

The impact of stress on pathogenetic mechanisms of obesity (Systematic review)

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Obesity is reaching the scale of a pandemic and is growing progressively every year. Taking into account the introduction of quarantine in many countries of the world associated with COVID-19, a large number of patients are in a state of constant stress, hypodynamics, hypoxemia, which contributes to the prevalence of this nosology. Under such conditions, there is a need for a detailed analysis of the impact of stress and other factors on the pathogenetic links in the development of obesity, determines the relevance of our study and the need to find more effective preventive measures in the practice of family medicine.

The objective: is to analyse the pathogenetic mechanisms of obesity under the influence of stress and other factors using systematic analysis of literature data.

Materials and methods. A systematic review of literature sources in the field of obesity and its pathogenetic aspects was conducted by keywords: pathogenesis of obesity, overweight, stress, hypothalamic-pituitary-adrenal system, orexin, serotonin for the period 2015–2020. The search was carried out mainly in PubMed and Cochrane databases. The bibliosemantic method and the method of systematic analysis were used.

Results. According to the results of searches in the PubMed and Cochrane databases, 58131 sources were found by keywords, from which 29 most relevant research goals were selected, including: 16 systematic reviews, 2 meta-analyses, 3 multicenter data and 8 cohort studies. It is established that despite the diversity of pathogenetic aspects of obesity, adipose tissue is an endocrine-active organ that changes the functional state of many organs and systems, leads to metabolic and hormonal changes, led primarily by disbalance of the hypothalamic region, which is responsible for somatoform and hormonal disorders, and for the body's protective reactions on exposition of many orexogenic factors.

Conclusion. A crucial point in the practice of a family doctor, which will help to effectively prevent the development of obesity and its non-infectious and infectious complications, is to study all possible risk factors, their complex interaction at all levels of pathogenetic changes. Taking into account the influence of stress factors on the hypothalamic region, which is one of the key links in the pathogenesis of metabolic and somatoform changes, will help to find more effective approaches to the correction of overweight.

Keywords: obesity, pathogenesis, stress, hypothalamic-pituitary-adrenal system, orexin, serotonin.

Вплив стресу на патогенетичні механізми розвитку ожиріння (Систематичний огляд)

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Ожиріння досягає масштабів пандемії і щорічно прогресивно зростає. Враховуючи введення карантинних умов у багатьох країнах світу, пов'язаних з COVID-19, досить велика кількість пацієнтів перебувають у стані постійного стресу, гіподинамії, гіпоксемії, що сприяє росту поширеності даної нозології. За таких умов виникає необхідність деталізованого аналізу впливу стресу та інших чинників на патогенетичні ланки розвитку ожиріння, що обумовлює актуальність даного дослідження і необхідність пошуку більш ефективних профілактичних заходів у практиці сімейного лікаря.

Мета дослідження: вивчити патогенетичні механізми розвитку ожиріння під впливом стресу та інших чинників за допомогою системного аналізу даних літератури.

Матеріали та методи. Здійснено систематичний огляд літературних джерел у проблематиці ожиріння щодо його патогенетичних аспектів за ключовими словами: pathogenesis of obesity, overweight, stress, hypothalamic-pituitary-adrenal system, orexin, serotonin за період 2015–2020 рр. Пошук здійснювали здебільшого в базах даних PubMed та Cochrane. Для аналізу застосовували бібліосемантичний метод та метод системного аналізу.

Результати. За результатами пошуку в базах даних PubMed та Cochrane було знайдено за ключовими словами 58 131 джерел, з яких відібрано 29, що найбільше відповідали меті дослідження, серед яких: 16 системних оглядів, 2 мета-аналізи, 3 багатоцентрових і 8 когортних досліджень. Встановлено, що незважаючи на багатогранність патогенетичних аспектів ожиріння, жирова тканина є ендокринно активним органом, який змінює функціональний стан багатьох органів і систем, призводить до метаболічних і гормональних змін, на чолі яких стоїть насамперед дисбаланс гіпоталамічної ділянки, яка відповідає як за соматоформні і гормональні розлади, так і за захисні реакції організму при дії безліч орексогенних чинників.

