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HYPOGLYCEMIC AND HYPOLIPIDEMIC ACTIVITY OF ARGININE CONTAINING BEARBERRY LEAVES EXTRACT IN INSULIN RESISTANT RATS

Introduction. *In recent decades, diabetes mellitus type 2 (DM2) has become one of the leading causes of deaths worldwide. A number of studies confirmed the causal relationship between the development of insulin resistance (IR) and DM2. At the same time, traditionally and for many years the plants or substances isolated from them have been using in the DM2 treatment and correction of its complications.*

The aim of the study *– to find out the effect of ethanolic polyphenol Bearberry leaves (Arctostaphylos uva-ursi) extract enriched with arginine (PE50_arg) on tolerance to glucose and lipid metabolism under experimental IR in rats.*

Research Methods. *Adult male outbred albino rats were used in the present study. Two experimental IR models were conducted: daily intraperitoneal administration of dexamethasone and a diet enriched with fructose. Treating was performed by oral administration of polyphenolic alcohol extract (PE50) and the corresponding extract with the addition of arginine (PE50_arg). IR was confirmed by measuring immunoreactive insulin (IRI) and plasma glucose levels. At the end of the experiment, the lipid profile was investigated in the obtained serum samples. The statistical processing of the data was carried out using the STATISTICA program (StatSoftInc., USA, version 6.0).*

Results and Discussion. *A diet for 7 weeks enriched with fructose caused IR in rats. Also we observed increased triacylglycerol (TAG), free fatty acids (FFA) and cholesterol (Ch) levels. Daily injections of dexamethasone, which maintained the hormone level for 5 weeks, led to the IR development. Under hormone-induced IR also FFA and TAG levels were elevated, but Ch concentration in blood plasma did not significantly change. Both extracts, PE50 and PE50_arg, improve cell sensitivity to insulin in experimental IR models. At the same time, PE50_arg has a more pronounced normalizing effect on the lipid parameters being investigated.*

Conclusions. *Our results suggest that PE50_arg may be a potentially promising anti-diabetic agent.*

KEY WORDS: **insulin resistance; diabetes mellitus type 2; bearberry; arginine; hypoglycemic action.**

INTRODUCTION. In recent decades, diabetes mellitus type 2 (DM2) has become one of the leading causes of deaths worldwide. The number of diabetic patients increases annually in all countries by 5–7 %, and every 12–15 years doubles [1]. According to the International Diabetes Federation (IDF) "Statista 2020", by 2045 projections the number of diabetics will rise to some 700 million diabetics globally. The disease increases mortality by 2–3 times and significantly shortens life expectancy [2].

A number of studies confirmed the causal relationship between the development of insulin resistance (IR) and DM2 [3]. IR state means a decrease in the biological response to the effects of insulin, which is accompanied by a decreased absorption of glucose by the insulin-sensitive tissues, mainly skeletal muscle, adipose tissue and the liver tissues, in other words, the resistance of cells of various organs and tissues to the insulin action [4]. Despite the fact that the exact mechanisms involved in the IR development have not been fully understood, specific changes in the lipid and lipid signaling molecules metabolism have been proved [5]. Furthermore, much attention was paid to correlation between free fatty acids (FFA) level and impaired glucose tolerance [6]. All of the above explains the increased interest of medical practitioners in experimental and clinical studies aimed at identifying molecular targets in order to develop new methods for the prevention and treatment of DM2.

Traditionally and for many years the plants or substances isolated from them have been using in the DM2 treatment and correction of its complications. The antidiabetic properties of more than 200 plants were confirmed and their list is constantly updated [7]. Initial screening of the ethanolic and water extracts of Bearberry leaves evaluating its glycemic potential was performed with three different doses given orally in normal rats by conducting fasting blood glucose (FBG) test and the oral glucose tolerance test (OGTT) [8]. Considering the literature data that alimentary arginine increases the cell

insulin-sensitivity, as a result, it stimulates the glucose flow into cells, as well as its metabolic transformations, developed Bearberry leaves extract was enriched with arginine [9]. All the technological procedures were performed at the National University of Pharmacy (NUPh) Pharmacognosy Department by the supervising of Prof. O. M. Koshovyi.

