ORIGINAL ARTICLE

GALANIN LEVELS IN HYPERTENSIVE PATIENTS WITH OBESITY

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ABSTRACT

The aim: To study the level of Galanin concentration in hypertensive patients with obesity, and to identify how the degree of hypertension and the degree of obesity affect the level of Galanin in patients with this comorbid pathology.

Materials and methods: The study included 58 patients with hypertension. Grade 1 was diagnosed in 12 (20.69%), grade 2 – 16 (27.59%), grade 3 – 30 (51.72%) examined patients. Of the patients enrolled to study, 32 were women and 26 were men, 32 to 79 years old (mean age – 57,5±10.11 years).

Results: The level of Galanin in all groups of hypertensive patients was significantly increased compared to the control group ($p < 0.001$). The concentration of the latter in the blood serum gradually increases according to the degree of hypertension, while ($p<0.01$), and the maximum level of Galanin was observed in group of patients with grade 3 hypertension (Me 164.47 pg/mL). The level of Galanin concentration in all subgroups of patients, depending on the presence and degree of obesity, was significantly increased compared to the control group ($p < 0.001$), the maximum level of Galanin was in the group with hypertension and obesity of 3 degrees (Me = 166.48 pg/mL).

Conclusions: In hypertensive patients with obesity, a significant increase in the concentration of Galanin was detected; most pronounced in arterial hypertension grade 3 and obesity grade 3. Galanin is possibly a biomarker of cardiovascular risk in a cohort of patients with abdominal obesity.

KEY WORDS: Galanin, arterial hypertension, obesity, carbohydrate metabolism, lipid metabolism

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INTRODUCTION

Hypertension is the most common disease of the cardiovascular system. Based on office blood pressure (BP), the global prevalence of hypertension was estimated at 1. 13 billion in 2015 [1], and in Central and Eastern Europe - more than 150 million. The total prevalence of hypertension in adults is about 30-45% [2], and the worldwide prevalence by age is 24% and 20% for men and women, respectively, in 2015 [1]. At the same time, by 2025 a further increase in the number of patients with hypertension by another 15-20% is predicted [3]. Compared to European countries, the prevalence of hypertension in Ukraine is 34,968 patients per 100.000 of population [4].

It is well known that obesity, especially its abdominal (visceral) form, is one of the most important risk factors for hypertension. In the Health ABC Study, it is abdominal obesity that is closely associated with the presence of hypertension, and the correlation was strong even in individuals with a low total body fat [5]. Population studies indicate that 2/3 of hypertensive patients are overweight or obese [6]. The World Health Organization has defined obesity and overweight as "pathological or excessive accumulation of fat that can adversely affect health" [7] and declared this pathology a global epidemic. The main reason of overweight and obesity is an energy imbalance, as a result of which the caloric intake exceeds energy needs of the body.

World studies have shown that appetite is regulated by a complex network of peptides that are synthesized in the peripheral and central nervous systems [8, 9]. Most peptides mediate their action in the hypothalamus, which leads to stimulation or inhibition of food intake [8 ,9, 10]. One such neuropeptide is Galanin (GAL), a peptide of 29 amino acids (30 in humans), which was discovered in 1983 in the intestines of pigs as an orexigenic neuropeptide that increases food intake. It is mainly synthesized in the nervous system, both in the central and peripheral and gastrointestinal tracts, as well as in adipose tissue, skeletal system, endocrine organs, as well as in immune and hematopoietic cells [11, 12].

Existing evidence suggests that GAL may contribute to the onset of metabolic syndrome in adults. Le Bu, Qian Yao, et al in 2014 found a significantly increased concentration of Galanin in patients with abdominal obesity, metabolic syndrome (MS), type 2 diabetes mellitus (DM 2), and gestational diabetes mellitus (GDM). At the same time, although the diagnostic and prognostic potential of GAL in patients with MS looks quite attractive, it has not been precisely established. However, several animal studies and some clinical studies have shown that GAL improves insulin sensitivity and improves glucose clearance in adipose tissue, skeletal muscles and cardiac muscle using type 4 glucose transporter receptors. It also inhibits glucose-stimulated insulin secretion both in humans and in animals [13-15].

