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ОРИГИНАЛЬНАЯ СТАТЬЯ

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The efficacy of liraglutide-based drugs on the model of induced metabolic syndrome in experimental animals

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Today, there is an annual increase in the prevalence of obesity and overweight worldwide. This problem is becoming particularly relevant, since these conditions serve as key risk factors for the development of a number of cardiovascular and metabolic disorders, including type 2 diabetes mellitus (T2DM). On the territory of the Russian Federation, drugs were presented as agonists of glucagon-like peptide of the first type (GLP-1) receptors, the active substance of which was produced exclusively by biotechnological means. It is important to note that solid-phase chemical synthesis is also one of the alternative methods for obtaining GLP-1 analogues. A significant advantage of this method over biotechnological synthesis is the exclusion of spontaneous amino acid substitutions and the absence of impurities characteristic of this method.

The aim. Evaluation of the biological activity of the domestic medicinal product liraglutide (Enligria®, solution for subcutaneous administration, 6 mg/ml, PROMOMED RUS LLC), obtained by chemical synthesis, and a foreign reference drug (Saxenda®, solution for subcutaneous administration, 6 mg/ml, NovoNordisk A/C), obtained biotechnologically.

Materials and methods. The effectiveness of liraglutide preparations was evaluated using a model of induced metabolic syndrome in CBA×C57BL/6 SPF mice (*n*=36, age 6 months) according to changes in body weight, feed intake, blood glucose and lipid levels, and adipose tissue mass.

Results. According to the results of the study, it was shown that Enligria® and Saxenda® drugs have comparable efficacy parameters and statistically significantly (p <0.05) reduce body weight (13.6±2.1% and 13.3±3.3%, respectively), glucose levels

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RESEARCH ARTICLE

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(18±3% and 16±9%), triglycerides (32±12% and 40±18 %) and cholesterol (16±7% and 18±9%) in the blood. Enligria® reduced the mass of structural subcutaneous fat by 32±3% (p <0.0001), and visceral fat by 34±4% (p <0.0001). The studied liraglutide preparations showed a pronounced hypoglycemic effect, observed in all dose ranges. The observed hypoglycemic effect was dose-dependent.

Conclusion. The results of the work indicate the high effectiveness of the synthetic drug Enligria®, which is expressed in reducing body weight and improving metabolic parameters.

Keywords: GLP-1 agonist; liraglutide; peptide; metabolic syndrome; type 2 diabetes mellitus; obesity; weight loss; glucose; lipids; experiment

Abbreviations: GLP-1 — glucagon-like peptide of the first type; DPP-4 — dipeptidyl peptidase 4; BMI — body mass index; BW — body weight; T2DM — type 2 diabetes mellitus; SS — saline solution; EC_{50} — half maximal effective concentration.

Исследование эффективности лекарственных препаратов лираглутида на модели индуцированного метаболического синдрома у экспериментальных животных

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На сегодняшний день наблюдается ежегодный рост темпов распространенности ожирения и избыточной массы тела во всем мире. Данная проблема приобретает особую актуальность, поскольку эти состояния служат ключевыми факторами риска развития целого ряда сердечно-сосудистых и метаболических нарушений, включая сахарный

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диабет 2 типа (СД2). На территории РФ в качестве агонистов рецепторов глюкагоноподобного пептида первого типа (ГПП-1) были представлены препараты, действующее вещество которых производилось исключительно биотехнологическим путём. Важно отметить, что так же одним из альтернативных способов получения аналогов ГПП-1 является твердофазный химический синтез. Существенным преимуществом данного метода перед биотехнологическим синтезом является исключение спонтанных замен аминокислот и отсутствие характерных для химического метода синтеза примесей.

Цель. Оценить биологическую активность российского лекарственного препарата лираглутида (Энлигрия®, раствор для подкожного введения, 6 мг/мл, ООО «ПРОМОМЕД РУС»), полученного методом химического синтеза, и зарубежного референтного препарата (Саксенда®, раствор для подкожного введения, 6 мг/мл, НовоНордиск А/С), полученного биотехнологическим путём.

Материалы и методы. Эффективность препаратов лираглутида оценивали на модели индуцированного метаболического синдрома у мышей CBA×C57BL/6 SPF-категории (n=36, возраст 6 мес.) по изменению показателей массы тела, потребления корма, уровня глюкозы и липидов в крови, а также массы жировой ткани.