The aim of the study. The present study was conducted to find out the effect of ethanolic polyphenol Bearberry leaves (Arctostaphylos uva-ursi) extract enriched with arginine (PE50_arg) on tolerance to glucose and lipid metabolism under experimental IR in rats.

RESEARCH METHODS. Adult male outbred albino rats weighing 175–200 g were used in the present study. Animals were obtained from and housed in vivarium of the NUPh Central Scientific-Research Laboratory. For experimental IR induction in rats were used two different models. Glucocorticoid-induced IR was developed by daily intraperitoneally administration of dexamethasone (15 mkg/kg/day) for 5 weeks (Dex) [10]. Diet-induced IR was caused by "watering" with 20 % fructose water solution (with free access) during 7 weeks – high-fructose diet (HFD). The animals of the intact control and the dexamethasone groups had free access to tap water. All the groups were fed with rat-food pellet ad libitum. Animals, which were randomized to group treatment, were given polyphenol ethanolic extract (extractor – 50 % ethanol, PE50) and PE50_arg beginning from the 5th week of the experiment for 2 weeks in dose 100 mg/kg b.w. Intact control group received the same volume of physiological solution. As reference preparation was used Arphasetin infusion in dose 18 ml/kg b.w. Thereby, there were 9 groups (n=6): 1 – intact control (IC); 2 – HFD induced IR (IR_HFD); 3 – IR_HFD treated by PE50 (IR_HFD_PE50); 4 – IR_HFD treated by PE50_arg (IR_HFD_PE50_arg); 5 – IR_HFD treated by Arfasetin (IR_HFD_Arf); 6 – dexamethasone induced IR (IR_Dex); 7 – IR_Dex treated by PE50 (IR_Dex_PE50); 8 – IR_Dex treated by PE50_arg (IR_Dex_PE50_arg); 9 – IR_HFD treated by Arfasetin (IR_Dex_Arf).

IR was confirmed by measuring immunoreactive insulin (IRI) level ("DRG", Germany) and fasting blood plasma glucose (FBG) level (NPP Felicit-Diagnostics Ltd., Ukraine) after 5 weeks and 7 weeks of experiment. Rats with HOMA index more than 3.0 were considered diabetic (IR) and were used in the experiment and on-line calculated (http://actendocrinology.ru/calc). Animals were removed from the experiment by decapitation under thiopental anesthesia and blood serum samples were prepared to evaluate lipid profile in blood serum were determined total lipids (TL), triacylglycerols (TAG), free fatty acids (FFA) and total cholesterol (Ch) using commercially available kits (NPP Felicit-Diagnostics Ltd., Ukraine; DiaSys, Germany). The experiment was carried out with the approval of the Institutional Animal Ethics Committee.

The statistical processing of the data was carried out using the STATISTICA program (StatSoftInc., USA, version 6.0).

RESULTS AND DISCUSSION. Performing research tasks, it was found that keeping animals on HFD was accompanied by an increase in glucose level by 50 % and 68 % to the end of 5th and 7th weeks of the experiment, respectively. To evaluate the IR development the insulin content in blood plasma was also determined (Table 1). Recalculation showed that the HOMA index was significantly increased in the control periods. Thereby, the data obtained indicate a decrease in the cell insulin sensitivity and the IR development. It is known that the state of hyperglycemia and IR is also accompanied by the oxidative stress development, increased lipid peroxidation and lipid metabolism disorders [11].