Заключення. Вирішальним моментом у практиці сімейного лікаря, що допоможе ефективно здійснювати профілактику розвитку ожиріння і його неінфекційних та інфекційних ускладнень, є вивчення всіх можливих чинників ризику, їх комплексної взаємодії на всі ланки патогенетичних змін. Урахування впливу стресових факторів на гіпоталамічну ділянку, яка є однією з ключових ланок патогенезу метаболічних і соматоформних змін, сприятиме пошуку більш ефективних підходів корекції надмірної маси тіла.

Ключові слова: ожиріння, патогенез, стрес, гіпоталамо-гіпофізарно-надширшкові система, орексин, серотонін.

Влияние стресса на патогенетические механизмы развития ожирения (Систематический обзор)

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Ожирение достигает масштабов пандемии и ежегодно прогрессивно растет. Учитывая введение карантинных условий во многих странах мира, связанных с COVID-19, достаточно большое количество пациентов находятся в состоянии постоянного стресса, гиподинамии, гипоксемии, что способствует росту распространенности данной нозологии. При таких условиях возникает необходимость детального анализа влияния стресса и других факторов на патогенетические звенья развития ожирения, обуславливает актуальность нашего исследования и необходимость поиска более эффективных профилактических мероприятий в практике семейного врача.

Цель исследования: изучить патогенетические механизмы развития ожирения под влиянием стресса и других факторов с помощью системного анализа данных литературы.

Материалы и методы. Осуществлен систематический обзор литературных источников по проблематике ожирения, его патогенетических аспектов, по ключевым словам: pathogenesis of obesity, overweight, stress, hypothalamic-pituitary-adrenal system, orexin, serotonin за период 2015–2020 гг. Поиск осуществляли в основном в базах данных PubMed и Cochrane. Для анализа применяли библиосемантический метод и метод системного анализа.

Результаты. По результатам поиска в базах данных PubMed и Cochrane было найдено по ключевым словам 58 131 источников, из которых отобрано 29 наиболее соответствующих цели исследования, среди которых: 16 системных обзоров, 2 мета-анализа, 3 многоцентровых и 8 когортных исследований. Установлено, что несмотря на многогранность патогенетических аспектов ожирения, жировая ткань является эндокринно активным органом, который изменяет функциональное состояние многих органов и систем, приводит к метаболическим и гормональным изменениям, во главе которых стоит, прежде всего, дисбаланс гипоталамической области, которая отвечает как за соматоформные и гормональные расстройства, так и за защитные реакции организма при воздействии множества орексигенных факторов.

Заключение. Решающим моментом в практике семейного врача, который поможет эффективно осуществлять профилактику ожирения и его неинфекционных и инфекционных осложнений, является изучение всех возможных факторов риска, их комплексного взаимодействия на все звенья патогенетических изменений. Учет влияния стрессовых факторов на гипоталамическую область, которая является одним из ключевых звеньев патогенеза метаболических и соматоформных изменений, будет способствовать поиску более эффективных подходов коррекции избыточной массы тела.

Ключевые слова: ожирение, патогенез, стресс, гипоталамо-гипофизарно-надпочечниковая система, орексин, серотонина.

The term “obesity” according to ICD-11 is defined as «ABCD» (adiposity-based chronic disease), which more clearly outlines the problem than before [1, 2, 3]. Every year, 2.8 million people die from obesity in the world [4].

Obesity, like nosology, is spreading at a significant rate. More and more people lead a hypodynamic lifestyle, do not follow the principles of healthy eating. Taking into account the recent events in the world related to quarantine conditions in result of COVID-19 in many countries, a large number of patients are in a constant stress, hypodynamia, hypoxemia, which contributes to the prevalence of this nosology. Long-term neglect of such a nosological unit leads to a significant increase of non-communicable diseases in the world. In addition, in condition when the significant number of countries is in quarantine associated with the COVID-19 pandemic, obesity becomes an additional risk factor for severe COVID-19. It is a well-known fact that overweight patients have impaired mechanical ventilation, furthermore, obesity is a chronic inflammatory disease in which increased production of cytokines, altered reactivity of natural killers occur [5]. According to statistics, obese patients have more severe course of COVID-19, are much more likely to be admitted to inpatient treatment and intensive care units, requiring oxygen therapy [6]. In most countries that analyzed the situation of hospitalized young patients with COVID-19, it was found that half of the patients had a BMI >25 kg/m² (US=48.3%, UK=72%, France=50%) [4, 6, 7, 8, 9, 10]. The lack of attention paid in recent years to this category of patients is largely revealed today, not only in our country.

