Медицинская иммунология
2021, Т. 23, № 4,
стр. 775-780
© 2021, СПб РО РААКИ

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 4, pp. 775-780
© 2021, SPb RAACI

РОЛЬ GSK-3 В Wnt/β-CATENIN-СИГНАЛЬНОМ ПУТИ ПРИ ОЖИРЕНИИ

Кулакова А.С.[1], Снимщикова И.А.[2], Плотникова М.О.[2]

[1] ГАУЗ «Брянская областная больница № 1», г. Брянск, Россия
[2] ФГБОУ ВО «Орловский государственный университет имени И.С. Тургенева», г. Орел, Россия

Резюме. На механизм адипогенеза оказывают влияние многочисленное количество факторов, важными из них являются компоненты Wnt-сигнального пути. Поиск возможных маркеров развития заболеваний, связанных с ожирением, обусловил интерес к изучению GSK-3 (glycogensyntase kinase), β-катенина. GSK-3β – внутриклеточная серин/треониновая киназа, обнаружена в цитоплазме, ядре, митохондриях, синтезируется во всех тканях организма и участвует в регуляции таких процессов, как метаболизм, клеточная пролиферация, апоптоз и другие. GSK-3β в активном состоянии фосфорилирует и ингибирует гликогенсинтазу. Когда инсулин связывается с рецептором на клетке через инозитол-3-фосфат, то активация протеинкиназа B(Akt1) активируется и, в свою очередь, фосфорилирует и ингибирует GSK-3β. Также GSK-3β участвует в регуляции обмена глюкозы. Важная функция GSK-3β – ингибирование белка β-катенина. Когда клетка GSK-3β в комплексе с белками APC и Axin покоится, то происходит связывание и фосфолирование транскрипционного фактора β-катенина, затем его убиквинтирование и деградация. Когда Wnt действует на клетку белков, то белок Dvl активируется, связывается с GSK-3β, высвобождая β-катенин, что препятствует его распаду. При этом роль GSK3α/β в воспалительной реакции адипоцитов до сих пор полностью не исследована, поэтому представляется перспективным изучение места GSK-3 в Wnt/β-catenin-сигнальном пути при ожирении.

Целью исследования явилась оценка активности компонентов Wnt-сигнального пути у пациентов с ожирением посредством определения уровня GSK-3 и β-катенина в сыворотке крови. В исследование были включены 32 пациента, у которых было определено ожирение I-III степени с прогрессирующими формами, сахарный диабет отсутствует. Чтобы определить концентацию GSK-3α, GSK-3β и β-катенина в сыворотке крови, был использован метод иммуноферментного анализа. Данные представлены в виде абсолютного и относительного (%) числа больных; среднего арифметического; медианы, 1-го и 3-го квартилей – Me ($Q_{0,25}$-$Q_{0,75}$). В сыворотке крови пациентов, страдающих ожирением, выявлено повышение уровня GSK-3α (785 (371-1317,5) пг/мл) в 7,5 раз по сравнению со здоровыми лицами 105 (102,5-110) пг/мл, ($p < 0,001$), также повышение уровня GSK – 3β в сыворотке крови, уровень которого у пациентов с ожирением составил 295 (190-695) пг/мл, что на 18,3% превышало аналогичные показатели, полученные у здоровых лиц 241 (218,75-287,5) пг/мл, $p = 0,111$. Была отмечена тенденция к увеличению количества GSK-3 в зависимости от степени ожирения, при этом часто наблюдается снижение β-катенина, что согласуется с исследованиями ряда авторов. Эти данные можно рассматривать в качестве прогностического критерия течения патологических процессов при ожирении.