The relationship between GAL and hypertension has not been fully understood. Some studies have reported the effect of GAL on the regulation of BP and heart rate (HR) in animals [16]. A recent study by Fang P., Yu M., 2017 showed that plasma GAL levels were significantly reduced in patients with obesity and arterial hypertension (AH) compared with the obese control group, while GAL levels were significantly increased in the

control group with obesity compared to the overweight control group. In addition, plasma GAL concentration negatively correlated with diastolic blood pressure (DBP) in obese and hypertensive individuals [17, 18]. However, a study by other scientists found a slight negative correlation with systolic blood pressure (SBP) and there was no correlation between serum GAL levels with DBP in hypertensive patients with obesity. [19].

Due to the lack of unanimous opinion regarding the concentration of GAL and its role in comorbid pathology, namely, hypertension and obesity, this issue remains relevant today. Probably, further research in this direction is required to clarify the prospects for the use of the GAL neuropeptide in routine clinical practice as a marker of cardiovascular risk.

THE AIM

In our work we aim to study the level of Galanin concentration in hypertensive patients with obesity, and to identify how the degree of hypertension and the degree of obesity affect the level of Galanin in patients with this comorbid pathology.

MATERIALS AND METHODS

The study included 58 patients with hypertension, who were on inpatient treatment in the cardiology department of the Kharkiv city clinical hospital No 27. Of the patients enrolled to study, 32 were women and 26 were men, 32 to 79 years old (mean age – 57.5±10.11 years), who previously have not been receiving regular antihypertensive therapy. The diagnosis was verified on the basis of clinical, laboratory and instrumental methods of investigation. Exclusion criteria for patients with this study, in addition to patients with symptomatic hypertension, were patients with cancer, acute and chronic inflammatory processes, concomitant diseases of the thyroid gland, and diabetes mellitus. The control group included 20 sex-matched practically healthy persons. According to the Helsinki Declaration, all patients were informed of a clinical trial and agreed to participate.

All patients had BP measured in a sitting position after a 5-minute rest according to the method of M.S. Korotkova. The guidelines by of European Society of Cardiology (ESC) / European Society of Hypertension (ESH), criteria of Ukrainian Association of Cardiology were used for verification of the diagnosis and estimation of the hypertension grade [20].

At the same time, grade 1 hypertension was diagnosed in 12 (20.69%) patients, grade 2 hypertension – 16 (27.59%), and grade 3 hypertension – 30 (51.72%) examined patients. The diagnosis of obesity is established in accordance with the classification based on the determination of body mass index (BMI). This classification is developed by the National Institutes of Health by the United States of America, and approved by the World Health Organization. Anthropometric measurements included height (cm), weight (kg), waist circumference (WC, cm) and hips circumference (HC, cm). It was followed by calculation of BMI (kg/m^2), according to the formula BMI = body weight /height^2 as well as calculation of the waist to hip ratio (WHR). A sign of visceral or abdominal type of adipose tissue distribution was WC > 94 cm for male and >102 cm for female. A WC / HC value > 0.90 for male and > 0.85 for female attesting to the presence of abdominal (visceral, central) type of adipose tissue distribution. Blood for biochemical research was carried out in the morning on the next day after admission of the patient to the hospital after 6–12-hours starvation. Blood was taken from the ulnar vein. At the same time, all patients were in the same physical activity conditions.

Galanin levels (pg/mL) were determined by enzyme immunoassay method using Elabscience® Human GAL (Galanin) ELISA Kit reagents (USA). In order to control carbohydrate metabolism, the glucose level was determined by the fasting glucose oxidase method, the content of glycosylated hemoglobin (HbA1c) in whole blood was determined by photometric method by reaction with thiobarbituric acid using a commercial test system of the company "Reagent" (Ukraine). The levels of total cholesterol (TC, mmol/l), high-density lipoprotein cholesterol (HDL CS, mmol/l) and triglycerides (TG, mmol/l) were determined by enzymatic method using standard kits. The level of very low-density lipoprotein cholesterol (VLDL CS, mmol/l) was calculated using the by the value of the ratio: VLDL CS = TG/2.2. Low - density lipoprotein cholesterol (LDL CS, mmol/l) was determined using the formula Friedewald: LDL CS = TC - (HDL CS + TG/2.2). Coefficient of atherogenicity (CA) was calculated by the Klimov formula: CA = (TC - HDL CS) / HDL CS.

Mathematical computer processing of results was carried out with the help of the software package Statistica 10.0 (StatSoft Inc.). The mean value (Mean) and standard deviation (SD) were determined. Analysis of the data was carried out by methods of nonparametric statistics. In samples with the non-parametric data distribution the results are presented as Me (LQ; UQ), where Me – median of index, LQ - lower quartile, UQ – upper quartile. The Mann–Whitney U-test was used for comparison of the results between groups. Spearman's rank correlation coefficient was used for estimation of the relationship between two variables. The null hypothesis is excluded at the level of $p < 0.05$ significance.

