Bombesin Stimulates Pancreatic β-Cells in Rats with Experimental Diabetes Mellitus

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 7, pp. 33-35, July, 1998
Original article submitted June 30, 1997

Intracerebroventricular (1.5 pM) and intraperitoneal (1.0 nM) injections of bombesin for 10 days enhance insulin synthesis and secretion and reduce glycemia in rats with streptozotocin-induced diabetes mellitus as compared with nontreated diabetic rats. In intact rats insulin synthesis in β-cells is stimulated only by intracerebroventricular injections of bombesin.

Key Words: *insulin; bombesin; pancreas; diabetes mellitus*

Our previous studies have demonstrated that the development of diabetes mellitus is accompanied by accumulation of neurons producing gastrin-releasing peptide in the paraventricular nucleus of the hypothalamus and an increase in the content of this peptide in these neurons [3]. It has been shown that bombesin (BB)-like peptides (gastrin-releasing peptide) inhibit food-procuring behavior in animals [7] and participate in the regulation of the pancreatic endocrine function [8,12]. In the present study we investigate the effects of chronic intracerebroventricular (ICV) and intraperitoneal injections of bombesin in intact rats and in rats with streptozotocin-induced diabetes mellitus on the function of β-cells.

MATERIALS AND METHODS

Experiments were carried out on 96 male Wistar rats weighing 250-270 g. Diabetes mellitus was induced by a single injection of streptozotocin (Sigma) in a dose of 50 mg/kg. A stainless steel cannula was implanted into the right lateral cerebral ventricle for ICV injection of BB. Synthetic BB (Peninsula Laboratories Inc.) was injected daily for 10 days: ICV dose was 1.5 pmol BB in 3 μl 0.9% NaCl and intraperitoneal dose was 1.0 nmol BB in 0.5 ml 0.9% NaCl. Diabetic rats received BB starting from the 25th day after streptozotocin injection, when the major clinical symptoms of diabetes mellitus developed [2]. Control animals were injected with equivalent volumes of 0.9% NaCl. The animals were decapitated under Nembutal narcosis (40 mg/kg) 24 h after the last BB injection (after a 16-h fast), blood glucose and insulin concentrations were measured, and the pancreas was isolated for immunocytochemical analysis. Insulin in pancreatic β-cells was visualized by the method of indirect immunofluorescence using kits manufactured by Peninsula Laboratories Inc. and quantified using a Lyumam-I2 computer-assisted cytofluorimetric system (LOMO, Russia) as described previously [4]; the content of insulin was expressed in arbitrary microunits (μU). Blood insulin concentration was measured by radioimmunoassay using INS-PG-^{125}I kits (Belarus') and blood glucose was determined by the glucose oxidase method with Diakom glucose GO kits (Diakom-Sinteko, Russia).

RESULTS

We found that in intact animals the content of insulin in pancreatic β-cells increased only after chronic ICV injections of BB (Table 1). It should be noted that BB had no effect on the mean number of β-cells in pancreatic islets (49.9±2.3 in intact animals) and the content of glucose and insulin in peripheral blood.

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0007-4888/98/0007-0670$20.00

TABLE 1. Effect of BB Injections on Blood Concentrations of Glucose and Insulin and the Content of Insulin in β-Cells in Intact Rats and in Rats with Experimental Diabetes Mellitus (*M*±*m*)

Groups, interentions	Blood glucose concentration, mmol/l	Blood insulin concentration, pmol/l	Insulin content in β-cells, μU
Intact	3.59±0.06	59.7±5.4	1893.5±4.9
ICV injections of 0.9% NaCl	3.64±0.07	62.2±5.8	1897.1±5.2
intraperitoneal injections of BB	3.60±0.14	53.2±9.4	1878.4±7.8
ICV injections of BB	3.76±0.16	58.2±5.8	2592.3±12.0***
Diabetes mellitus	8.49±0.41**	17.9±2.7***	1389.6±7.3***
ICV injections of 0.9% NaCl	8.52±0.47**	16.8±3.8***	1392.4±6.9***
intraperitoneal injections of BB	6.77±0.44**	39.2±2.7**	2183.7±13.8***
ICV injections of BB	5.83±0.46*	53.6±5.9	2496.1±11.2***

Note. *$p<0.05$, **$p<0.005$, ***$p<0.001$ compared with intact animals.

The development of diabetes mellitus was accompanied by destructive changes in the Langerhans islets: the number of β-cells decreased to 15.3±1.4 ($p<0.0001$) together with a decrease in blood and cellular insulin content. This resulted in a rise of serum glucose concentration (Table 1). Chronic intraperitoneal and ICV injections of BB to diabetic animals had no effects on destructive alterations in the Langerhans islets (the mean number of β-cells was 13.3±0.7 per islet, $p>0.05$). However, the content of insulin in β-cells rose and surpassed that in β-cells of intact animals. The content of insulin in peripheral blood increased and in animals receiving ICV injection it practically attained the level observed in intact animals. These shifts resulted in a drop of blood glucose, although glycemia remained above the control level. Stimulation of insulin synthesis and secretion was more pronounced in ICV than in intraperitoneal route of BB, particularly in diabetic animals ($p<0.001$).

Despite the facts that receptors to BB-like peptide were found on pancreatic cells [10], there are no publications on direct insulin-stimulating effect of BB-like peptides after peripheral administration to intact animals. It is generally assumed that BB specifically acts on pancreatic α-cells [8,12], which manifests itself in glucagon-stimulated hyperglycemia potentiating insulin secretion [9]. On the other hand it has been shown that BB restricts damage to the Langerhans islets in alloxan-induced diabetes mellitus [12]. These effects may arise in diabetic animals receiving chronic intraperitoneal injections of BB.

Our experiments showed that chronic ICV injections of BB stimulate the synthesis and secretion of insulin. Under these conditions some neurotransmittory and neuromodulatory effects of the peptide are realized. It is well documented that central administration of BB-like peptides produces an anorexigenic effect [11] due to modulation of physiological activity of the ventromedial nucleus of the hypothalamus [5]. A high density of gastrin-releasing-peptide/BB-immunoreactive fibers in the area of the nucleus of the vagus nerve [6] attests to a possibility of modulating their functional activity by the hypothalamus. This seems quite reasonable in light of the existence of the hypothalamo-vagal pathway of regulation of insulin secretion originating from the neurons of the paraventricular nucleus [1], including gastrin-releasing-peptide-synthesizing neurons which are activated in diabetes mellitus [3].

Thus, we have shown that chronic administration of BB stimulates insulin synthesis and secretion in rats with experimental diabetes mellitus. This opens new prospects in the correction of diabetes mellitus with this bioactive substance.

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