Ключевые слова: ожирение, GSK-3α, GSK-3β, β-катенин, Wnt-сигнальный путь

Адрес для переписки:

Кулакова Анастасия Сергеевна
ГАУЗ «Брянская областная больница № 1»
241033, Россия, г. Брянск, пр. Станке Димитрова, 86.
Тел.: 8 (980) 310-12-33.
E-mail: Kulakovaas@mail.ru

Address for correspondence:

Kulakova Anastasiia S.
Bryansk Regional Hospital No. 1
241033, Russian Federation, Bryansk,
Stanko Dimitrov ave., 86.
Phone: 7 (980) 310-12-33.
E-mail: Kulakovaas@mail.ru

Образец цитирования:

А.С. Кулакова, И.А. Снимщикова, М.О. Плотникова «Роль GSK-3 в Wnt/β-catenin-сигнальном пути при ожирении» // Медицинская иммунология, 2021. Т. 23, № 4. С. 775-780.
doi: 10.15789/1563-0625-ROG-2287

© Кулакова А.С. и соавт., 2021

For citation:

A.S. Kulakova, I.A. Snimshchikova, M.O. Plotnikova "Role of GSK-3 in Wnt/β-catenin signaling pathway in obesity", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2021, Vol. 23, no. 4, pp. 775-780.
doi: 10.15789/1563-0625-ROG-2287

DOI: 10.15789/1563-0625-ROG-2287

ROLE OF GSK-3 IN Wnt/β-CATENIN SIGNALING PATHWAY IN OBESITY

Kulakova A.S.[a], Snimshchikova I.A.[b], Plotnikova M.O.[b]

[a] *Bryansk Regional Hospital No. 1, Bryansk, Russian Federation*
[b] *I. Turgenev Oryol State University, Orel, Russian Federation*

Abstract. The complexity of the adipogenesis mechanism results from the impact of multiple cues, among which an important place is held by the components of the Wnt signaling pathway. The search for potential markers of the development of diseases related to obesity aroused an interest in the study of GSK-3 (glycogen synthase kinase), β-catenin. GSK-3β is an intracellular serine / threonine kinase found in the cytoplasm, nucleus, mitochondria, synthesized in all body tissues and involved in regulating metabolic processes, cell proliferation, apoptosis etc. The first of the discovered functions of GSK-3β was the regulation of glycogen synthesis. Active GSK-3β phosphorylates and thereby inhibits glycogen synthase. As a result of the insulin binding to the cell receptor via inositol-3-phosphate, protein kinase B (Akt1) is activated, which, in turn, phosphorylates and inhibits GSK-3β. In addition, GSK-3β is involved in the regulating glucose metabolism. The most important function of GSK-3β is the inhibition of the β-catenin protein. In a resting cell, GSK-3β in complex with the APC and Axin proteins binds and phosphorylates the β-catenin transcription factor, which leads to its ubiquitination and degradation. When Wnt proteins act on the cell, the Dvl protein is activated, which, by binding to GSK-3β, releases β-catenin, preventing its degradation, however, the role of GSK3α/β in the adipocyte inflammatory response has not yet been fully investigated, therefore it seems promising to study the role of GSK-3 in the Wnt/β-catenin signaling pathway in obesity.

The aim of the study was to assess the activity of the components of the Wnt signaling pathway in obese patients by measuring the serum level of GSK-3 and β-catenin. There were enrolled 32 patients with progressive forms of I-III degree obesity in the absence of diabetes mellitus. The concentration of serum GSK-3α, GSK-3β, and β-catenin was measured by enzyme-linked immunoassay. Data are presented as absolute and relative (%) number of patients; arithmetic mean; medians, 1 and 3 quartiles – Me ($Q_{0.25}$-$Q_{0.75}$). Obese patients contained a 7.5-fold increased serum level of GSK-3α (785 (371-1317.5) pg/ml) compared to healthy individuals 105 (102.5-110) pg/ml, ($p < 0.001$), paralleled with increased amount of GSK-3β, which level in obese patients was 295 (190-695) pg/ml, which is by 18.3% higher than those in healthy individuals 241 (218.75-287.5) pg/ml, $p = 0.111$. Amount of GSK-3 depending on the degree of obesity tended to increase, most often coupled to decreased β-catenin level which is consistent with the literature data and can be considered as a prognostic criterion for the course of pathological processes in obesity.