RESULTS

In the course of our research, we found a significant increase in the level of GAL. The median GAL in patients of the main group was 146.49 with an interquartile range from 53.86 to 164.72 (pg/mL). Compared with the control group, the Median is 30.58 with an interquartile range from 28.07 to 31.90 (pg/mL) (Fig.1.).

In order to determine the effect of increased BP on the GAL value, patients were divided into 3 groups depending of the degree of hypertension (Table I).

It was found that the level of the studied neuropetide GAL in all groups of hypertensive patients was significantly increased compared to the control group ($p < 0.001$). As can be seen from Table I and Fig. 2., the concentration of the latter in the blood serum gradually increases according to the degree of hypertension, while ($p<0.01$), and the maximum level of GAL was observed in 3 groups of patients with grade 3 hypertension (Me 164.47 pg/mL).

To analyze the effect of the level of weight gain on the concentration of the studied orexigenic neuropetide,

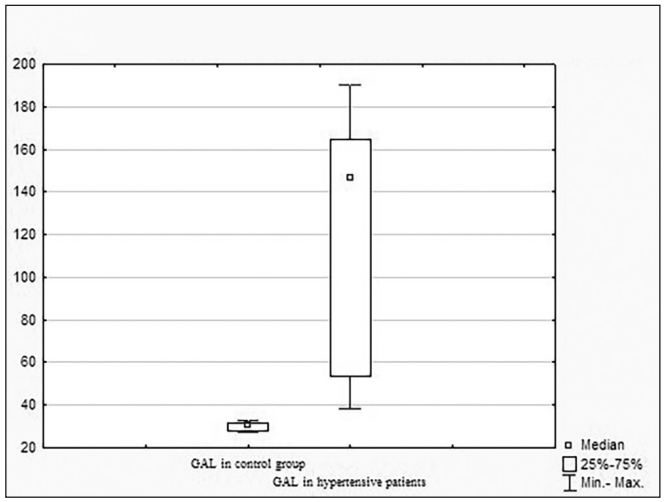

Fig. 1. The level of GAL (pg/mL) in control group and hypertensive patients.

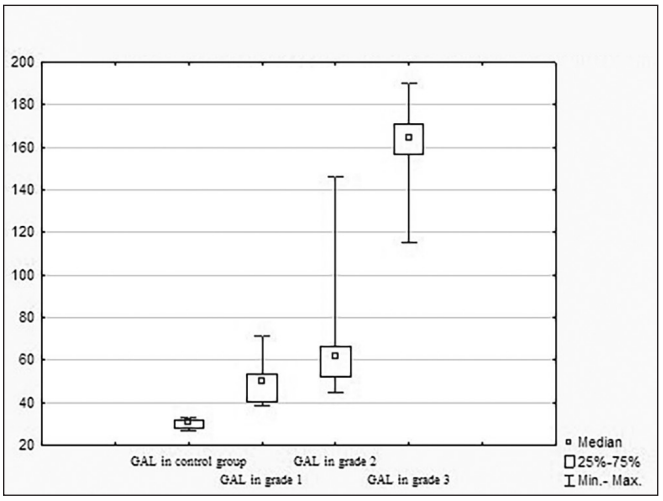

Fig. 2. The level of GAL (pg/mL) in hypertensive patients depending on grade of AH.

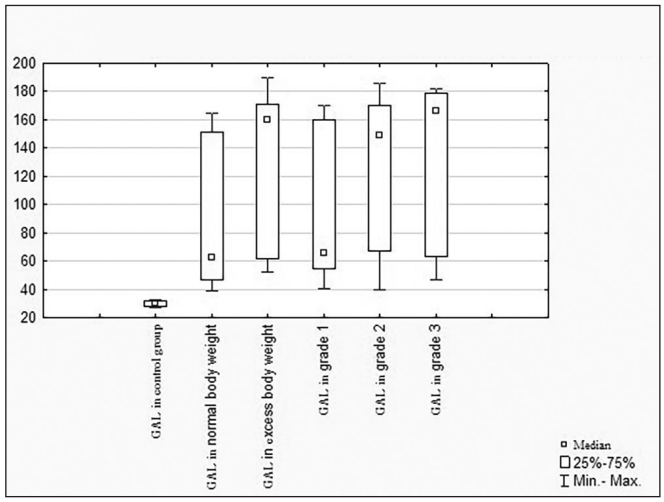

Fig. 3. GAL level (pg/mL) depending from the presence and degree of obesity.

groups of obese and non-obese patients were identified. As we can see from Table II, the concentration of the latter in blood serum significantly differed between the control group in comparison with the patients of the above groups ($p<0.01$). At the same time, the median in obese patients (Me 146.75 pg/mL) had the highest value, but there were no significant differences between non-obese and obese patients ($P_{1-2}>0.05$).

