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ENGLISH VERSION: THE DEVELOPMENT MECHANISMS OF OVERWEIGHT IN YOUNG PEOPLE

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Surveyed individuals of both sexes aged 18-25 years, were divided into two groups according to body mass index (BMI), 41 people - with normal weight (BMI 18,5-24,9 kg/m^2) and - 27 with the overweight (BMI above 25 kg/m^2). Indicators of total cholesterol, triglycerides, HDL and LDL cholesterol, glucose, insulin, insulin resistance index HOMA-IR have been studied. The level of chronic systemic inflammation was determined by the level of tumor necrosis factor-alpha and ceruloplasmin (CP). We determined the levels of neuropeptides - Agouti-related protein - AgRP and cocaine- and amphetamine-regulated transcript - CART. In the group of people with overweight were significantly increased insulin levels by 47,38%, HOMA-IR index by 44,02%, the CP by 10,98%, AgRP neuropeptides by 62,72%. It is suggested that under the conditions of excess uptake of nutrients, the formation of hyperinsulinemia and insulin resistance insulin contributes to increased of AgRP neuropeptide secretion and early formation of pathological range.

Keywords: overweight, chronic systemic inflammation, neuropeptides, energy metabolism.

High-calorie foods with a much larger share of fats and carbohydrates, violations of diet, insufficient, to the amount of eaten food, level of physical activity are key factors for the obesity in the members of modern society. Changing the value of food, when their energy value begins to dominate on the relaxing and social ones, contributes to an overeating and steady growth of body weight [26].

The abnormal growth of prevalence of the weight gain and obesity in the world requires a more careful attention from the medical and scientific community and social institutions. In particular, a well-founded connection between an overweight and such diseases as type 2 diabetes, hypertension, osteoarthritis should cause concern [11].

Currently, it is considered that the accumulation of lipids in the adipose tissue is interfaced to a chronic inflammatory process of low intensity, which is a systemic process, not connected with an infectious one [28]; but it is one that promotes the violation of mechanisms of regulation of energy homeostasis and leads to the dyslipidemia, atherosclerotic lesion of arteries, and endothelial dysfunction.

It has been suggested that the development of inflammation in the adipose tissue may be the regulatory signal of local level and the systemic one as well - for energy metabolism, particularly, for the energy expenditures [3].

With obesity, exactly the adipose tissue is a major source of chronic inflammation [27]. The increase of the adipose tissue mass leads to the local response to hypoxia [14], which is the basis of a stress response of the adipose tissue in the form of oxidative stress, endoplasmic reticulum stress and inflammatory stress.

An activation of nuclear transcription factor NF-κB happens in the adipocytes and macrophages of persons with an obesity under the hypoxic conditions by an alternative mechanism for ensuring thus the development of chronic inflammation in the adipose tissue [14].

In general, the development and existence of the chronic systemic inflammation is a pathogenetic basis for creating a number of somatic diseases in the future. The development of obesity with the following manifestations of the chronic inflammation in the young age is even more threatening because of the loss of working capacity and its possible loss during the working age. Thus, the purpose of our study was to determine the mechanisms of formation and development of overweight in the young people.

Materials and methods

Order to solve this goal, we conducted a study involving 68 people of both sexes, aged 18-25 years. We got a permission for the study from a Commission on Bioethics of Higher State Educational Establishment of Ukraine "Ukrainian Medical Stomatological Academy". We received a voluntary consent from all participants before the test to take part in the research.

We have been conducted the anthropometric studies to define the body weight, height, waist girth (WG), hip girth (HG), their ratio, to calculate the body mass index (BMI, WHO, 1998). According to BMI, we formed two groups. The control group consisted of 41 persons (20 males and 21 females) with the normal weight (BMI 18,5-24,9 kg/m^2), the main group consisted of 27 persons, (16 males and 11 females) with the overweight (BMI above 25 kg/m^2).

Blood for the laboratory tests was given in the morning on an empty stomach from the cubital vein to the vacutainers ("Becton Dickinson", USA). Lipid metabolism was evaluated by determining the level of total cholesterol (CL), triglycerides (TG), HDL cholesterol (HDL CL) in the blood serum using test system ("Diakon DS", Russia), and LDL cholesterol (LDL CL, «LaChema», Czech Republic).