Table 1 – **Fasting blood plasma glucose, immunoreactive insulin and HOMA indices after 5th and 7th week of the experiment**

Groups/indices		Time					
		initial	5th week	7th week	7th week / treatment		
					PE50	PE50_arg	Arf
HFD	FBG mmol/l	4.17±0.65	6.27±0.79*	7.01±0.93*	5.57±0.56*	5.38±0.49*	5.53±0.46*
	IRI pmol/l	72±7	97±8*	109±11*	78±5*	77±9*	87±7*
	HOMA	1.92±0.12 (N<3,0)	3.89±0.29*	4.86±0.31*	2.73±0.34*	2.65±0.31	3.08±0.19*
Dex	FBG mmol/l	4.03±0.31	6.97±0.57*	7.34±0.51*	5.98±0.49*	5.54±0.37	5.87±0.65*
	IRI pmol/l	77±5	101±9*	117±11*	79±9	80±8	87±7*
	HOMA	1.99±0.65 (N<3,0)	4.51±0.97*	5.50±1.11*	2.89±0.67*	2.84±0.34	3.27±0.45*

Note. Data were expressed as mean±SD.
* – p≤0.05 vs. intact group; ** – p≤0.05 vs. IR_HFD group and IR_Dex group respectively.

The effectiveness of different modifications of diet enriched with fructose, which lead to IR and DM2 development, was proved by experiments and explained by theory. It is known that fructose metabolism differs from glucose conversion and occurs along a pathway that is independent of insulin. Fructose in the liver under the influence of fructokinase is converted to fructose-1-phosphate, which, with the participation of aldolase, is broken down to glyceraldehyde and dihydroxyacetone phosphate. The obtained products are included in the process of gluconeogenesis, as well as converted to acetyl-CoA, followed by inclusion in lipogenesis [12]. Strengthening gluconeogenesis, which is not controlled by insulin, makes the main contribution to the development of hyperglycemia (Table 1). Moreover, there is literature data that in rats kept on a diet with a high level of fructose, it reduces the expression of insulin receptor substrate 1 (IRS-1) and phosphatidylinositol 3-kinase (PI3K) to insulin and the development of IR [13]. Acetyl-CoA overproduction can lead to hypertriglyceridemia and hypercholesterolemia development, which are observed in our experiment (Table 2). The PE50_arg introduction to HFD group animals during 2 weeks led to a significant decrease in blood glucose (Table 1). The PE50_arg introduction inhibited the development of hyperglycemia, reduced insulin levels (Table 1), and normalized the content of neutral lipids in the blood in animals kept on HFD (Table 2).

Dexamethasone-induced IR is also well-established model, but has another metabolic mechanism. The results of the dexamethasone injection after 5 weeks showed that the blood glucose level of animals in this group by 82 % was higher than the values of the intact group (Table 1). It was found out that the insulin signal implementation in target tissues is carried out with the participation of IRS, PI3K, which activates the protein kinase B (Akt). Akt-serine/threonine kinase, in turn, activates the translocation of glucose transporter type 4 (glut-4) and stimulates the glucose uptake into the cell. The dexamethasone administration is accompanied by inhibition of Akt insulin-dependent phosphorylation, which leads to glucose uptake inhibition and the IR development. It is known that glucocorticoids stimulate fatty acids and TAG synthesis in the liver, as a result, elevated level of these lipids in the blood [14]. The data obtained in our work confirm this thesis (Table 2); at the same time the Ch content under the dexamethasone action did not significantly change. As for hypoglycemic action, the PE50_arg administration during 14 days led to a significant decrease in the glucose level (Table 1) more pronounced compared with PE50 administration. A significant decrease in the HOMA index was also observed.

The results of this study demonstrated that arginine addition to the polyphenol preparation improved its hypoglycemic action.

The arginine administration is known to stimulate the expression of PI3K and Akt which entails an increase in the sensitivity of cells to insulin [15]. This evidence found the confirmation in our current experiment. It is known that a prolonged increase in FFA content in the blood is an important manifestation of IR development, which mediated by endoplasmic reticulum stress and activation of c-Jun N-terminal kinases (Jnk) [16]. The decrease in the content of FFA observed in our work (Table 2) leads to an increase in the target cells sensitivity to the insulin action. Most likely it was caused by improving of FFA oxidation in the liver by the arginine action [17]. Also, it is quite probable explanation for the cholesterol content decrease in blood serum (Table 2).