For the purpose of further, more detailed study of the influence of the degree of obesity on the concentration of the neuropetide observed by us, both in the group of patients with obesity and without obesity, subgroups were identified depending on the BMI, which are presented in Table III and in Fig. 3. It was found that the level of the latter in all the above subgroups of patients was significantly increased compared to the control group ($p < 0.001$), and the maximum level of GAL was observed in the group of patients with hypertension and obesity grade 3 (Me = 166.48 pg/mL). A significant difference between the group with normal body weight and the group of hypertensive patients with obesity grade 3 ($P_{1-5} < 0.05$). In other groups of patients, no reliable relationships were established ($p>0.05$). Our attention is drawn to the GAL level (Me = 159.88 pg/mL) in hypertensive patients with overweight, which was higher than the GAL level in patients with the 1 degree (Me = 65.77 pg/mL) and 2 degree (Me = 148.86 pg/mL) of obesity, respectively.

To identify the relationship between GAL, which was studied in the work with the level of SBP, DBP, HR and BMI in a sample of hypertensive patients with different body weight, a correlation analysis was performed. Attention is drawn to the reliable direct linear relationship between GAL and SBP ($r = 0.60$; $p < 0.001$), as well as between GAL and DBP ($r = 0.33$; $p < 0.05$), and in the first case, the binding force is noticeable, in the second, the binding force is moderate. The analysis of correlations of the studied indicator did not establish reliable relationships with BMI and HR. A matrix graph of these indicators is shown in Figure 4. These reliable correlations explain the data obtained above, about the maximum significant increase in the level of galanin concentration in hypertensive patients grade 3 in comparison with the indicators of the control group.

The following analysis of correlations between GAL and parameters of carbohydrate and lipid metabolism in these patients did not establish reliable relationships of the studied neuropetide with blood glucose, HbA1c, CA, TC, HDL CS and LDL CS. However a reliable direct linear relationship of a weak character with VLDL CS was established ($r = 0.30$; $p < 0.05$).

DISCUSSION

This neuropeptide exerts its effect by activating the Galanin receptors (GalR1, GalR2, GalR3 - all of which are associated with the G protein). These receptors are widely distributed in the mammalian brain and are involved in the rectification of K^+ channel signaling pathways (GIRK) and myogenic associated protein (MAPK). Galanin plays an important role in the regulation of energy balance and modulation of food intake [21].

GalR1 mRNA is abundantly expressed in many brain regions, including areas of the hypothalamus. Its expression level, rather than GalR2 gamma mRNA or GalR3 mRNA, correlates pos-