Keywords: obesity, GSK-3α, GSK-3β, β-catenin, Wnt- signaling pathway

Introduction

"The Wnt signaling pathway plays a key role in many processes, including cell proliferation, tissue regeneration, and embryonic development. Impaired signaling is involved in the pathogenesis of various human diseases. Two signaling pathways in the WNT system exist: canonical and non-canonical. The canonical pathway involves activation of the β-catenin transcriptional coactivator. The pathways activated by WNT ligands independently of β-catenin are classified as non-canonical WNT pathways. A key element of the canonical Wnt/β-catenin pathway is the regulation of the β-catenin protein, which acts as a transcriptional cofactor and performs dual functions as well as also participates in cell adhesion, forming a stable complex with cell adhesion molecules of the cadherin family. In the absence of WNT ligands, cytosolic β-catenin interacts with other components of the destruction complex, including Axin 1, adenomatous polyposis coli (APC), glycogen synthase kinase-3 (GSK-3), casein kinase 1 (CK1), protein phosphatase 2A (PP2A), and protein containing β transducin repeat E3 –ubiquitin ligase (β-TrCP)" [1, 5].

"Glycogen synthase kinase 3 (GSK-3) was first described more than 30 years ago as an enzyme phosphorylating glycogen synthase after ligating insulin and thereby inhibits its activity. Later, the isoforms of this protein were discovered: α and β. The GSK-3α isoform is highly homologous to GSK-3β (98% identity in the kinase domain)" [13].

"The aberrant activity of GSK-3 is associated with the pathogenesis of many diseases, such as atherosclerosis, pathology of the cardiovascular system, neurological disorders, oncopathology, immune disorders, etc. It is known that the inhibitory activity of GSK-3β leads to decreased glycogen synthesis in the

liver and muscles, as well as increased blood glucose levels, therefore GSK-3β is presumably associated with the pathogenesis of diseases such as diabetes mellitus and obesity" [8, 10].

According to current concepts [5, 11], WNT/β-catenin signaling inhibits adipogenesis. Studies carried out by foreign authors [6, 11] revealed the transmission of WNT signals in the regulation of adipocyte differentiation. "In particular, activation of the canonical pathway in pre-adipocytes by overexpression of Wnt1 or β-catenin mutant with a defect in GSK3β phosphorylation has been shown to inhibit adipogenesis. Similarly, treatment with GSK3β pharmacological inhibitors blocked adipocyte differentiation" [7].

It is known that IL-6 is not only a pro-inflammatory cytokine, but also regulates energy and glucose metabolism. A group of scientists [15] in experiments with pigs found that blocking IL-6 trans-signaling can prevent the recruitment of macrophages from adipose tissue with a high fat content, but does not induce body weight gain and improved insulin resistance. "Overexpression of the IL-6 gene induces a significantly reduced body weight, improves insulin sensitivity, and increases the mRNA level of lipolysis genes. There is a strong link between IL-6 and obesity-associated inflammation. Presumably, the mechanism of Gsk3β expression regulated by IL-6 in LPS (lipopolysaccharide)-induced pig adipocytes is as follows: LPS increased the level of Gsk3β phosphorylation and then inhibited the activity of Gsk3β kinase. Inhibition of Gsk3β attenuated LPS-induced IL-6 production in porcine adipocytes. It is believed that the infection and inflammation by their ability to increase pro-inflammatory cytokines, chemokines and adhesion molecules play a key role in the pathophysiology of insulin resistance and type 2 diabetes. Studies carried out by the group of authors [13, 15] have shown that GSK-3 plays a central role in the regulating such inflammation. In particular, it was found that inhibition of GSK3α/β suppresses inflammation in response to various stimuli such as TNF-α, IL-1β and LPS in vitro". Thus, it apperas that GSK-3 plays a role in many inflammatory diseases. For example, according to Lappas M. et al., GSK-3 activity increases in adipose tissue and skeletal muscles of pregnant women with gestational diabetes mellitus and regulates proinflammatory mediators caused by infections and inflammations [8, 9, 10].

Thus, according to studies by a number of authors [7, 8, 10, 13, 15], an increase in GSK3 activity leads to the development of insulin resistance; however, the role of GSK3α/β in the inflammatory response of adipocytes has not yet been fully investigated, therefore it seems promising to study the place of GSK-3 in the Wnt/β-catenin signaling pathway in obesity. **The aim of the study** was to assess the activity of the Wnt signaling pathway in obese patients by determining the level of GSK-3 in the blood serum.