Результаты. По результатам проведённого исследования было показано, что препараты Энлигрия® и Саксенда® имеют сопоставимые параметры эффективности и статистически значимо (p <0,05) снижают массу тела (13,6±2,1 и 13,3±3,3%, соответственно), уровень глюкозы (18±3 и 16±9%), триглицеридов (32±12 и 40±18%) и холестерина (16±7 и 18±9%) в крови. Препарат Энлигрия® снижал массу структурного подкожного жира на 32±3% (p <0,0001), а висцерального жира на 34±4% (p <0,0001). Исследуемые препараты лираглутида показали выраженное гипогликемическое действие, наблюдавшееся во всех диапазонах исследуемых доз. Наблюдаемый гипогликемический эффект носил дозозависимый характер.

Заключение. Результаты работы свидетельствуют о высокой эффективности синтетического препарата Энлигрия®, выраженной в снижении массы тела и улучшении метаболических параметров.

Ключевые слова: агонист ГПП-1; лираглутид; пептид; метаболический синдром; сахарный диабет 2 типа; ожирение; снижение массы тела; глюкоза; липиды; эксперимент

Список сокращений: ГПП-1 — глюкагоноподобный пептид первого типа; ДПП-4 — дипептидилпептидаза 4; ИМТ — индекс массы тела; МТ — масса тела; СД2 — сахарный диабет второго типа; ФР — физиологический раствор; EC_{50} — полуэффективная концентрация.

INTRODUCTION

Obesity is one of the most important health problems. According to the WHO, there are currently more than 1.6 billion people over 15 years of age with excess body weight (body mass index [BMI] = 25.0–29.0 kg/m^2) and more than 400 million people suffering from obesity (BMI > 30 kg/m^2) [1–3]. An epidemiological link has been established between excess body weight and type 2 diabetes mellitus (T2DM): over 75% of cases are associated with excess body weight and obesity. More than 50% of patients with T2DM have a BMI > 30 kg/m^2 [1, 3]. It is important to note that people with excess body weight and obesity are also significantly more likely to be diagnosed with hypertension (34–64%), gallbladder disease (35–45%) and osteoarthritis (5–17%) [4].

Over the past decade, the possibilities for treating obesity and T2DM have significantly expanded due to the emergence of a new class of medicines — glucagon-like peptide-1 (GLP-1) receptor agonists. Previously, medicines with active ingredient produced exclusively by biotechnological means were presented on the pharmacy market as GLP-1 receptor agonists [5]. However, the disadvantages of biotechnological production, including the need to ensure the genetic stability of producer strains and the potential risk of developing adverse reactions of immune system, demonstrated the need to study and develop alternative methods for producing GLP-1 receptor agonists. One of the alternative methods for producing GLP-1 analogs is chemical synthesis [1, 4, 6]. Modern automated directed synthesis systems allow to obtain linear peptides up to 100 amino acids long. A significant advantage of this method is the exclusion of spontaneous substitutions of the amino acid sequence, typical for biotechnological synthesis, and the purity of the product (there are no impurities of residual nucleic acids and producer proteins), which eliminates the risk of immunogenicity while maintaining effectiveness, and also ensures a high safety profile of the drug[1] [7–9].

Until recently, only foreign drugs from the group of GLP-1 receptor agonists were registered in the Russian Federation: Saxenda® (INN: liraglutide), Victoza® (INN: liraglutide) and Ozempic® (INN: semaglutide), which are products of Novo Nordisk A/S (Denmark). In September 2023, the Russian company PROMOMED RUS registered the first liraglutide drug — Enligria®, a solution for subcutaneous administration, 6 mg/mL, registration certificate No. LP-008822, the active ingredient of which is obtained synthetically. Figure 1 shows the structure of liraglutide.

[1] FDA. ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin Guidance for Industry. Guidance for Industry. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/andas-certain-highly-purified-synthetic-peptide-drug-products-refer-listed-drugs-rdna-origin

THE AIM. To evaluate comparative efficacy of the Russian liraglutide medicine (chemical synthesis) and the foreign reference medicine (biotechnological synthesis).