Carbohydrate metabolism was evaluated over the concentration of glucose ("Diakon DS", Russia) and insulin in the blood serum ("DRG", Germany). The HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) index was calculated by the formula: HOMA-IR = glucose on an empty stomach (mmol/l) × insulin on an empty stomach (mcU/ml) / 22,5 [16]. The presence of a chronic systemic inflammation was determined by the level of tumor necrosis factor-alpha (TNF-α) by ELISA ("Вектор-Бест", Russia) and by the level of ceruloplasmin (CP) using "Реагент" (Ukraine).

The level of neuropeptides of Agouti-related protein (AgRP) ("Cloud-Clone Corp", USA) and cocaine- and amphetamine-regulated transcript (CART), ("RayBiotech", USA) in the blood serum was investigated by ELISA using StatFax 303 Plus analyzer.

Statistical analysis of data was performed using STATISTICA 6.1 software package (StatSoft Inc, USA). The arithmetic average (M) and its error (m) was calculated accordingly. The correlation relationship of parameters were determined by the Spearman's rank correlation coefficient. Statistical significance was calculated by the Mann-Whitney criteria; the differences was considered as statistically significant when the probability of error was $p<0,05$.

Results and discussion

As shown by the studies, the anthropometric indicators of young people with the overweight are significantly different from the indicators of people with the normal weight. It was determined the probable differences of mass and BMI of people with the overweight from the indicators of people from the control group by 34% and 34,5%, respectively (Table 1).

Table 1

Anthropometric indices of people from the surveyed groups (M±m, lower and upper quartiles)

Parameters	People with the normal weight n=41	People with the overweight n=27
Age, years	18,87 ± 0,17 (18,0; 19,0)	19,52 ± 0,44 (18,0; 20,0)
Height, cm	173,80 ± 0,96 (170,0; 179,0)	173,59 ± 2,08 (168,0; 181,0)
Body mass, kg	64,39 ± 1,05 (58,0; 70,0)	86,28 ± 2,72* (75,0; 95,0)
BMI, kg/m^2	21,29 ± 0,25 (20,07; 22,34)	28,63 ± 0,72* (26,24; 29,67)
Waist girth, cm	71,68 ± 0,92 (67,0; 75,0)	87,44 ± 2,0* (80,0; 95,0)
Hip girth, cm	96,76 ± 0,69 (94,0; 99,0)	111,0 ± 1,79* (104,0; 116,5)
Ratio between of the waist girth and hip girth	0,73 ± 0,02 (0,70; 0,78)	0,79 ± 0,02 (0,75; 0,85)

*Note: hereinafter in the tables * - p<0,05 compared with the people with the normal weight.*

To evaluate the relative advantage in deposition of the abdominal adipose tissue we measured the waist girth. The average value of WG in people with the overweight exceeded the value of the control group by 21,9%, and the value of HG exceeded by 14,2% ($p<0,05$).

The study of the lipid metabolism indicators showed no significant alteration of the indicators of CL, TG, LDL CL, HDL CL levels (Table 2).

Table 2

Lipid and carbohydrate metabolism indices in people from the surveyed groups (M±m, lower and upper quartiles)

Parameters	People with the normal weight n=41	People with the overweight n=27
CL, mmol/l	3,46 ± 0,09 (3,1; 3,8)	3,65 ± 0,13 (3,2;4,1)
TG, mmol/l	0,59 ± 0,03 (0,5; 0,7)	0,63 ± 0,05 (0,4;0,7)
LDL, g/l	1,31 ± 0,04 (1,13; 1,50)	1,38 ± 0,05 (1,15;1,55)
HDL, mmol/l	1,02 ± 0,04 (0,81;1,17)	0,90 ± 0,05 (0,72;1,05)
Insulin, mcU/ml	10,70 ± 0,87 (6,30;13,70)	15,77 ± 1,55* (9,30; 19,50)
Glucose, mmol/l	4,14 ± 0,11 (3,75; 4,58)	4,29 ± 0,07 (4,12; 4,51)
HOMA-IR index	2,09 ± 0,18 (1,22; 2,75)	3,01 ± 0,30* (1,69; 3,80)

The indicators of carbohydrate metabolism were characterized by the following changes. It was determined the likely increase in the insulin level by 47,38% and the indicator of insulin resistance index by 44,02% in the group of people with the overweight comparing to the group of people with the normal weight. The glucose level on an empty stomach remained in both groups without differences.