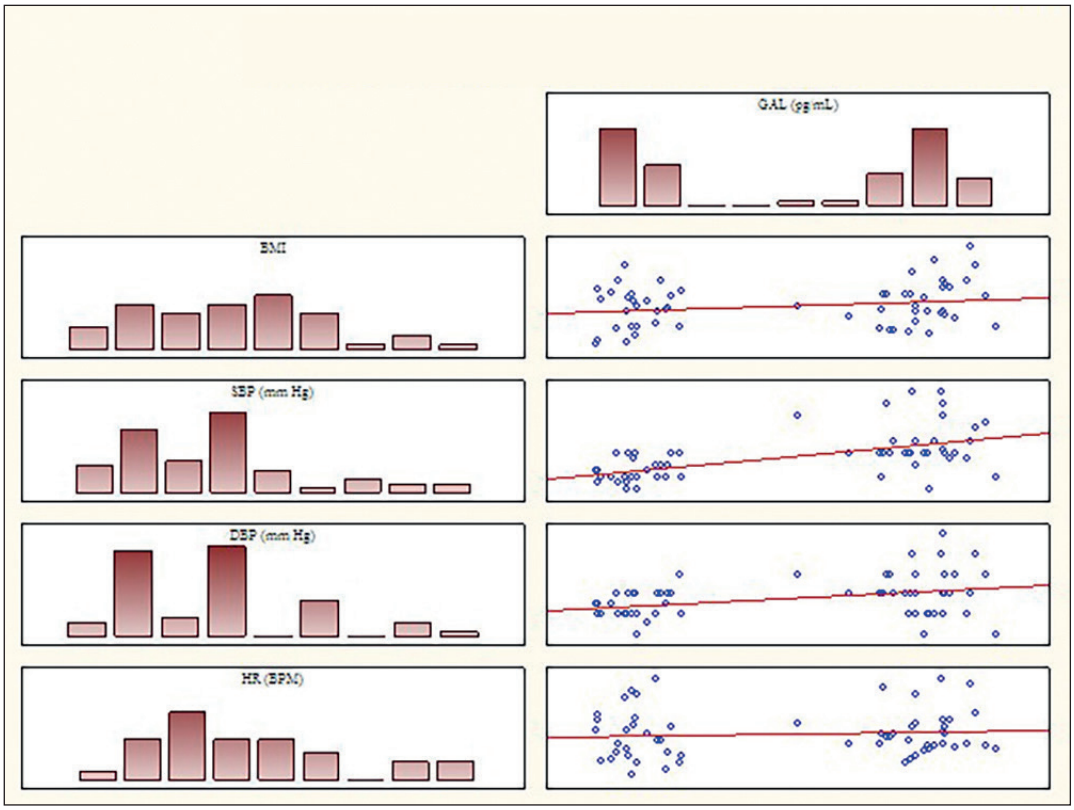

Fig. 4 Matrix diagram for GAL, BMI, SBP, DBP, HR in hypertensive patients.

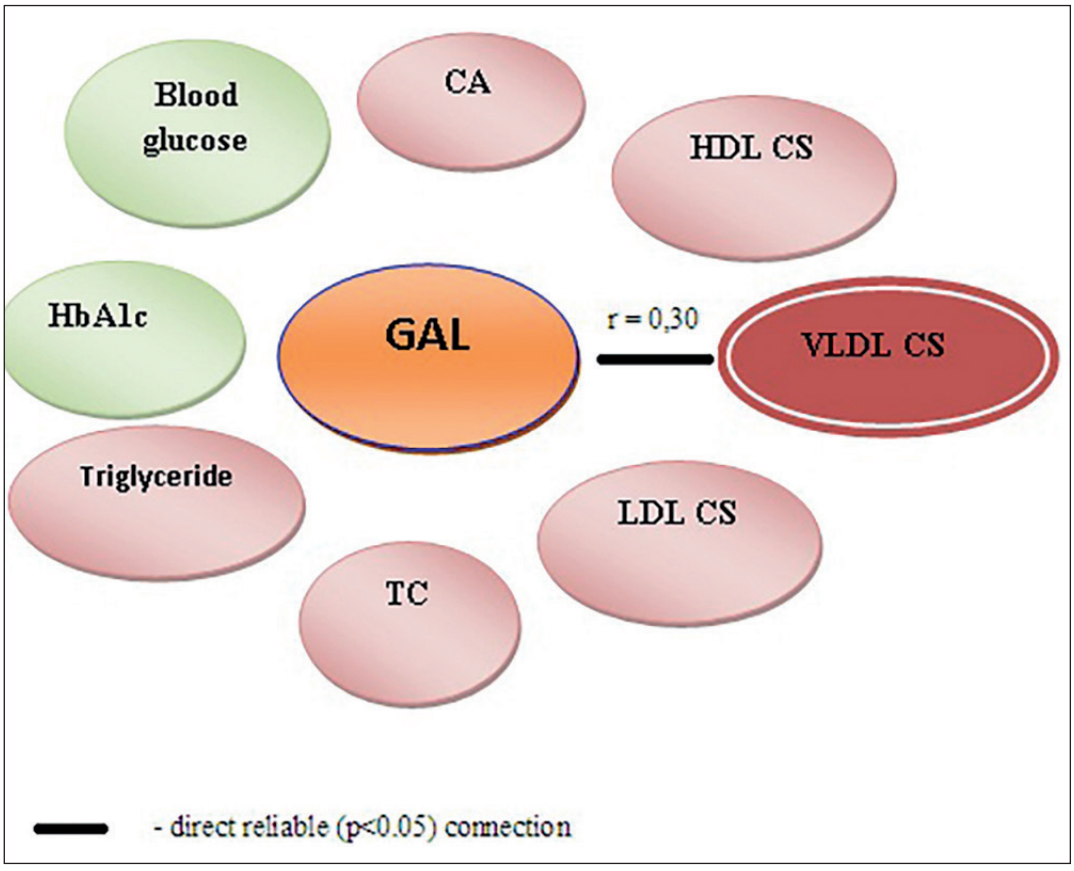

Fig. 5. Correlations between Galanin and indicators of carbohydrate and lipid metabolism - direct reliable (p<0.05) connection.

itively with the Gal content in the nuclei of the hypothalamus of GAL transgenic mice [22, 23].