MATERIALS AND METHODS

Test system

The study was conducted using the automated Phenomaster platform (TSE Instruments, Germany) to obtain a statistically significant effect in a biological experiment in accordance with the Guidelines for Preclinical studies[2]. The work used 36 male CBA×C57BL/6 mice aged 6 months of SPF category produced by the Center for Genetic Resources of Laboratory Animals of the ICiG SB RAS. The duration of adaptation after receipt from the nursery was more than 14 days. Mice were kept in groups of 2 in individually ventilated GM500 cages (Tecniplast, Italy) with a floor area of 500 cm^2 and a height of 16 cm. Wood chips of deciduous species (fraction 3, IP Filonich, Russia) were used as bedding. Cages were changed at least every 3 weeks. The temperature in the animal housing facilities ranged from 20 to 24°C, relative humidity — from 30 to 70%. Light mode is direct, 12-hour, light on at 09 a.m. To enrich the habitat, the animals were given nesting material and cardboard shelters. Materials entering the animals were sterilized by autoclaving.

The experiment used a diet-induced model of metabolic syndrome in mice [6, 9, 10]. Animals received a high-calorie diet (35% P-22 feed [Bio-Pro, Russia], 35% condensed milk, 30% melted beef fat) and 30% fructose syrup for at least 3 months. By the start of the study, the mice had a BMI of 45–50 g and a pronounced metabolic syndrome, confirmed by a glucose tolerance test. The animals were divided into 3 experimental groups of 12 individuals each.

Ethics approval

The study design and animal housing conditions were selected in accordance with the Guidelines of the EEC No. 33 dated November 14, 2023. Throughout the study, the animals had unlimited access to food and purified water. A Bioethical approval of the study plan was carried out by the Commission on Bioethics of the Institute of Biomedical Problems of the Russian Academy of Sciences (Protocol No. 648 dated September 28, 2023). When handling animals, the requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 1986) were observed.

Design of experiment

Distribution into experimental groups

Mice were distributed into experimental groups by randomization using GraphPad Prizm v. 8 Software. The cage was used as an element of randomization.

Dosage regimen

The study drug and saline solution (SS) were administered subcutaneously, into the withers, 1 time/day, starting from day 1 of the experiment. Administration was carried out using 0.5 mL injection syringes with G29 needles (5 mL/kg total).

Due to the fact that subcutaneous injections, themselves, are a source of stress for animals, the animals were accustomed to manipulations for 1 week of the experiment. To do this, 5 ml/kg of SS was administered subcutaneously daily. Then, the mice in the experimental group began to be injected with the studied liraglutide (Enligria®, solution for subcutaneous administration, 6 mg/mL, PROMOMED RUS LLC, Russia), the mice in the comparison group — with a commercially available liraglutide drug (Saxenda®, solution for subcutaneous administration, 6 mg/mL, Novo Nordisk A/S, Denmark), and the mice in the control group continued to be injected with SS. The doses of liraglutide were sequentially increased, starting from the first test dose — 0.1 mg/kg. The criterion for increasing the dose was the absence of changes in the body weight (BW) of mice by more than 2% in 3 days. Liraglutide and SS were administered subcutaneously 1 time/day in the evening (before the daily peak of feed consumption). The duration of administration of substances was 21 days.

Duration of the study

The experiment was conducted from Augst 10, 2023 to September 05, 2023.

The duration of administration of substances was 21 days. In total, mice received 4 injections of 0.1 mg/kg, 9 injections of 0.2 mg/kg, 4 injections of 0.4 mg/kg and 5 injections of 0.8 mg/kg in 22 days. In total, mice received 7.8 mg/kg of liraglutide.

[2] Guidelines for conducting preclinical studies of medicines. Part one. Moscow: Grif and K; 2012. 944 p. EDN: SDEWMP. Russian

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In vivo study

The BW of mice was measured daily, starting from the first day of the experiment, with an accuracy of ±0.1 g using ViBRA AJ-2200CE (Japan). The consumption of food and water in the holding cages was carried out daily, starting from the first day of the experiment, by the difference in the mass of the feed/water issued and their residues on the next day (24 ± 2 h). The mass of food and drinks was determined with an accuracy of ±0.1 g using CO 2200 scales (Vibra, Japan). Blood glucose (not fasting) was measured before the start of substance administration and at each dose change using a OneTouch Verio Reflect portable glucometer (LifeScan, Switzerland) and test strips for it according to the manufacturer's instructions. Blood for measurement in a volume of 3–5 µL was obtained by puncture of the tip of the tail.

