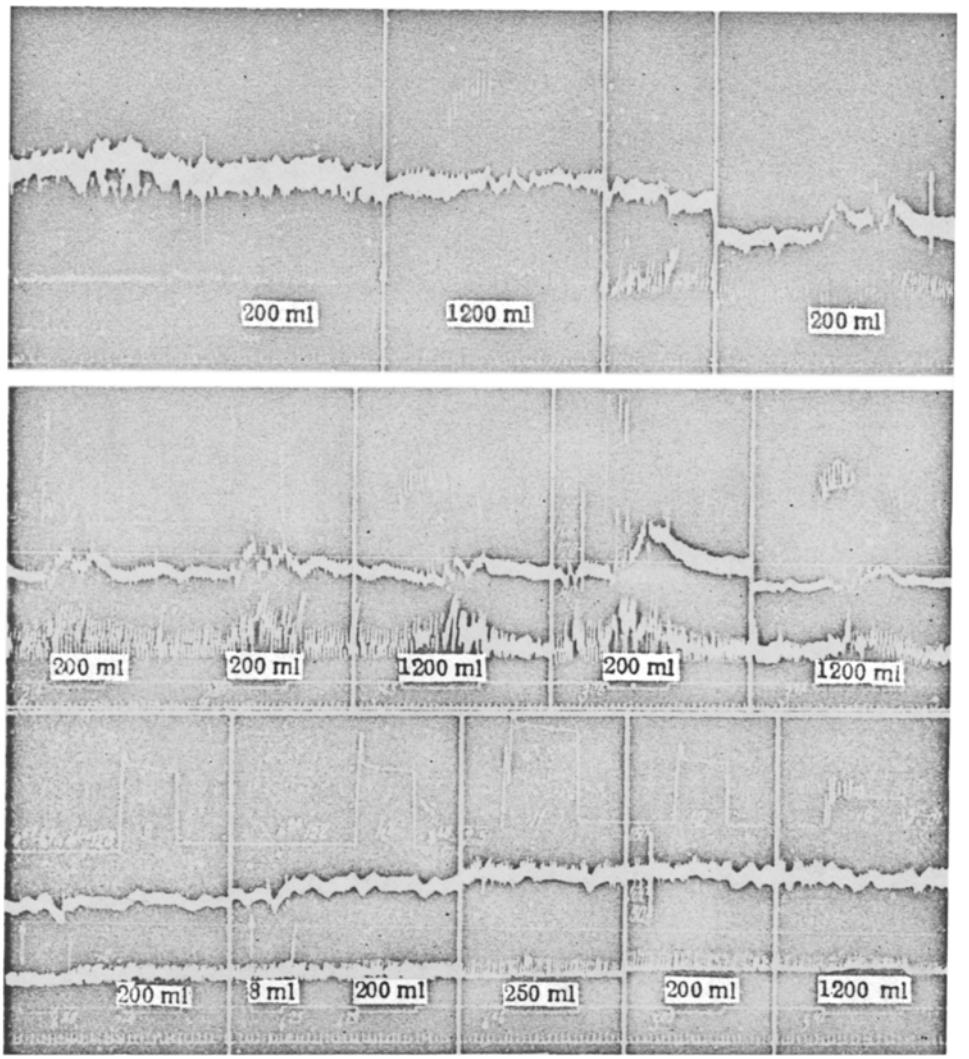

Fig. 2. Alterations in the interoceptive reflexes following injection of insulin (10 units/kg) against a background of hyperglycemia. Dzhanka, Experiment November 25, 1955. Before insulin, glucose was introduced thrice intravenously in the amount of 56 cc of a 40% solution. Reflexes from rectum—1, 3, 4, 5, 7, 9, 10, 11, 12; reflexes from stomach— 2, 6, 8, 13. Significance of tracings same as in Fig. 1.

Thus, in dogs there was a more rapid drop in blood sugar levels after insulin was injected, these precomatose levels being maintained for a longer time, this determining the rapid transition to the phase of depressed interoceptive reflexes as well as the predominance of this phase of the experiments conducted without anesthesia.

In the preconvulsive, as well as in the postconvulsive, periods the pressor interoceptive reflexes were suppressed.

At low glycemic levels we observed the inversion of pressor reflexes into depressive reactions, this being true of the mechanical receptors of the stomach and rectum as well as the sino-carotid reflex. This last was seen against a background of a weakened or absent pressor sino-carotid reflex after restoration of blood flow in the carotid artery (Fig. 3, tracings 8 and 9).

There are grounds for the supposition that this peculiarity of the sino-carotid reflex, observed in a period of diminished or absent pressor interoceptive reflexes, is a consequence of decreased irritability of the vasomotor center accompanied by an increase of inhibitory influences upon it.

The described alterations in the interoceptive reflexes were not observed in control experiments.

As an additional control, we introduced glucose in every experiment in which the blood glucose level had been lowered. This fully confirmed the findings in our short experiments [8] as to the normalizing effect of glucose both in the first hypoglycemic phase as well as in the second (Figs. 1-3).

