MECHANISMS OF CENTRAL CONTROL OF THE BLOOD SUGAR

M. G. Amiragova and B. V. Stul'nikov

UDC 612.826.1+612.34

In acute experiments on adult cats injection of microdoses of insulin (0.025 unit/kg in 0.025 ml physiological saline) into the posterior hypothalamic nucleus caused the blood sugar level to be raised 10 and 70 min after the injection. The change in the blood sugar level correlated with the EEG activation reaction of the posterior hypothalamic nucleus in response to insulin injection, which spread to the lateral hypothalamus. Meanwhile hormonal action on the posterior hypothalamic nucleus following bilateral coagulation of the lateral hypothalamus no longer caused the rise in blood sugar after 10 min. This suggests that the lateral hypothalamus particpates in the formation of hyperglycemic responses within this time interval of insulin action on the posterior hypothalamic nucleus.

KEY WORDS: blood sugar; insulin; posterior hypothalamic nucleus; lateral hypothalamus

Recent investigations have conclusively proved that insulin can pass through the blood–brain barrier [3, 9, 10, 12], a fact which suggests that insulin may particpate in the central regulation of its own synthesis and of the blood sugar level. Some workers have shown [7, 8, 13] that insulin, injected intracisternally, causes a greater fall of the blood sugar level than if injected into the cerebrospinal fluid. However, the value of these investigations is diminished by the fact that the workers concerned used large doses of insulin which, on entering the general circulation, could induce a hypoglycemic effect and thereby mask the true action of insulin on the brain centers. In addition, when injected intracisternally, insulin acts on brain structures with different functions and the change in the blood sugar level thus produced is the resultant of the integral response of the various central mechanisms controlling the blood sugar level. As has been shown in the writers' laboratory [4], of all hypothalamic structures studied the posterior hypothalamic nucleus (PHN) is the most sensitive to insulin. Other workers have postulated [6, 15, 17] that PHN participates in the control of the blood sugar concentration but the mechanisms whereby this effect is produced are unknown.

The object of this investigation was to study these mechanisms by injecting microdoses of insulin into PHN.

EXPERIMENTAL METHOD

Acute experiments were carried out on adult cats starved for 18-20 h before the experiments began. The animals were anesthetized with urethane (1.5-2.0 g/kg). Electrodes were inserted into the hypothalamic structures stereotaxically following coordinates taken from Jasper and Ajmone-Marsan's atlas [11]. Insulin was injected into PHN in a dose of 0.025 unit/kg body weight in a volume of 0.025 ml. All insulin injection experiments were accompanied by recording of the EEG and histological verification. The results of experiments in which an EEG response to injection of insulin was observed were included in the series. The

Laboratory of Neuroendocrine Regulation, P. K. Anokhin Institute of Normal Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician V. N. Chernigovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 80, No. 12, pp. 3-6, December, 1975. Original article submitted March 5, 1975.

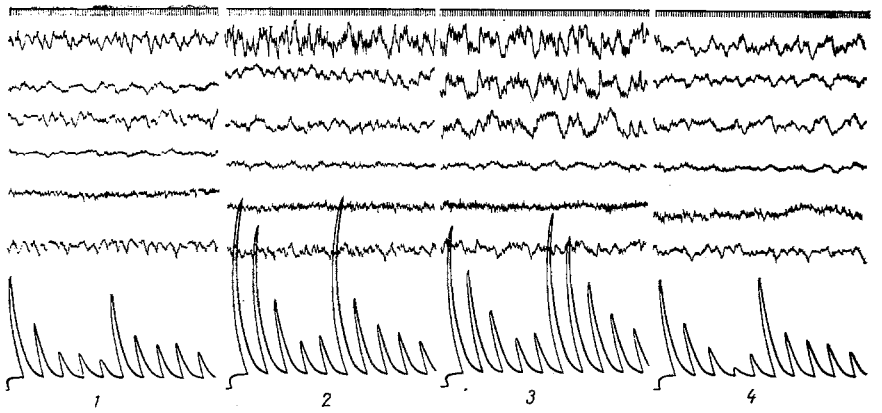

Fig. 1. Changes in EEG after injection of microdoses of insulin into PHN: 1) initial EEG; 2) EEG 1 min after injection of insulin; 3) EEG 10 min after injection of insulin; 4) EEG 30 min after injection of insulin. From top to bottom: right PHN, right lateral hypothalamus, right ventromedial hypothalamic nucleus, left lateral hypothalamus, left ventromedial hypothalamic nucleus, right PHN, right lateral hypothalamus. Monopolar recording for right lateral hypothalamus, bipolar for all other hypothalamic structures. Calibration: 50 μV, 1 sec. Analysis: channel 1 — right PHN, channel 2 — right lateral hypothalamus.

TABLE 1. Blood Sugar (in mg %) of Cats after Injection of Insulin into PHN and in Control Experiments with No Action on Hypothalamus (M ± m)

Group of animals	Before injection of insulin	After injection of insulin					
		after 10 min	change in concentration	after 40 min	change in concentration	after 70 min	change in concentration
With intact lateral hypothalamus (urethane anesthesia)	356±16	363±22	+8±2 <0,02	360±13	+5±9 >0,5	374±18	+17±5,1 <0,02
With bilateral destruction of lateral hypothalamus (urethane anesthesia)	320±10	316±11	−3,4±5,5 >0,5	323±10	+4±4 >0,2	343±18	+32±10 <0,05
Control — no action on hypothalamus (urethane anesthesia)	357±11	358±13	+0,3±2,7 >0,5	358±14	+1,0±2,8 >0,5	359±14	+2,0±3,0 >0,5

Legend. Time of taking blood samples in control experiments corresponds to times in experiments in which insulin was injected into PHN.

blood sugar was determined [14] before and 10, 40, and 70 min after injection of the hormone. The location of the electrodes was confirmed histologically [16]. Statistical analysis of the experimental results was carried out by the difference method [2].