Euthanasia

Euthanasia of mice was performed by inhalation of isoflurane followed by exsanguination. Mice were placed in a priming chamber for induction anesthesia (isoflurane 5%). After loss of posture and slowing of breathing, without stopping isoflurane inhalation using a mask, the chest was opened in the mice and the maximum possible volume of blood (≈1 mL) was taken from the right ventricle using a 2 ml injection syringe. At the end of the procedure, to guarantee the death of the animal, the heart was cut off from the main vessels.

Collection and handling of blood samples

The collected blood was placed in microcentrifuge tubes with a clot activator and separation gel. After clotting, but no later than 2 h after blood collection, the serum was separated by centrifugation at 2500 g and room temperature for 15 min. The serum was decanted into labeled 1.5 ml microcentrifuge tubes, frozen and stored at a temperature not higher than minus 18°C until analysis, but no longer than 1 month.

Necropsy

During necropsy, a visual assessment of fat depots was performed and internal organs were excised to determine their BW.

Visual assessment of fat depots: subcutaneous fat depots (interscapular, anterior subcutaneous, brachial, inguinal and popliteal) and visceral (mesenteric, perirenal, pericardial, gonadal) were examined. Each depot was evaluated in points according to the following scale: 0 — not expressed (adipose tissue is practically absent); 1 — moderately expressed; 2 — well expressed (there is a lot of adipose tissue). The total score for the animal was calculated as the sum of the scores for all fat depots.

During necropsy, the following organs were excised and weighed (±1 mg, Vibra ALE323R scales, Japan): visceral fat, brain, thymus, heart, lungs, spleen, pancreas, liver, kidney, adrenal glands, testicles, epididymides, accessory apparatus (prostate and seminal vesicles complex), triceps muscle of the lower leg.

Biochemical blood test

The concentration of glucose, triglycerides and cholesterol was analyzed in the serum. The analysis was performed on an automatic analyzer A25 (Biosystems, Spain) using Hospitex Diagnostics reagent kits and control materials (Italy) according to the reagent manufacturer's instructions.

Statistical processing

Dose-effect curves were analyzed by nonlinear regression. MS Excel Software (v. 16.82, Microsoft Corp., USA) and Prism (v. 10.2, GraphPad, USA) were used for data analysis. Data are presented as mean arithmetic and standard deviation (M ± SD). Statistical data analysis was performed using one-way (factor "group") and two-way (factors "group" and "time") analysis of variance with subsequent pairwise comparisons using the Sidak or Tukey test. Differences were considered significant at $p < 0.05$.

RESULTS

Change in body weight

Data on the BW of mice are presented in Figure 2. Getting used to the subcutaneous injection procedure was accompanied by some decrease in BW (-6.4 ± 0.3%). After 4 days of administration, the BW stabilized. Then, the animals of the experimental groups began to be injected with medicine T (study) or R (compared medicine), and the mice of the control group continued to be injected with SS. The administration of liraglutide led to a progressive decrease in the BW of mice in the experimental groups (T and R), while the BW of mice in the control group did not change significantly. Differences in the BW of mice in the control and experimental groups reached the level of statistical significance from day 4 of drug administration ($p < 0.05$). The maximum decrease in BW was 13.6 ± 2.1 and 13.3 ± 3.3% for T and R, respectively.

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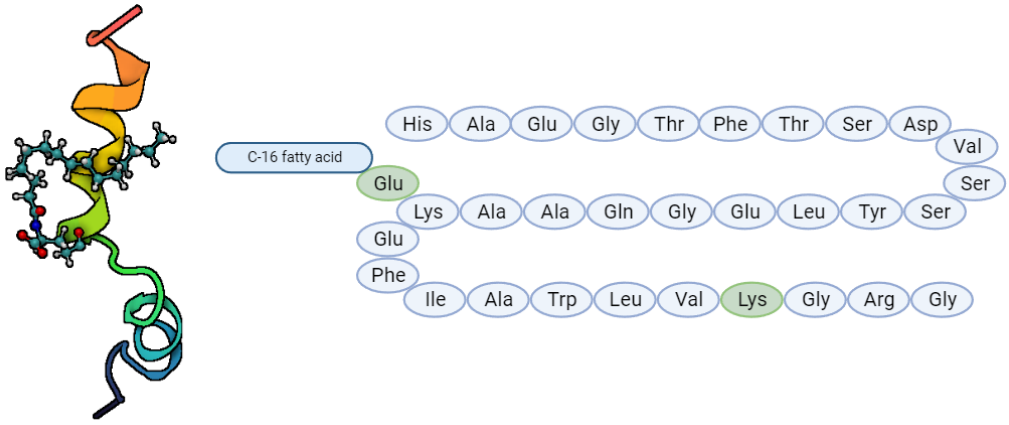