The study of CP level showed its increase by 10,98% in people with the overweight. The level of TNF-α remained unchanged (Table 3). The comparison of values of neuropeptide indicators in people with the normal weight and the overweight determined an increase of AgRP by 62,72% ($p<0,05$). CART level tended to decrease, but the likely differences between the two groups were not found (Table 3).

Table 3

Indices of inflammatory markers and neuropeptides in people from the surveyed groups (M±m, lower and upper quartiles)

Parameters	People with the normal weight n=41	People with the overweight n=27
CP, mg/l	217,67 ± 2,33 (213,50;220,50)	241,58 ± 7,97* (210,0; 267,70)
TNF-α, pg/ml	11,26 ± 1,00 (7,50; 12,20)	10,84 ± 0,88 (7,60; 13,70)
CART, pg/ml	20438,11 ± 4178,66 (389,20; 27581,0)	11847,49 ± 4844,98 (525,60; 6359,0)
AgRP, pg/ml	9,79 ± 1,22 (3,50; 13,30)	15,93 ± 2,29* (7,50; 24,0)

In order to establish the relationship between the studied parameters we made a correlation analysis.

We observed the positive correlation of a moderate intensity between the levels of HDL and LDL ($r = 0,32$, $p<0,05$) in persons with the overweight, and the correlation of a very slight intensity between HDL and TG levels ($r = 0,16$, $p<0,05$).

We established the relationships of an insulin level and the indicators of lipid metabolism. In the main group, we observed the positive relationships of a very slight intensity between the insulin level and LDL level ($r = 0,0985$, $p<0,05$), the level of glucose and insulin level ($r = 0,058$, $p<0,05$), and the negative relationships between the insulin level and CL level ($r = -0,0687$, $p<0,05$), the level of insulin and triglyceride level ($r = -0,062$, $p<0,05$). It was also found a slight positive correlation between the glucose level and CL level ($r = 0,275$, $p<0,05$), and a very slight correlation between the level of glucose and TNF-α level ($r = 0,113$, $p<0,05$) in people of the main group.

We defined a very slight positive relationship between the indicators of glucose level and the levels of TNF-α ($r = 0,11$, $p<0,05$), insulin ($r = 0,14$, $p<0,05$), and CL ($r = 0,033$ $p<0,05$), accordingly, in people with the overweight. During the correlation analysis, we revealed also a very slight positive relationship between CL level and TNF-α level ($r = 0,033$, $p<0,05$), and the CP and LDL levels ($r = 0,131$, $p<0,05$) in people with the overweight.

We identified the positive correlation of slight intensity between the levels of insulin and TG ($r = 0,198$, $p<0,05$), a very slight relationships between the insulin level and CL level ($r = 0,003$, $p<0,05$), and the levels of glucose and insulin ($r = 0,04$, $p<0,05$), as well as the negative relationship between the insulin level and LDL level ($r = -0,094$, $p<0,05$) in the control group.

Investigating the people from the control group, we found a slight positive correlation between the levels of HDL and LDL ($r = 0,084$, $p<0,05$), HDL and CL ($r = 0,04$, $p<0,05$), HDL and glucose ($r = 0,057$, $p<0,05$), we also defined a slight positive correlation between the indicators of the glucose level and CL ($r = 0,24$, $p<0,05$), TG ($r = 0,27$, $p <0,05$), LDL ($r = 0,218$, $p<0,05$) levels, respectively, and a very slight relationship between the levels of glucose and CP ($r = 0,148$, $p<0,05$).

The representatives of the control group revealed a very slight positive relationship between the level of TNF-α and LDL ($r = 0,114$, $p<0,05$) and CP ($r = 0,0529$, $p<0,05$) levels, respectively. We noticed the likely positive correlations of moderate intensity between the level of AgRP neuropeptide level and insulin level ($r = 0,317$, $p<0,05$) in people from the main group and the levels of CART neuropeptide and insulin ($r = 0,418$, $p<0,05$) in the control group.

In general, we surveyed the young people aged 18-25 years. The people from the main group had the significantly higher body weight, body mass index, waist girth and hip girth. According to the WHO classification, a person with a BMI between 25,0 and 29,99 has a overweight that is classified as a pre-obesity [22].