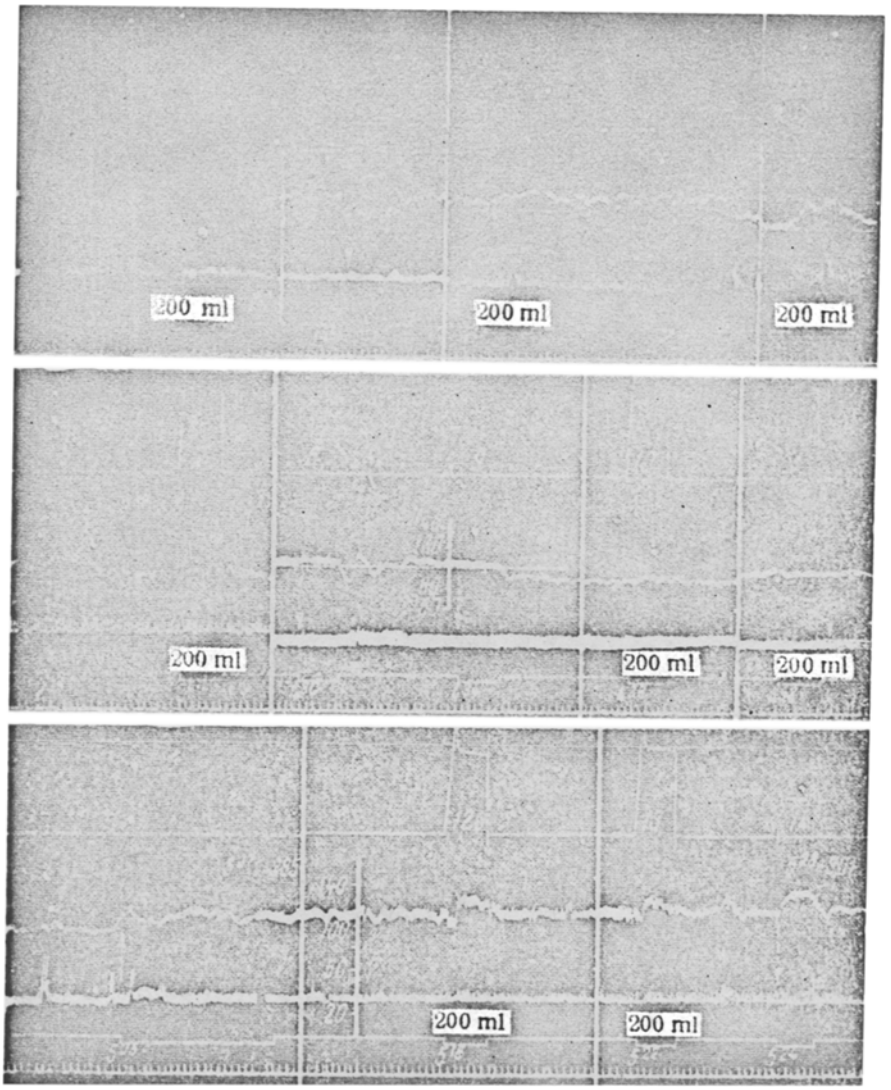

Fig. 3. Interoceptive reflexes under conditions of hypoglycemia provoked by insulin (2 units/kg). Druzhok experiment April 22, 1955. Reflexes from rectum – 2, 4, 5, 7, 11, 12, 13. Significance of tracings same as in Fig. 1. carotid artery clamped – ↓.

This normalizing influence of glucose permits a physiological explanation of its therapeutic actions in various phases of hypoglycemia. Basically, the glucose restores the normal relationships between the central nervous system and the internal organs which had been upset by the hypoglycemia.

In our opinion, our experimental data permits some discussion on the theoretical basis and practical application of insulin therapy in psychotic patients.

At present we know many psychic disturbances associated with pathological alterations in reception of impulses from the internal organs [1, 2, 4, 5, 13]. Judging from the clinical literature, the therapeutic insulin effect is obtained under conditions of suppression of the interoceptive reflexes. To this state of affairs testify such remarks as the need of lowering the glycemia quickly (intravenous insulin is advocated) with the goal of bypassing the period of preshock excitation and having the patient go into shock directly [12, 3]. Also, large doses of insulin are recommended with prolongation of the period of hypoglycemic shock [11], especially in cases of chronic schizophrenia [14], as well as simultaneous use of insulin and prolonged periods of interrupted sleep, the theory being to deepen the guarding reflex repression [6].

To all this must be added the fact that in hyperpyrexic therapy there is also suppression of the interoceptive reflexes as we have clearly demonstrated in our experiments on dogs having artificial fever [10].

Summarizing, it may be possible that the therapeutic basis for both fever and insulin therapy is the same. Basically, the temporary suppression of the interoceptive reflexes (especially if the interoceptive impulses are pathologic) permits a normalization of the functional interrelationships between the central nervous system and the internal organs and also a normalization of the functional state of the brain itself.

SUMMARY

Nonnarcotized dogs were employed in a study of hypoglycemic states. There was observed in these series experiments, first, an increased reflex response from both interoceptive stimuli from the rectum and stomach and also the baroceptive reflex from the carotid sinus. This was succeeded by a second phase of diminution and even total repression of the reflexes.

The dominating influence of the sugar blood level is pointed out. The reasons for some of the apparent differences in the results of the series and short experiments are discussed.

Finally, this temporary suppression of interoceptive reflexes is suggested as being the basis for the therapeutic effects of both insulin shock and fever therapy of schizophrenic patients.

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