EXPERIMENTAL RESULTS

It will be clear from Table 1 that, in response to injection of insulin into PHN the blood sugar level rose after 10 min (M ± m = +8 ± 2; P < 0.02). The change in the blood sugar level after 40 min was not significant: Although in some experiments the blood sugar level continued to rise, in others it was lower than initially. However, 70 min after

injection of the hormone the changes in the blood sugar concentration were significant and its mean level was significantly higher than initially ($M \pm m = +17.0 \pm 5.1$; $P < 0.02$). It is interesting to note that electrical stimulation of PHN also led to a statistically significant increase in the blood sugar concentration at all times studied (for 60 min). This points to the nonspecific character of this response to different types of PHN stimulation.

In response to injection of insulin into PHN, just as to its electrical stimulation, the lateral and ventromedial zones of the hypothalamus also were involved in the EEG-activation process (Fig. 1). One of the writers [5] showed previously that electrical stimulation of the lateral hypothalamus leads to elevation of the blood sugar level. To detect the mechanisms of the rise of blood sugar in response to injection of insulin into PHN, a similar series of experiments was therefore carried out except that the lateral hypothalamic structures were first destroyed electrically (by passing a direct current of 2-3 mA for 2-3 min).

As Table 1 shows, coagulation of the lateral hypothalamus itself led to a marked decrease in the initial blood sugar level. Meanwhile destruction of the lateral hypothalamus also affected the changes in the blood sugar concentration in response to injection of insulin into PHN. For instance, instead of the significant increase in blood sugar in response to injection of insulin into PHN in animals with an intact lateral hypothalamus 10 min after the injection, in animals with destruction of this region the changes in blood sugar at this time were not significant: Their mean value was -3.4 ± 5.5 mg % ($P > 0.05$), and changes in individual experiments were in different directions. The changes were of the same character at the next time interval, after 40 min ($M \pm m = +4.0 \pm 4.0$ mg %; $P > 0.2$). However, after 70 min the blood sugar level in all animals was higher than initially ($M \pm m = +32 \pm 10$ mg %; $P < 0.05$).

It is interesting to note that under thiopental anesthesia no activation response of PHN to injection of insulin could be detected electrographically (probably as a result of blockade of its reticular structures). The changes in the blood sugar concentration described above also were absent, so that correlation can be traced between the EEG reaction and the change in blood sugar in response to injection of insulin into PHN.

The increase in the blood sugar concentration in response to action directed toward PHN cannot be regarded as the result of a fall in the blood insulin level, for simultaneous determination of insulin in the blood showed a significant increase in its concentration [1].

The results of these experiments thus show that elevation of the blood sugar level following injection of insulin into PHN is caused by the direct action of the hormone on that structure and that the lateral hypothalamus participates in the mechanism of elevation of the blood sugar in the initial period (the first 10 min); the mechanisms of elevation of the blood sugar level in the later stages require special analysis.

LITERATURE CITED

1. M. G. Amiragova and B. V. Stul'nikov, Dokl. Akad. Nauk SSSR, 213, 746 (1973).
2. I. A. Oivin, Pat. Fiziol., No. 4, 76 (1960).
3. V. I. Pokryshkin, Byull. Éksp. Biol. Med., No. 10, 5 (1972).
4. V. I. Pokryshkin, "Neurophysiological analysis of the action of insulin on the CNS," Candidate's Dissertation, Moscow (1971).
5. B. V. Stul'nikov, Byull. Éksp. Biol. Med., No. 10, 3 (1973).
6. B. K. Anand and S. Das, Ind. J. Med. Res., 43, 123 (1955).
7. I. Chowers, Exp. Neurol., 9, 197 (1961).
8. I. Chowers, S. Lavy, and L. Halpern, Exp. Neurol., 14, 383 (1966).
9. A. F. Debons, Am. J. Physiol., 215, 1403 (1970).
10. T. Deckert, J. Lyngsoe, and O. J. Rafaelsen, in: 2nd Meeting of the European Diabetes Association, Aarhus (1966).
11. H. H. Jasper and C. Ajmone-Marsan, A Stereotaxic Atlas of the Diencephalon of the Cat, Ottowa (1954).
12. R. U. Margolis and N. Altszuler, Nature, 215, 1375 (1967).
13. R. U. Margolis and N. Altszuler, Proc. Soc. Exp. Biol. (New York), 127, 1122 (1968).
14. N. Nelson, J. Biol. Chem., 153, 378 (1944).
15. A. Paton, J. Endocrinol., 15, 33P (1957).

16. F. C. Quzman, M. Alcaraz, and A. Fernandez-Guadiola, Bol. Inst. Estud. Med. Biol. (Mexico), 16, 29 (1958).
17. E. S. Redgate and E. Gellhorn, Am. J. Physiol., 174, 475 (1953).