STATE OF HYPOTHALAMO-HYPOPYSEO-ADRENAL SYSTEM IN INSULIN HYPOGLYCEMIA

L. M. Pinchuk

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Experiments on 59 rats showed that the blood glucose level falls sharply, CRF-activity rises, the ACTH concentration in the pituitary is almost halved, while the ascorbic acid concentration in the adrenals is lowered 30, 60, and 180 min after injection of insulin. After combined injection of insulin and glucose the blood sugar level was almost unchanged. Changes in CRF-activity, the pituitary ACTH concentration, and the adrenal ascorbic acid level were slight. Insulin hypoglycemia led to activation of all components of the hypothalamo-hypophyseo-adrenal system, including CRF production.

The hypophyseo-adrenal system, under whose influence gluconeogenesis is stimulated, plays an essential role in the regulation of the blood glucose level after injection of insulin. The mechanism of activation of the hormone-forming and hormone-excreting function of the anterior pituitary and adrenal cortex is not absolutely clear.

Only limited information [3] is available to show that insulin hypoglycemia leads to the rapid accumulation of corticotropin-releasing factor (CRF), the initial component in the mechanism of hypothalamo-hypophyseo-adrenal function, in the hypothalamus. Other facts to give a more detailed picture of relations between the three components (CRF, ACTH, and the glucocorticoid function of the adrenal cortex) in insulin hypoglycemia could not be found in the accessible literature.

It was accordingly decided to study the state of adrenocortical function, the ACTH concentration in the pituitary, and the CRF activity of hypothalamic extracts of rats during the development of insulin hypothalamic and during combined administration of insulin and glucose.

EXPERIMENTAL METHOD

Three groups of adult male rats were used. The rats of group 1 were the control and were not given insulin. The rats of group 2 were given insulin (10 units/100 g body weight) by intramuscular injection and sacrificed 30 min, 1 h, and 3 h later. The rats of group 3 received intraperitoneal injections of 20% glucose solution at the rate of 5 ml to 10 units insulin along with the injection of insulin and also 30 min later. These rats were decapitated 1 h after the first injection.

At all stages of the experiment the blood glucose concentration was determined [6]. The left adrenal and pituitary glands and the hypothalamus were removed from the animals after decapitation.

The state of adrenal function was judged from the ascorbic acid concentration in the glands determined by the method of Roe and Kuether [7]. The ACTH concentration in the pituitary was determined by the method of Birmingham et al. in Skebel'skaya's modification [4] on recipient rats.

To determine the CRF activity in the hypothalamus, the method of Arimura et al. [5] was used. This consists essentially of obtaining extracts of the hypothalamus and subsequently testing their activity on

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TABLE 1. State of the Hypothalamo-Hypophyseo-Adrenal System in Insulin Hypoglycemia (M ± m)

Character of experiment	No. of animals	Blood glucose (in mg %)	P	Ascorbic acid (in mg %)	P	ACTH (in i.u.)	P	CFR (in mg % of decrease in ascorbic acid)	P
Intact rats	18	91±2,0		422±5,2		7,8±0,34		144±2,6	
Injection of insulin:									
after 30 min	11	52±2,1	<0,001	300±3,0	<0,001	6,4±0,28	<0,001	158±2,4	<0,001
» 60 »	10	27±0,8	<0,001	215±3,7	<0,001	5,6±0,42	<0,001	160±3,6	<0,001
» 180 »	10	22±0,8	<0,001	220±3,2	<0,001	4,2±0,36	<0,001	169±4,2	<0,001
Injection of insulin and glucose	10	82±2,1	<0,001	370±2,4	<0,001	7,0±0,52	>0,05	150±1,2	<0,05

recipient mice whose own hypothalamo-hypophyseo-adrenal system had first been blocked with a mixture of pentobarbital, morphine, and chlorpromazine. The CRF activity of the extract was expressed in the decrease in the ascorbic acid concentration in the adrenals of 51 recipient rats in mg %.

The main experiments were carried out on 59 male rats; 118 recipient rats were used to determine the ACTH concentration in the pituitary and the CRF activity of the hypothalamic extracts.

EXPERIMENTAL RESULTS

The results in Table 1 show that ordinary values of the ascorbic acid concentration in the adrenals were present in the intact rats. The pituitary ACTH level and the CRF activity of the hypothalamic extracts agreed with data in the literature [1-4]. Injection of insulin led to a sharp and progressive decrease in the blood glucose level which continued for 3 h. Corresponding changes in the dynamics of the parameters of the hypothalamo-hypophyseo-adrenal system took place: the ascorbic acid concentration in the adrenals was reduced, the ACTH concentration in the pituitary was almost halved, and the CRF activity of the hypothalamic extracts was increased.

The comparison of these findings suggests that as insulin hypoglycemia develops all components of the hypothalamo-hypophyseo-adrenal system are activated and, in particular, CRF formation is increased. The fact that it was the decrease in the blood sugar level itself (and not the action of insulin as a foreign protein) which was decisive was revealed by experiments in which insulin and glucose were given simultaneously. As Table 1 shows, in this group of experiments there was no significant decrease in the blood glucose level. The changes in CRF activity of the hypothalamic extracts and the ACTH concentration in the pituitary were correspondingly negligible, while the ascorbic acid level in the adrenal did not fall as low as after injection of insulin alone. It can thus be concluded that a decrease in the blood glucose concentration to hypoglycemic levels is a powerful stimulus for the hypothalamic cells which produce or liberate CRF.

The accumulation of CRF is evidently the trigger component which determines the subsequent activation of pituitary adrenocorticotropic function and activity of the adrenal cortex.

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