Materials and methods

There were enrolled 32 patients with progressive forms of I-III degree obesity in the absence of diabetes mellitus, aged 40±10 years. To determine serum concentration of GSK-3α, GSK-3β and β-catenin, considered as physiological normal range, we examined 20 sex- and age-matched healthy individuals in the control group free of chronic diseases, lacking signs of acute infectious diseases upon examination and not registered with dispensaries.

Body mass index was calculated by using the Quetelet formula: BMI = body weight (kg)/height (m2). Serum concentrations of GSK-3α, GSK-3β and β-catenin were determined by enzyme-linked immunosorbent assay (ELISA) using Human GSK kits, Sunlong Biotech Co., Ltd, China; Human beta catenin, Sunlong Biotech Co., Ltd, China.

The results were statistically processed using the Microsoft Excel XP software package. Data are presented as absolute and relative (%) number of patients; arithmetic mean; medians, 1 and 3 quartiles – Me ($Q_{0.25}$-$Q_{0.75}$). Differences between groups in quantitative parameters were calculated by using the nonparametric Mann–Whitney U-test, were considered significant at $p < 0.05$.

The exclusion criteria from the study were as follows: age of the patients under 18 and over 65 years old, concomitant exacerbated or decompensated somatic diseases, concomitant acute respiratory infections, pregnancy, sepsis, immunosuppression due to neoplasms or HIV infection, active viral hepatitis, patient refusal to participate. The study, after obtaining informed consent from each patient, was carried out in accordance with the Good Clinical Practice and the principles of the Declaration of Helsinki, approved by the Ethics Committee of FSBEI HE "Oryol State University named after I.S. Turgenev".

Results and discussion

As a result of the examination of obese patients, it was found that 18 (56.25%) of them had degree 1 obesity, 12 patients (37.5%) – degree 2, 2 patients (6.25%) – degree 3. Analyzing the anthropometric data showed that the average height rate was 170±15 cm, weight – 95±15 kg, respectively.

According to the data of general clinical, laboratory and instrumental studies, it was found that accelerated ESR and eosinophilia was revealed in the general blood test in 2 (6.25%) patients, in one person (3.125%) –increased leukocyte count; 2 (6.25%) – altered general urine test containing increased leukocyte count, presence of bacteria and salts; biochemical blood assay analysis in 6 (18.75%) subjects showed increased total cholesterol, 4 patients

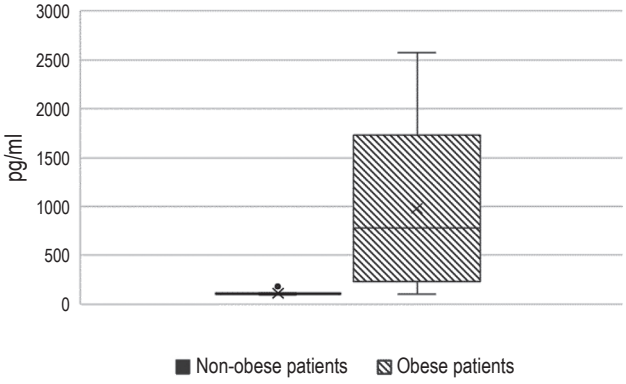

Figure 1. GSK-3α concentration in blood serum (pg/ml)
Note. For distributions that differ from normal in Figures 1, 2, Me (median) is given; 25-75 percentiles (upper and lower quartiles $Q_{0.25}$-$Q_{0.75}$); minimum and maximum sample values; outlier / single data point.

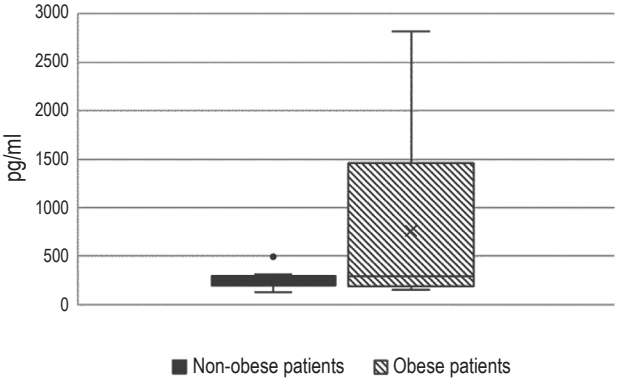

Figure 2. GSK-3β concentration in blood serum (pg/ml)
Note. As for Figure 1.