It is interesting that in all protocols, national recommendations, guidelines and any scientific and practical publications, the main point of treatment is a change in lifestyle (mainly a change in eating

behavior), but the cause of such behavior as well as methabolic and hormonal problems are almost not considered. It is difficult for a patient to change his behavior «by force of will», especially if the hormonal background «interferes», which leads to a fairly common phenomenon of «yo-yo», especially when all the factors influencing the development of this disease are not taken into account. Under such conditions, there is a need for a detailed analysis of the effects of stress and other factors on the pathogenetic links of obesity, which determines the relevance of our study and the need to find more effective preventive measures in the general practice.

The objective: is to analyse the pathogenetic mechanisms of obesity under the influence of stress and other factors using systematic analysis of literature data.

MATERIALS AND METHODS

A systematic review of literature sources in the field of obesity and its pathogenetic aspects was conducted by keywords: pathogenesis of obesity, overweight, stress, hypothalamic-pituitary-adrenal system, orexin, serotonin for the period 2015–2020. The search was carried out mainly in PubMed and Cochrane databases. The bibiosemantic method and the method of systematic analysis were used.

RESULTS AND DISCUSSION

According to the results of searches in the PubMed and Cochrane databases, 58 131 sources were found by keywords, of which 29 were selected for analysis that best met the purpose of the study, including: 16 systematic reviews, 2 meta-analyzes, 3 multicenter data and 8 cohort studies.

It was established that despite the multifaceted pathogenetic aspects of “obesity”, adipose tissue is considered as an endocrine

Biologically active substances involved in the pathogenesis of obesity

Orexigenic	Anorexigenic
<ul style="list-style-type: none"> – Orexin A and B (hypocretins) – Melanin-concentrating peptide – Norepinephrine (α2-receptors) <ul style="list-style-type: none"> – Neuropeptide Y – β-endorphin – Agut-related peptide <ul style="list-style-type: none"> – Galanin – Somatoliberin <ul style="list-style-type: none"> – Cortisol – Thyroxine 	<ul style="list-style-type: none"> – Serotonin – Cocaine and amphetamine-regulating transcriber <ul style="list-style-type: none"> – Norepinephrine (α1 and β2 receptors) – α-melanocytostimulating hormone – Corticoliberin – Tyroliberin – Leptin – Vasopressin – Neurotensin – Oxytocin – Urocortin «Ghrelin» <ul style="list-style-type: none"> – Insulin – Cholecystokinin <ul style="list-style-type: none"> – GABA – Dopamine

organ that causes changes of the functional state of all organs, that is why it is often the part of work of endocrinologists. Today, the term “endocrine obesity” is more used in diagnoses of hypothyroidism, syndromes of hypogonadism, hypercorticism, hyperandrogenemia, hypercorticism, polycystic ovary syndrome [1]. But the hormone-active role of alimentary obesity is underestimated in general practice.

The pathogenesis of obesity can be traced from electrolyte changes to phenotypic traits, which are presented in the literature, in particular, there was a significant difference in the level of potassium, calcium, phosphate ($p < 0.005$) in obese patients compared to normal weight patients, while as the level of magnesium in obese patients is significantly lower than in patients with BMI $< 25 \text{ kg/m}^2$ ($p < 0.001$) [11, 12, 13]. The negative effect of abdominal obesity on the “metabolic health” of the body by hyperproduction of leptin and proinflammatory cytokines by adipocytes has been studied [14, 15]. Conditionally, the entire pathogenesis can be divided into variable and invariant components. Today, only genetic and partially hormonal determinants cannot be changed, but this aspect are studied by genetic engineering.

For a more detailed understanding of the pathogenetic mechanisms of obesity, all biologically active substances (amines and neuropeptides) involved in its formation can be divided into two components, the disbalance of which leads to the accumulation of adipose tissue – see table [16].