Thus, the obtained results indicate that prolonged HFD and dexametason administration for 7 weeks contributed to the development of carbohydrate metabolism disorders (glucose resistance and hyperglycemia), which may serve as criteria for IR development. The 2-weeks PE50 and PE50_arg administration under IR led to improvement of these disorders.

Table 2 – **The effect of PE50 and PE50_arg on the content of individual lipid fractions in the blood serum of rats with IR**

	TL mg/g tissue	TAG mg/g tissue	FFA mmol/g tissue	Ch mmol/g tissue
IC	171±7	6.17±0.56	4.13±0.57	17.7±2.05
IR_HFD	229±13*	10.29±1.21*	6.11±0.45*	25.6±2.62*
IR_HFD_PE50	264±27**	7.42±0.67**	5.43±0.41**	21.9±1.71
IR_HFD_PE50_arg	249±19**	6.57±0.87**	4.65±0.37**	17.8±1.82
IR_Dex	273±15*	11.97±1.19	7.18±0.24*	19.3±1.21
IR_Dex_PE50	251±18**	8.14±0.97	6.39±0.41**	18.4±1.14
IR_Dex_PE50_arg	231±17**	6.57±0.67	4.58±0.63**	19.4±2.3

Note. Data were expressed as mean±SD.
* – p≤0.05 vs. intact group; ** – p≤0.05 vs. IR_HFD group and IR_Dex group respectively.

CONCLUSIONS. 1. High-fructose diet during 7 weeks induced insulin resistance in rats.

2. Dexamethasone daily injections that maintained the hormone level during 5 weeks led to the insulin resistance development.

3. Both PE50 and PE50_arg improve insulin cell sensitivity under experimental IR models. At the same time PE50_arg has more pronounced normalizing effect on studied lipid indices.

4. Our results suggest that PE50_arg may be a potentially promising anti-diabetic agent.

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ГІПОГЛІКЕМІЧНА ТА ГІПОЛІПІДЕМІЧНА ДІЯ АРГІНІНВМІСНОГО ЕКСТРАКТУ З ЛИСТЯ МУЧНИЦІ ЗВИЧАЙНОЇ НА ТЛІ ІНСУЛІНОРЕЗИСТЕНТНОСТІ В ЩУРІВ

Резюме

Вступ. *В останні десятиліття цукровий діабет 2 типу став однією з провідних причин смерті в усьому світі. Результати ряду досліджень підтвердили причинно-наслідковий зв'язок між розвитком інсулінорезистентності (ІР) і цим захворюванням. Водночас традиційно і протягом багатьох років рослини або речовини, виділені з них, використовують для лікування цукрового діабету 2 типу та корекції його ускладнень.*

Мета дослідження *– з'ясувати вплив поліфенольного спиртового екстракту з листя мучниці звичайної, який збагачено аргініном, на толерантність до глюкози і метаболізм ліпідів при експериментальній інсулінорезистентності в щурів.*

Методи дослідження. *Експеримент проведено на дорослих щурах-альбіносах. Було використано різні моделі інсулінорезистентності, такі, як щоденне внутрішньочеревне введення дексаметазону і дієта, збагачена фруктозою. Для корекції перорально вводили поліфенольний спиртовий екстракт та поліфенольний спиртовий екстракт з додаванням аргініну. Інсулінорезистентність підтверджували шляхом вимірювання рівня імунореактивного інсуліну та рівня глюкози в плазмі крові. Після закінчення експерименту у відібраних зразках сироватки крові визначали показники ліпідного профілю. Статистичну обробку даних здійснювали за допомогою програми STATISTICA (StatSoftInc., США, версія 6.0).*