Thus obtained by us in this study, the lower level of Galanin concentration in patients with degrees 1 and 2 of obesity compared with patients with overweight may be partially due to the binding of GAL with GalR1, which inactivates the activity of this neuropeptide. At the same time, it is possible that GAL triggers an apoptotic cascade, which leads to the death of cells

Table I. GAL level in patients with various hypertension grade and in the control group, Me (LQ; UQ)

Index	Control group (n= 20)	Hypertensive patients (n= 58)			P (Mann–Whitney U-test)
		grade 1 (n= 12)	grade 2 (n= 16)	grade 3 (n= 30)	
GAL (pg/ mL)	30.58 (28.07 – 31.90)	50.22 (40.19 – 53.55)	61.83 (52.12 – 66.45)	164.,47 (156.82 – 170.72)	$p_{0-1} < 0.001$ $p_{0-2} < 0.001$ $p_{0-3} < 0.001$ $p_{1-2} < 0.01$ $p_{1-3} < 0.001$ $p_{2-3} < 0.001$

Table II. GAL level in hypertensive patients depending of the level of weight gain and in the control group, Me (LQ; UQ)

Index	Control group (n= 20)	Hypertensive patients without obesity (n= 19)	Hypertensive patients with obesity (n= 39)	P (Mann–Whitney U-test)
GAL (pg/mL)	30.58 (28.07 – 31.90)	134.25 (52.64 -164.72)	146.75 (54.55 – 166.48)	$p_{0-1} < 0.001$ $p_{0-2} < 0.001$ $p_{1-2} > 0.05$

Table III. GAL level in in the control group and hypertensive patients depending of the presence and degree of obesity, Me (LQ; UQ)

Index	Control group (n= 20)	Hypertensive patients without obesity (n= 19)		Hypertensive patients with obesity (n= 39)			P (Mann–Whitney U-test)
		Normal body weight (n= 10)	Excess body weight (n= 9)	Grade 1 (n= 17)	Grade 2 (n= 13)	Grade 2 (n= 9)	
GAL (pg/mL)	30.58 (28.07 – 31.90)	62.25 (46.38 – 151.28)	159.88 (61.55 – 170.58)	65.77 (54.55 – 159.75)	148.86 (67.12 – 170.05)	166.48 (63.45- 178.81)	$p_{0-1} < 0.001$ $p_{0-2} < 0.001$ $p_{0-3} < 0.001$ $p_{0-4} < 0.001$ $p_{0-5} < 0.001$ $p_{1-2} > 0.05$ $p_{1-3} > 0.05$ $p_{1-4} > 0.05$ $p_{1-5} < 0.05$ $p_{2-3} > 0.05$ $p_{2-4} > 0.05$ $p_{2-5} > 0.05$ $p_{3-4} > 0.05$ $p_{3-5} > 0.05$ $p_{4-5} > 0.05$

producing neuropeptide. The maximum concentration of Galanin in patients with grade 3 obesity may indicate that GalR1 level at this degree of obesity is insufficient for GAL inactivation.

Sternson SM, 2011 showed that the increase in expression and circulating GAL level depends on the level of circulating triglycerides (TG), VLDL CH, the ratio of esterified and non-esterified fatty acids in the diet. Research Results of Fang Penghua, et al. in 2016 showed that in obese individuals, the concentrations of GAL and Galanin-like peptide (GALP) in plasma were high, and the latter neuropeptides correlated positively with an increased concentration of TG in these individuals [17]. A similar significant correlation of GAL level with TG was obtained by Alotibi MN. et al in serum of patients with MS [19].

We also obtained a reliable positive correlation between GAL and VLDL CS (Figure 5.), which explains the above data on the maximum significant increase in the level of GAL concentration, compared with the indicators of the control group and the group with normal body weight in patients with hypertension and obesity of the 3rd degree.

CONCLUSIONS

1. In hypertensive patients with obesity, a significant increase in the concentration of Galanin was detected; most pronounced in arterial hypertension grade 3 and obesity grade 3.
2. Orexigenic neuropeptide Galanin is possibly a biomarker of cardiovascular risk in a cohort of patients with abdominal obesity.

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The Authors declare no conflict of interest.

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