According to the modern views, the leading pathogenetic mechanisms of obesity are reduced to a violation of the energy balance [13]. Energy intake from the food exceeds its exes, resulting the energy excess accumulates in the body and connects to the reaction of triglyceride synthesis with their reinforced deposition in the adipose depot [20]. The violation of a diet balance and, the most important, the chronic hypodynamia and significant reduction in physical activity contributes to the accumulation of triglycerides in the adipose tissue. Sedentary lifestyle, lack of physical activity and exercises reduce the energy consumption that in combination with the exceeded energy intake play a major role in causing the overweight due to the fat deposits such as the subcutaneous fat, abdominal fat, and fat of internal organs. The imbalance between the energy intake from the food and its consumption for energy needs has a prime importance in almost 90% of obesity cases [12]. Usually, the physical activity significantly reduces in women and men with age, while the energy value of the food remains still preliminary, creating undesirable metabolic disorders.

It is known that people with the overweight and obesity (BMI 25-30) have an increased risk of diabetes, cardiovascular disease, and hypertension [8, 23].

We have identified the credibly increased indicators of waist girth in people with the overweight up to 87,44 ± 2,0 cm on average. At the same time according to the current diagnostic criteria of metabolic syndrome and risk of development of cardiovascular disease, the maximum allowable rates of waist girth is ≥94 cm for men and ≥80 cm for women [9]. That indicates the threatening condition in surveyed persons regarding the overweight and further development of the metabolic syndrome.

During our research we found that despite the probable increase in body weight and BMI, the lipid metabolism indicators in the people of both groups did not differ, but we got the data about the credible increase of the insulin level and HOMA-IR index, which calculation is the most effective method of assessment of insulin resistance in patients with the overweight.

Excess of coming energy contributes to the development of hyperinsulinemia and insulin resistance. Even a small increase of insulin level in plasma can cause a severe insulin resistance. Insulin resistance is associated with an increased risk of diabetes and cardiovascular diseases, and it is an important component of the pathophysiological mechanisms of obesity connection with

these types of diseases, including the metabolic syndrome.

According to our data, on the background of the high insulin level, the indices of glucose level hardly differed in people from the main and control groups. Similar data on the unmodified glucose level in patients with the arterial hypertension with the obesity was received by Goptsyi O.V. [1].

On the other hand, one of the key points of intracellular signaling responsible for the development of insulin resistance is NF-κB signaling path [5]. The nuclear factor of κB transcription, as a major intracellular regulator of inflammatory reactions, changes the gene expression of cytokines and adhesion molecules that leads to an increase and spreading of inflammation to other cells, thus contributing to the process of inflammation. Based on the studies, we developed the concept of permanent activation of NF-κB as a possible typical pathological process, when this factor is involved in the formation of "vicious circle": insulin resistance - inflammation – atherosclerosis [2].

In turn, the majority of the anti-inflammatory cytokines increase the expression of NF-κB and cause a reciprocal activation of their synthesis [7].

The relation between the indicators of lipid, carbohydrate metabolism and the markers of inflammation was found, in particular, the leading pathogenetic role of chronic systemic inflammation in the development of insulin resistance, metabolic syndrome, and type 2 diabetes was confirmed [21].

One of the most sensitive markers of systemic inflammation may be CP [4], whose level was credibly higher in people with the overweight. In our opinion, the likely increase of CP level is the first sign of the formation of chronic inflammation processes in people with the overweight. At the same time, other pro-inflammatory cytokine - TNF-α - remained unchanged.

Obviously, our data shows no significant alteration of TNF-α level that may be due to the not enough weight gain in respondents, but it could also be because the gradual weight gain will lead to changes in the level of TNF-α after CP. This is confirmed by the presence of large numbers in the vast majority of slight and very slight connections between the lipid, carbohydrate metabolism and markers of systemic inflammation, including CP and TNF-α.

Similar results were obtained by Chukaeva I.I. and colleagues, according to which a positive correlation of medium strength between the level of stimulated glucose with TNF-α ($r = 0,69$, $p < 0,05$) and interleukin-4 ($r = 0,64$, $p<0,05$) was found [6]. The positive connection of moderate intensity between the level of glucose and TNF-α ($r = 0,31$, $p<0,05$), the strong connection between the levels of insulin and TNF-α ($r = 0,91$, $p < 0,05$) were found in people with the arterial hypertension and obesity [1].

