A POSSIBLE DIRECT ACTION OF HYPOTHALAMIC FACTORS ON DEVELOPMENT OF PANCREATIC HORMONAL ACTIVITY

A. Ya. Sapronova

UDC 612.349.7.018-06:612.826.4

KEY WORDS: encephalectomy; decapitation; hypothalamus; reactivity; fetus.

The writer showed previously that encephalectomy and decapitation of 17-18-day rat fetuses *in utero* inhibits the development of mechanisms of insulin release in response to stimulation, as a result of which the rat fetal pancreas remains refractory to glucose until the end of the prenatal period of development [1]. This effect is abolished after injection of homogenate of the hypothalamus into the encephalectomized fetus, which suggests that the hypothalamic region of the brain plays a role in the regulation of insulin release from the insular tissue of the fetus [1]. Data obtained in recent years on adult animals also indicate that, besides a nervous conduction component, the hypothalamo-insular axis also includes a neurohormonal (humoral) component [3, 7, 11].

The object of this investigation was to determine how the hypothalamus controls the insular function of the fetal pancreas: Do hypothalamic factors act directly on the pancreas or is their effect mediated through the pituitary, as is the case with pituitary-dependent endocrine glands.

TABLE 1. Release of Immunoreactive Insulin (IRI) into Medium, Induced by Glucose, from Pancreas of Encephalectomized Fetuses after Preincubation in Hypothalamic Incubation Medium

Experimental conditions	IRI concentration in incubation medium, μU/mg/60 min	
	basal level (2.08 mM glucose)	stimulated level (15 mM glucose)
Encephalectomy + preincubation in incubation medium of hypothalamus from:		
Adult rats	115,4±7,12 (9)	96,5±6,4
Newborn rats	96,0±9,6 (12)	116,8±8,7
21.5-day fetuses	65,7±1,4 (15)	69,2±1,6
Encephalectomy + precincubation in incubation medium of cerebral cortex from:		
Adult rats	99,2±5,8 (10)	102±8,7
Newborn rats	93,1±12,5 (6)	92,3±14,8
21.5-day fetuses	86,9±4,9 (11)	80,9±4,8

Legend. Here and in Table 2, number of fetuses shown in parentheses.

Laboratory of Hormonal Regulation, N. K. Kol'tsov Institute of Developmental Biology, Academy of Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. P. Avtsyn.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 11, pp. 526-527, November, 1985. Original article submitted April 19, 1985.

0007-4888/85/0011-1473$09.50

TABLE 2. IRI Release into Medium, Induced by Glucose, from Pancreas of Decapitated Fetuses after Replacement Injection of Adult Rat Hypothalamic Homogenate into Them

Experimental conditions	IRI concentration in incubation medium, μU/mg/60 min	
	basal level (2.08 mM glucose)	stimulated level (15 mM glucose)
Decapitation	158,4±12,1 (11)	154,0±7,8
Decapitation + hypothalams homogenate	122,0±12,2 (11)	140,2±14,2
Decapitation + cortex homogen	104,8±16,1 (8)	103,0±13,7

EXPERIMENTAL METHOD

The experimental animals were Wistar albino rats. To remove the hypothalamus, the rat fetuses underwent encephalectomy *in utero* [2], and as the experimental model of hypophysectomy, decapitation of the fetuses *in utero* was used [9]. The operation on the fetuses was performed after 17.5-18.5 days of development and the reactivity of the fetal pancreas was studied after 21.5 days of intrauterine life. To study the possibility of a direct effect of hypothalamic factors on the developing pancreas, experiments were carried out in which glands of encephalectomized fetuses were incubated in medium used previously to incubate the hypothalamus. For this purpose, a fragment of hypothalamus, including the median eminence and also the cerebral cortex, was isolated from adult male rats, newborn rats, and 21.5-day rat fetuses, killed by decapitation. The brain regions, isolated in the cold, were transferred to flasks containing 1 ml of Krebs–Ringer bicarbonate buffer (pH 7.4), containing 2.08 mM glucose, 2 mg/ml bovine serum albumin, and 1000 KIU/ml of trasylol. Three fragments of adult hypothalamus, four fragments of neonatal hypothalamus, or five fragments of fetal hypothalamus were added to 1 ml of buffer and gassed with a mixture of 95% O_2 + 5% CO_2. After incubation for 30 min at 37°C and gentle shaking, the incubated samples were pooled and centrifuged during cooling (3000 rpm) for 15 min. Similar procedures were carried out at the same time with the cerebral cortex. Pancreatic fragments from 21.5-day encephalectomized fetuses (one fragment per flask), after preincubation in ordinary Krebs–Ringer bicarbonate solution, were transferred into medium obtained after incubation of the hypothalamus or cerebral cortex, after which the pancreatic fragments were gassed with a mixture of 95% O_2 + 5% CO_2 and incubated in medium with low (2.08 mM) and high (15 mM) glucose concentrations (60 min in each). Experiments also were carried out in which homogenate of the hypothalamus or cerebral cortex of adult rats was injected into 21.5-day-old decapitated fetuses. Fragments of hypothalamus and cerebral cortex, isolated in the cold, were placed in glass homogenizers, and homogenates were prepared in physiological saline. Next, 0.05 ml of the freshly prepared homogenate, in the proportion of three hypothalamic fragments to one fetal pancreas, was injected subcutaneously into the spinal region of some of the decapitated fetuses *in utero*. Decapitated fetuses into which homogenate of cerebral cortex was injected served as the control. The fetuses were removed from the uterus 30 min after the injection and the pancreatic fragments were incubated in the usual manner.