Результати й обговорення. *Дієта з високим вмістом фруктози протягом 7-ми тижнів викликала резистентність до інсуліну в щурів. Також спостерігали збільшений рівень триацилгліцеролів, вільних жирних кислот і холестеролу. Щоденні ін'єкції дексаметазону, які підтримували рівень гормону протягом 5-ти тижнів, зумовили розвиток резистентності до інсуліну. При інсулінорезистентності, яка була індукована гормонами, рівень вільних жирних кислот і триацилгліцеролів також був підвищений, однак концентрація в плазмі крові холестеролу достовірно не змінювалась. Поліфенольний спиртовий екстракт*

та поліфенольний спиртовий екстракт з додаванням аргініну покращували чутливість клітин до інсуліну в експериментальних ІР-моделях. Водночас поліфенольний спиртовий екстракт з додаванням аргініну мав більш виражену нормалізуючу дію на досліджувані ліпідні показники.

Висновок. *Результати нашого експерименту свідчать про те, що аргінін може бути потенційно перспективним протидіабетичним засобом.*

КЛЮЧОВІ СЛОВА: **інсулінорезистентність; цукровий діабет 2 типу; мучниця звичайна; аргінін; гіпоглікемічна дія.**

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ГИПОГЛИКЕМИЧЕСКАЯ И ГИПОЛИПИДЕМИЧЕСКАЯ АКТИВНОСТЬ ЭКСТРАКТА ИЗ ЛИСТЬЕВ ТОЛОКНЯНКИ ОБЫКНОВЕННОЙ С ДОБАВЛЕНИЕМ АРГИНИНА НА ФОНЕ ИНСУЛИНОРЕЗИСТЕНТНОСТИ У КРЫС

Резюме

Вступление. *В последние десятилетия сахарный диабет 2 типа стал одной из ведущих причин смертности во всем мире. Результаты ряда исследований подтвердили причинно-следственную связь между развитием инсулинорезистентности (ИР) и этим заболеванием. В то же время традиционно и в течение многих лет растения или вещества, выделенные из них, используют для лечения сахарного диабета 2 типа и коррекции его осложнений.*

Цель исследования *– выяснить влияние спиртового полифенольного экстракта из листьев толокнянки обыкновенной, который обогащен аргинином, на толерантность к глюкозе и метаболизм липидов при экспериментальной инсулинорезистентности у крыс.*

Методы исследования. *Эксперимент проведен на взрослых крысах-альбиносах. Были использованы различные модели инсулинорезистентности, такие, как ежедневное внутрибрюшное введение дексаметазона и диета, обогащенная фруктозой. Для коррекции перорально вводили полифенольный спиртовой экстракт и полифенольный спиртовой экстракт с добавлением аргинина. Инсулинорезистентность подтверждали путем измерения уровня иммунореактивного инсулина и уровня глюкозы в плазме крови. По окончании эксперимента в отобранных образцах сыворотки крови определяли показатели липидного профиля. Статистическую обработку данных осуществляли с помощью программы STATISTICA (StatSoftInc. США, версия 6.0).*

Результаты и обсуждение. *Диета с высоким содержанием фруктозы в течение 7-ми недель вызывала резистентность к инсулину у крыс. Также наблюдали увеличенный уровень триацилглицеролов, свободных жирных кислот и холестерола. Ежедневные инъекции дексаметазона, которые поддерживали уровень гормона в течение 5-ти недель, обусловили развитие резистентности к инсулину. При инсулинорезистентности, которая была индуцирована гормонами, уровень свободных жирных кислот и триацилглицеролов также был повышен, однако концентрация в плазме крови холестерола достоверно не изменялась. Полифенольный спиртовой экстракт и полифенольный спиртовой экстракт с добавлением аргинина улучшали чувствительность клеток к инсулину в экспериментальных ИР-моделях. В то же время полифенольный спиртовой экстракт имел более выраженное нормализующее действие на исследуемые липидные показатели.*

Вывод. *Результаты нашего эксперимента свидетельствуют о том, что полифенольный спиртовой экстракт может быть потенциально перспективным противодиабетическим средством.*

КЛЮЧЕВЫЕ СЛОВА: **инсулинорезистентность; сахарный диабет 2 типа; толокнянка обыкновенная; аргинин; гипогликемическое действие.**

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