BIOGERONTOLOGY

Prospects of Using Pancragen for Correction of Metabolic Disorders in Elderly People

O. V. Korkushko, V. Kh. Khavinson*, V. B. Shatilo, I. A. Antonyk-Sheglova, and E. V. Bondarenko

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We examined two groups of older persons: 30 healthy and 33 patients with type 2 diabetes mellitius. Nocturnal melatonin production was significantly reduced by 70% in patients with DM2 compared to healthy individuals of the corresponding age. In patients with DM2, pancragen significantly decreased glucose level on an empty stomach and in standard glucose tolerance test and reduced plasma concentrations of insulin and insulin resistance index. In patients receiving no pancragen, no changes in carbohydrate metabolism indices were observed. Thus, disturbances in the melatonin-producing function of the pineal gland in elderly individuals contribute to the development of insulin resistance. Administration of the tetrapeptide pancragen is a promising approach to the correction of insulin resistance in elderly individuals.

Key Words: *elderly age; type 2 diabetes mellitius; insulin; peptide; pancragen*

Insulin resistance (IR) and hyperinsulinemia are independent risk factors for coronary heart disease and type 2 diabetes mellitius (DM2) [3,10]. The frequency of detection of IR and hyperinsulinemia increases with age [2,9,11].

The role of the pineal gland and melatonin in the regulation of carbohydrate metabolism was recently established. Removal of the pineal gland promotes the development of tissue IR, impairs glucose tolerance, decreases the content of glucose transporter GLUT4 in the adipose and muscle tissues, reduces glycogen synthesis in the liver and muscles [1,9,13], increases blood levels of glucose, insulin, and triglycerides [7,8].

Impairment of the melatonin-producing function of the pineal gland during aging [4,6,12] may contribute to the development of IR in elderly individuals, while administration of peptide bioregulators would improve disturbed carbohydrate metabolism.

Here we studied the relationship between the level of nocturnal excretion of 6-hydroxy melatonin sulfate (6-GMS) and carbohydrate metabolism in elderly people and evaluated the effectiveness of synthetic tetrapeptide pancragen [5] in the treatment of metabolic disorders in elderly patients with DM2.

MATERIALS AND METHODS

All participants signed informed consent form. The protocol and research program were approved by local Ethic Committee.

The study included two groups of individuals aging 60-74 years: 30 healthy and 33 patients with DM2.

The patients with DM2 were on hypoglycemic diet (No. 9) for at least 3 months before the study, performed moderate exercises, and took glucose-lowering

Institute of Gerontology, National Academy of Medical Sciences of Ukraine, Kiev, Ukraine; *St. Petersburg Institute of Bioregulation and Gerontology, North West Branch, Russian Academy of Medical Sciences, Russia. ***Address for correspondence:*** ibg@gerontology.ru. V. Kh. Khavinson

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TABLE 1. Fasting Plasma Glucose Concentration and Standard GTT in Elderly DM2 Patients Treated by Different Schemes

Plasma glucose concentration, mmol/liter			Before treatment	After treatment
Group 1	fasting		9.1±0.4	9.0±0.4
	standard GTT	1 hour	12.0±0.5	11.7±0.5
		2 hours	11.2±0.4	11.0±0.4
Group 2	fasting		9.4±0.3	8.3±0.4*
	standard GTT	1 hour	12.8±0.4	11.5±0.3*
		2 hours	11.5±0.4	10.3±0.3*

Note. Here and in Table. 2: *$p<0.05$ compared to the indicator before treatment.

drugs glibenclamide in a dose of 15 mg/day, but they had not achieved the optimum level of glycemia, which was seen from glycosylated hemoglobin over 7.5%. After examination, diabetic patients were randomized into two groups not differing by age, body mass index, and levels of glucose and glycosylated hemoglobin.