EXPERIMENTAL RESULTS

Experiments to incubate pancreatic fragments of encephalectomized fetuses in medium in which fragments of the hypothalamus of adult animals, newborn rats, and 21.5-day fetuses had been preincubated, did not lead to compensation of the effects of the operation, and the pancreas remained refractory to glucose. For instance, no difference was found between the basal and glucose-stimulated levels of immunoreactive insulin in the medium in any of the experimental groups (Table 1). This is evidence that hypothalamic insulinotropic factors, which determine recovery of the insulin response to glucose after injection of hypothalamic homogenate into encephalectomized fetuses [1], have no direct stimulating action on the fetal insular tissue *in vitro*. This is confirmed by the results of experiments in which hypothalamic homogenate was injected into decapitated fetuses, i.e., in the absence of the pitu-

itary hypothalamic homogenate does not restore normal insulin release in response to elevation of the glucose concentration in the medium (Table 2). This indicates that the pituitary participates in hypothalamic control of the endocrine function on the pancreas in rat fetuses.

These results are in good agreement with the writer's previous observations on restoration of reactivity of the B-cells of decapitated fetuses after combined incubation with the adenohypophysis and its hormones [8], and also with data in the literature on the effect of the pituitary gland and its trophic hormones on pancreatic B-cell function in adult animals [4, 5, 9, 10].

It can be postulated that fetal pancreatic B-cells, unlike the corresponding cells of adult animals, are refractory to direct humoral hypothalamic influence, and that humoral connections between the hypothalamus and pancreas in rat fetuses are maintained through the participation of the pituitary.

LITERATURE CITED

1. M. S. Mitskevich and A. Ya. Sapronova, Zh. Évol. Biokhim. Fiziol., 17, 127 (1981).
2. M. S. Mitskevich, O. N. Rumyantseva, E. V. Proshlyakova, and G. P. Sergeenkova, Ontogenez, 1, 631 (1970).
3. G. H. Brouwer, M. S. Lamtey, and J. M. Martin, Life Sci., 30, 703 (1982).
4. J. Brunstedt and J. H. Nielsen, Acta Endocrinol. (Copenhagen), 96, 498 (1981).
5. S. Dunmore, J. Morton, A. Beloff-Chain, and G. Taylor, Biochem. Soc. Trans., 11, 201 (1983).
6. A. Jost, C. R. Acad. Sci. (Paris), 225, 322 (1947).
7. M. Khip, L. Lautala, H. Akerblom, et al., Life Sci., 33, 2311 (1983).
8. M. S. Mitskevich and A. Ya. Sapronova, Endokrinologie, 79, 227 (1982).
9. J. H. Nielsen, Endocrinology, 110, 600 (1982).
10. J. Pierluissi and J. Campbell, Diabetologia, 18, 223 (1980).
11. F. Rohner-Jeanrenaud and B. Jeanrenaud, Ann. Endocrinol., 44, 217 (1983).

EXPERIMENTAL EXOGENOUS ACTIVATION OF THE KININ-FORMING SYSTEM AND FUNCTIONAL MORPHOLOGY OF GASTRIC FUNDAL GLANDS

I. V. Sukhodolo, L. N. Batsula, T. I. Fomina, and L. A. Bogatyreva

UDC 612.325:612.323/-06.612.321.018:577.175.85

KEY WORDS: kallikrein-kinin system; enzyme activity; cells of fundal glands; gastric mucosa.

Control over gastric function is maintained by many mechanisms, among which not the least important is the kallikrein-kinin system (KKS) [3, 5]. Different states of the KKS (activation and inhibition) are reflected differently in the excretory, secretory, and motor activity of the stomach [2]. The KKS plays a definite role in gastroenteric pathology, for the number of its various components changes in chronic gastritis, in peptic ulcer, and in nonspecific ulcerative colitis [3, 6-8].

Components of the KKS are found in the gastric mucosa, gastric juice, and mucus [10-12], and their quantity varies in the gastrin, histamine, and insulin tests [1, 4]. However, no definite opinion has yet been formed on the effect of activation of the KKS on the functional morphology of the intact gastric mucosa.

The dynamics of histochemical parameters of function of the parietal and chief cells, and the surface and pit epitheliocytes of the fundal glands of the rat stomach was studied in the present investigation during activation of the KKS by kallikrein.

Central Research Laboratory, Tomsk Medical Institute.

Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 100, No. 11, pp. 528-530, November, 1985. Original article submitted February 15, 1985.