The results of the experimental studies have provided the possibility to suggest that the signaling module of nuclear factor of κB-IKKβ/NF-κB transcription mediates the fundamental connection between the excessive intake of nutritive substances and the dysfunction of the hypothalamic signaling [29].

It is known, the hypothalamus plays a central role in the regulation of appetite and energy expenditure. In particular, the mediobasal hypothalamic arcuate nucleus, which is critical for the regulation of appetite, food intake and energy homeostasis, contains two types of neuron populations with opposite effects on food consumption [18]. The balance between the activity of these neuronal areas is critical for the regulation of body weight.

The medial group of NPY/AgRP neurons expresses the orexigenic peptides, neuropeptide-Y (NPY) and AgRP, which cause an increase in food consumption [25].

Agouti-related protein (Agouti-Related Protein — AgRP) holds a central place in the energy metabolism. It impacts the modulation of efficiency of signaling function of hypothalamic receptors to the type 3 and 4 melanocortin (Melanocortin Receptors - McR), resulting the appetite stimulates and the energy consumption decreases [15].

Anorexigenic lateral neurons express alpha-melanocyte-stimulating hormone (α-MSH), which is a derivate of proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (Cocaine and amphetamine- regulated transcript - CART). CART is an anorexigenic peptide that plays a central role in the regulation of feeding behavior, level of appetite, thermogenesis and is a major messenger of nociceptive system [10].

The central control of an energy balance depends on the ability of POMC or AgRP hypothalamic neurons to sense and to respond to the changes in the peripheral energy depots.

A high density of receptors to the peripheral hormones expressed in the POMC/CART and NPY/AgRP neurons, including insulin and leptin. Insulin informs the central nervous system on the state of saturation and obesity, and together with the leptin mediate the long-term regulation of energy balance. Available data suggest that insulin and leptin act for the brain as negative feedback signals of obesity [17]. The central action of insulin contributes to anorexia by inhibiting the expression of NPY and stimulating the expression of POMC [19]. Both, insulin and leptin activate POMC neurons, but they regulate AgRP differently, when leptin inhibits, insulin stimulates its synthesis [24].

According to our data, exactly in people with the overweight there was an increase in insulin level and level of AgRP neuropeptide comparing to a group of people with the normal weight by 62,72%, the indices of CART level were higher in the control group. It should be noted a clear correlation of indicators of neuropeptide and insulin levels. Moreover, in people with the overweight was observed a credibly positive correlation of moderate intensity between the level of orexigenic AgRP neuropeptide and insulin ($r = 0,317$, $p<0,05$), while in people with the normal weight from the control group a correlation between the levels of anorexigenic CART neuropeptide and insulin ($r = 0,418$, $p<0,05$) was found.

It is confirmed at present that the energy excess intake in the human body is the result of violation of eating behavior. The violation of eating behavior accompanied by an increased and unbalanced supply of nutrients along with the hypodynamia become the major factors that contribute to the increase of energy storage. Thus, the concept of energy imbalance, along with the alimentary disorders includes the physical activity decrease, when the low physical inactivity creates an energy excess and increases the weight gain. In turn, as a result, the formation of two interrelated parts - the formation of insulin resistance and chronic inflammation, which clearly correlates with the beginning of failure in hypothalamic signaling observed.

We believe that due to the intake of moderate intensity of nutrients, the insulin level is sufficient to inhibit the selection of orexigenic neuropeptides according to the feedback principle, delivering a saturation signal to the central structure. But under the conditions of excess uptake of nutrients, due to the formation of hyperinsulinemia

and insulin resistance, exactly the insulin, not leptin, contributes to an increased release of AgRP neuropeptide and early formation of pathological range. Given that, the arcuate nuclei neurons of the hypothalamus expressing the AgRP neuropeptide, stimulate the food intake, providing an anabolic effect, its increased level promotes the further weight gain.

The changes on the level of central regulation mechanisms of energy homeostasis support determined by the increase of orexigenic AgRP neuropeptide production, the gradual formation of insulin resistance and chronic systemic inflammation occurring in the young people with the overweight, indicate the beginning of the formation of pathogenetic basis of metabolic syndrom in our view.

Given the young age of the respondents and their lack of acute and chronic inflammatory diseases at the moment, such condition already requires a mandatory physiological correction by the formation of a healthy lifestyle, especially by the implementing of a balanced diet with a reduced calories and optimal physical activity.

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