Group 1 patients (N=16) in addition to glibenclamide (15 mg/day) were given tetrapeptide pancragen (100 mg *per os* 2 times a day for 3 weeks). Group 2 patients (N=17) continued glibenclamide (15 mg/day) during this period. Examination was conducted before randomization, after treatment, and 2 weeks after termination of pancragen administration.

The concentrations of 6-GMR in the urine were determined by ELISA using ABL Humburg Gmbh kits on a Multiscan EX analyzer (Labsystems). Nocturnal urinary 6-GMR was calculated as the product of 6-GMS concentration and volume of urine collected from 22:00 to 7:00.

The levels of glycated hemoglobin were determined using Cobas Integra 400 plus immunoturbidimetric analyzer (Roche Diagnostic). The concentration of glucose in blood plasma was measured by an enzymatic method using BioTest kits (Pliva-Lachema). In diabetic patients, the standard glucose tolerance test (GTT) was performed. After measuring fasting plasma glucose, the examinee took 75 g glucose dissolved in 300 ml of water and plasma glucose concentration was measured after 60 and 120 min. Fasting insulin in the plasma of venous blood was determined by radioimmunoassay using standard kits (Immunotech). IR index was calculated (HOMA-IR, the homeostasis model assessment index):

$$\text{HOMA-IR}=\text{FPG}\times\text{FIRI}/22.5,$$

where FPG is fasting plasma glucose (mmol/liter); FIRI is fasting immunoreactive insulin (μU/ ml).

HOMA-IR>2.77 indicated the presence of IR.

The data were processed by methods of variation statistics using Microsoft Excel. Statistically significant differences and changes in the parameters were estimated by parametric Student's t test.

RESULTS

In most (70%) of elderly DM2 patients, nocturnal excretion of 6-HMS was 5.5±0.6 μg, *i.e.* was significantly lower than in healthy elderly subjects (11.7±1.3 μg). Thus, the decrease in melatonin-producing function of the pituitary gland is a possible factor influencing the development of IR in elderly people.

In healthy elderly people, fasting plasma glucose was 5.88±0.38 mmol/liter. In DM2 patients, pancra-

TABLE 2. Plasma Glucose and Insulin Concentration and HOMA-IR in Elderly DM2 Patients before and after Treatment

Indicator	Group 1		Group 2	
	before treatment	after treatment	before treatment	after treatment
Fasting plasma glucose concentration, mmol/liter	9.1±0.4	9.0±0.4	9.4±0.3	8.3±0.4*
Fasting plasma insulin concentration, μU/ml	19.2±2.0	18.8±1.9	20.5±1.9	18.3±1.7
HOMA-IR, rel. units	7.8±0.8	7.5±0.7	8.5±0.8	6.9±0.7*

gen significantly decreased fasting plasma glucose (by 11.7% from its initial level before treatment, Table 1). When conducting standard GTT, plasma glucose concentrations after 1 and 2 h were also significantly lower (10.2 and 10.4% respectively) than before pancragen treatment.

In patients receiving pancragen, apart from significant decrease in glucose levels, a tendency to a decrease in plasma insulin concentration was observed. This led to a significant decrease in HOMA-IR by 18.8% as compared to the corresponding value before treatment (Table 2), which suggests that pancragen shifts HOMA-IR to a value observed in healthy subjects (2.34±0.44 rel. units).

Two weeks after pancragen withdrawal, the additional glucose-lowering effect persisted in 9 of 16 patients (60%) who continued taking the former dose of glibenclamide. In patients who did not receive pancragen, no changes in plasma glucose and insulin concentrations and HOMA-IR were observed.

These findings suggest that in the majority of elderly DM2 patients, nocturnal production of melatonin is significantly reduced compared to healthy individuals of the corresponding age. Disturbances of the melatonin-producing function of the pineal gland are possible factors influencing the development of insulin resistance in elderly age. Administration of the tetrapeptide pancragen is a promising approach to correction of insulin resistance in advanced age.

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