TABLE 1. GSK-3α AND GSK-3β CONCENTRATION IN BLOOD SERUM DEPENDING ON THE PATIENTS DEGREE OF OBESITY (pg/ml)

Protein (m)		Study groups by degree of obesity		p
		I degree	II degree	
GSK-3α		690.111	1159.167	0.056
GSK-3β		663.333	726.667	0.624
β-catenin		168.78	126.25	0.004
number of patients	n	18	12	
	%	56.25	37.5	
Protein (m)		**I degree**	**III degree**	**p**
GSK-3α		690.111	2567.0	0.023
GSK-3β		663.333	1850.0	0.128
β-catenin		168.78	130.0	0.205
number of patients	n	18	2	
	%	56.25	6.25	
Protein (m)		**II degree**	**III degree**	**p**
GSK-3α		1159.167	2567.0	0.043
GSK-3β		726.667	1850.0	0.133
β-catenin		126.25	130.0	0.455
number of patients	n	12	2	
	%	37.5	6.25	

Note. p, significance of differences between indicators is calculated according to the nonparametric Mann–Whitney U test, the differences are considered reliable and statistically significant when $p < 0.05$; m, sclerostin and β-catenin, concentration mean (pg/ml).

(12.5%) – increased level of bilirubin, 3 patients (9.38%) – increased transaminases (ALT, AST) level.

In patients with complaints of epigastric pain (14 people), EGD was performed, which data confirmed chronic gastritis in 14 (43.75%) patients. At the same time, the Helicobacter pylori bacterium was detected in 6 (18.75%) patients (the Helpil test system for invasive rapid diagnosis of Helicobacter pylori infection by the urease activity of a biopsy sample obtained during an endoscopic examination of the gastric mucosa). According to the ultrasound of the abdominal cavity organs, fatty hepatosis was confirmed in 13 (40.625%) patients, biliary dyskinesia in 5 (15.625%) patients.

We compared the levels of GSK-3α and GSK-3β in obese patients (32 people) and healthy people with normal body weight (20 subjects). Serum GSK-3α levels were measured by enzyme-linked immunosorbent assay (Figure 1), and found significant changes such as increased GSK-3α in obese individuals (785 (371-1317.5) pg/ml) by 7.5-fold compared to healthy individuals 105 (102.5-110) pg/ml, ($p < 0.001$) (Figure 1).

The concentration of GSK-3β was determined by the method of enzyme-linked immunosorbent assay in the blood serum of patients (Figure 2). As shown by the results of studies, obese patients had a wide variability in concentration of serum GSK-3β, the level of which was 295 (190-695) pg/ml, this is 18.3% higher than in healthy individuals 241 (218.75-287.5) pg/ml, $p = 0.111$ (Figure 2).

As noted above, activation of the Wnt/β-catenin signaling pathway inhibits adipogenesis. Impaired Wnt/β-catenin signaling leads to spontaneous adipogenesis [2, 4, 6, 11]. Considering the important role of β-catenin in the regulation of adipogenesis, we were also interested in evaluating its production in obese patients. According to our previous studies [9], it was convincingly established that the mean β-catenin in the blood serum in obese people was higher (150.406±6.41584) than in healthy individuals (87.25±36.29348), $p < 0.001$. In overweight patients 141 (128.5-185) pg/ml, and in healthy individuals 66.0 (59.5-125), a wide variability in serum β-catenin concentrations was found, $p < 0.001$.