The central link in the pathogenesis of obesity is the hypothalamus, whose functions largely reveal the causes and aspects of overweight correction. Hypothalamus – the main organ that shapes eating behavior, as it contains the centers of hunger, satiety; thermoregulation; sleep / vitality; stress reactions; fertility [17, 18]. Quite often these functions are interconnected. Biological agents such as orexins (hypocretins) are produced by the lateral hypothalamus and serotonin – by the anterior part (suprachiasmatic nucleus). A large number of works have been devoted to its study or the most effective drugs that affect them (for example, sibutramine, orlistat) have been identified, although they have certain shortcomings [16, 19]. The pathogenetic link between weight gain and production of the above substances is associated primarily with stressful situations, the number of which increases given the presence of pandemics, anti-terrorist acts, economic crisis, and so on. Stress increases orexin production, which causes hyperphagia, hypertension and obesity [17, 20].

At the molecular level orexin A (OX-A) promotes the biosynthesis of the endocannabinoid 2-arachinoidglycerol (2AG), which stimulates appetite and inhibits α -melanocyte-stimulating hormone (α -MSH), which in turn activates the saturation center [21]. In addition, this neuropeptide is responsible for the formulation of motivational behavior, dependence and emotions, as it occupies a central place in the mesolimbic and mesocortical pathways. The hypocretins support the process of wakefulness (vitality) of the body. On the other hand, the literature notes a direct relationship between body weight and sleep disorders [22]. Serotonin, the so-called hormone of “happiness”, which is produced by 95% in the intestine from L-tryptophan and is contained in the neurons of the suprachiasmatic nucleus of the hypothalamus (1–2%), is activated by light stimuli, but its secretion greatly reduced by stress that leads to depression. Serotonin is converted to

melatonin in the pineal gland by N-acetyltransferase, which controls the circadian rhythm [23]. Melatonin, in turn in combination with insulin, is able to increase leptin secretion in adipocytes at night, which explains the decrease in appetite during sleep. Melatonin is an antagonist of cortisol, its synthesis is disrupted due to hypercortisolemia in chronic stress that lead to disturbance of the circadian rhythm, insomnia, decrease leptin secretion and increase of appetite [24].

Leptin secretion and activation of GABA-receptor mediated signaling due to the suppression of neuropeptide Y, leads to decreased appetite and reduced food intake [25]. For its part, GABA when administered orally reduces glycemia and glucose tolerance in obese patients [26, 27].

In recent years, more and more publications have emerged indicating the relationship between adipose tissue and the hypothalamic-pituitary-adrenal system. The aspect of the effect of adipocyte on steroid secretion and regulation of metabolic processes by hormones of the hypothalamic-pituitary-adrenal system is covered. Patients with obesity in response to stress have more cortisol secretion than people with normal body weight. Glucocorticosteroids promote the differentiation of preadipocyte into adipocyte, as well as increase the accumulation of lipids in the depot, turning brown adipose tissue into white, increase the number of proinflammatory cytokines (IL-6, TNF-alpha, monocytic chemotactic protein) [28].

Adipocytes express aromatase, an enzyme that converts testosterone to estrogen. As a result, overweight men suppress the gonadotropic function of the pituitary gland. A very important pathogenetic aspect is the mutual conversion of cortisol into cortisone, which is carried out by 11 β -hydroxysteroid dehydrogenase, an enzyme which is more represented in adipose tissue by the isoform – 11 β -hydroxysteroid dehydrogenase 1, which increases the activity of intracellular cortisol. A correlation was established between the number of 11 β -GSD1 receptors, mineralocorticoid mRNA and BMI [28].

It has been hypothesized that the release of adipocyte-oxidized linolenic acid derivatives, as well as ERK1 and ERK2 proteins, which are able to stimulate adrenal steroidogenesis, causes aldosterone activation. The mechanism of adipocyte aldosterone secretion has been confirmed by both in vitro and in vivo studies [28], which is associated with activation of the renin-angiotensin-aldosterone system and the development of hypertension.

In parallel, by examining the pathogenesis of stress, one can clearly identify its relationship to obesity. The primary link of stress is a stress factor, for each person it will be its own, which activates the nuclei of the brain stem, with the ascending pathways release of vasopressin and corticotropin from the paraventricular nuclei of the hypothalamus, which in turn control the secretion of adrenocorticotropin in the anterior lobe.

CONCLUSION

A crucial point in the practice of a family doctor, which will help to effectively prevent the development of obesity and its non-infectious and infectious complications, is to study all possible risk factors, their complex interaction at all levels of pathogenetic changes. Taking into account the influence of stress factors on the hypothalamic region, which is one of the key links in the pathogenesis of metabolic and somatoform changes, will help to find more effective approaches to the correction of overweight.

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