The table shows the concentration level of GSK-3α, GSK-3β and β-catenin depending on the degree of obesity (table 1). The study found that patients with grade III obesity had a significantly increased level of GSK-3α ($p = 0.043$) and increased level of GSK-3β ($p = 0.133$) compared to those with grade II obesity, and insignificant changes in the concentration β-catenin ($p = 0.455$). Patients with grade III obesity had significantly increased level of GSK-3α ($p = 0.023$) and increased level of GSK-3β ($p = 0.128$) compared to those with grade I obesity, decreased concentration of β-catenin was also noted ($p = 0.205$). In patients with grade II obesity had significantly increased level of GSK-3α ($p = 0.056$) and slightly increased level of GSK-3β ($p = 0.624$), simultaneously with strongly significantly decreased concentration of β-catenin ($p = 0.004$) (Table 1).

As mentioned above [8, 10, 13, 15] GSK-3 is a kinase involved in the insulin signaling pathway to control glycogen metabolism. However, GSK-3 is currently recognized as a multifunctional kinase that regulates a number of additional cellular functions. According to some studies [3, 12], small molecular weight inhibitors of GSK-3 have beneficial metabolic effects in rodents, including prevented obesity caused by overfeeding and improving glucose tolerance. Thus, in animal models it was revealed that activation of GSK-3β stimulates adipogenesis. Therefore, it seemed to us interesting to compare the serum concentrations of GSK-3α and GSK-3β in obese and healthy individuals. As a result, an increased level of GSK-3α and GSK-3β was revealed in obese individuals compared with healthy individuals, which is consistent with other publications [3, 10, 12].

It was shown that GSK-3 inhibitors increased the expression and nuclear translocation of β-catenin. GSK-3 phosphorylates β-catenin, causing its destabilization and degradation to maintain low cytosolic / nuclear β-catenin levels. The accumulated nuclear levels of β-catenin in cells treated with GSK-3 inhibitors indicate that GSK-3 activity is inhibited. In connection with the above data, our interest was aimed at assessing serum levels of GSK-3α, GSK-3β, and β-catenin in patients with different degree of obesity. Our data on changes in concentration of GSK-3α, GSK-3β and β-catenin depending on the degree of obesity may indicate that the Wnt/β-catenin signaling pathway involving GSK-3 plays a negative regulatory role in limiting adipocyte differentiation, i.e., interruption of Wnt/β-catenin signaling promotes adipogenesis, which is consistent with the results of several studies [2, 6, 10, 11, 14].

Conclusion

Thus, obese patients showed a wide variability in the level of the GSK-3α and GSK-3β proteins, which tended to increase depending on the degree of obesity. Moreover, increased level of serum GSK-3α and GSK-3β occurred in parallel with decreased β-catenin, which is consistent with the literature data and can be considered as a prognostic criterion for the course of pathological processes in obesity. Since the Wnt/β-catenin-dependent pathway inhibits adipogenesis, its activation represents an attractive target for drug development to combat obesity and associated metabolic complications.

There is no conflict of interest.

References

1. Ackers I., Malgor R. Interrelationship of canonical and non-canonical Wnt signalling pathways in chronic metabolic diseases. *Diabetes Vasc. Dis. Res., 2018, Vol. 15, no. 1, pp. 3-13.*
2. Ahmad B., Serpell C.J., Fong I.L., Wong E.H. Molecular Mechanisms of Adipogenesis: The Anti-adipogenic Role of AMP-Activated Protein Kinase. *Front. Mol. Biosci., 2020, no. 7, 76.* doi: 10.3389/fmolb.2020.00076.
3. Beurel E., Grieco S.F, Jope R.S. Glycogen synthase kinase-3 (GSK3): regulation, actions, and diseases. *Pharmacol. Ther., 2015, no. 148, pp. 114-131.*
4. Cawthorn W.P., Bree A.J., Yao Y., Du B., Hemati N., Martinez-Santibañez G., MacDougald O.A. Wnt6, Wnt10a and Wnt10b inhibit adipogenesis and stimulate osteoblastogenesis through a β-catenin-dependent mechanism. *J. Bone, 2012, Vol. 50, no. 2, pp. 477-489.*
5. Chen D., Xie R., Shu B., Landay A. L. Wei C., Reiser J., Spagnoli A., Torquati A., Forsyth C.B., Keshavarzian A., Sumner D.R. Wnt signaling in bone, kidney, intestine, and adipose tissue and inter-organ interaction in aging. *Ann. N. Y. Acad. Sci., 2019, Vol. 1442, no. 1, pp. 48-60.*
6. Christodoulides C. Lagathu C., Sethi J.K., Vidal-Puig A. Adipogenesis and WNT signaling. *Trends Endocrinol. Metab., 2009, Vol. 20, no. 1, pp. 16-24.*
7. Cline G.W., Johnson K., Regittnig W., Perret P., Tozzo E., Xiao L., Damico C., Shulman G.I. Effects of a novel glycogen synthase kinase-3 inhibitor on insulin-stimulated glucose metabolism in Zucker diabetic fatty (falfa) rats. *Diabetes, 2002, Vol. 51, no. 10, pp. 2903-2910.*
8. Colomiere M., Permezel M., Lappas M. Diabetes and obesity during pregnancy alter insulin signalling and glucose transporter expression in maternal skeletal muscle and subcutaneous adipose tissue. *J. Mol. Endocrinol., 2010, Vol. 44, no. 4, pp. 213-223.*
9. Doble B.W., Woodgett J.R. GSK-3: tricks of the trade for a multi-tasking kinase. *J. Cell Sci., 2003. Vol. 116, no. 7, pp. 1175-1186.*
10. Lappas M. Is increased in adipose tissue and skeletal muscle from women with gestational diabetes where it regulates the inflammatory response. *PLoS One, 2014, Vol. 9, no. 12, e115854.* doi: 10.1371/journal.pone.0115854.
11. Markussen L.K., Winther S., Wicksteed B., Hansen J.B. GSK3 is a negative regulator of the thermogenic program in brown adipocytes. *Sci. Rep., 2018, Vol. 8, no. 1, 3469.* doi: 10.1038/s41598-018-21795-y.
12. Ng L.F., Kaur P., Bunnag N., Suresh J., Sung I., Tan Q.H., Gruber J., Tolwinski N.S. WNT Signaling in Disease. *Cells, 2019, Vol. 8, no. 8, pp. 826-857.*
13. Rayasam G.V., Tulasi V.K., Sodhi R., Davis J.A., Ray A. Glycogen synthase kinase 3: more than a namesake. *J. Pharmacol., 2009, Vol. 156, no. 6, pp. 885-898.*
14. Shen H.H., Yang C.Y., Kung C.W., Chen S.Y., Wu H.M., Cheng P.Y., Lam K.K., Lee Y.M. Raloxifene inhibits adipose tissue inflammation and adipogenesis through Wnt regulation in ovariectomized rats and 3 T3-L1 cells. *J. Biomed. Sci., 2019, Vol. 26, no. 62.*
15. Wang L., Li X., Wang Y. GSK3β inhibition attenuates LPS-induced IL-6 expression in porcine adipocytes. *Sci. Rep., 2018, Vol. 8, no. 1, e15967.* doi: 10.1038/s41598-018-34186-0.

Авторы:

Кулакова А.С. *— врач-гастроэнтеролог ГАУЗ «Брянская областная больница № 1», г. Брянск, Россия*

Снимщикова И.А. *— д.м.н., профессор, заведующая кафедрой иммунологии и специализированных клинических дисциплин, директор Медицинского института ФГБОУ ВО «Орловский государственный университет имени И.С. Тургенева», г. Орел, Россия*

Плотникова М.О. *— старший преподаватель кафедры иммунологии и специализированных клинических дисциплин Медицинского института ФГБОУ ВО «Орловский государственный университет имени И.С. Тургенева», г. Орел, Россия*

Authors:

Kulakova A.S., *Gastroenterologist, Bryansk Regional Hospital No. 1, Bryansk, Russian Federation*

Snimshchikova I.A., *PhD, MD (Medicine), Professor, Head, Department of Immunology and Clinical Specialties, Director of the Medical Institute, I. Turgenev Oryol State University, Orel, Russian Federation*

Plotnikova M.O., *Senior Lecturer, Department of Immunology and Clinical Specialties of the Medical Institute, I. Turgenev Oryol State University, Orel, Russian Federation*

Поступила 15.03.2021
Отправлена на доработку 01.06.2021
Принята к печати 09.06.2021

Received 15.03.2021
Revision received 01.06.2021
Accepted 09.06.2021