Figure 1 – Structure of liraglutide

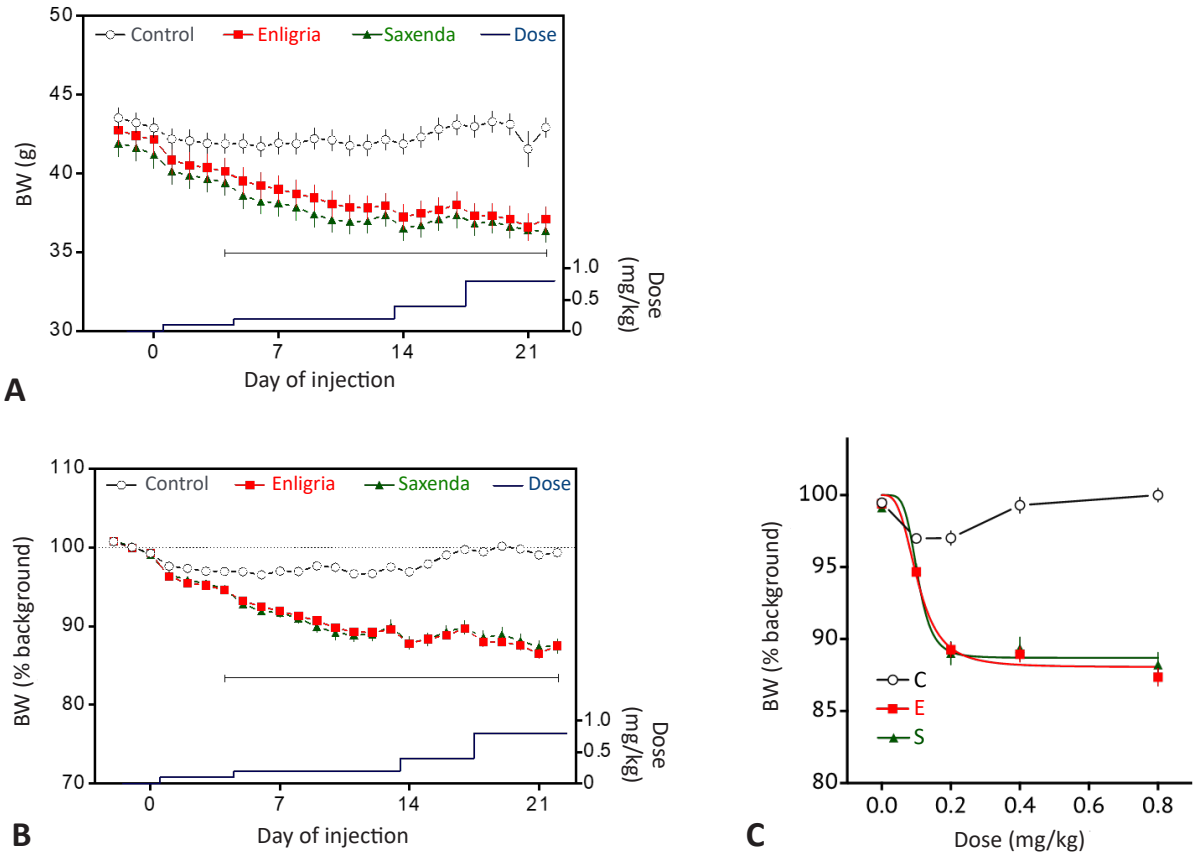

Figure 2 – Change in body weight of animals

Note: A — change in absolute body weight; B — change relative to body weight (expressed in relation to background values, before the start of substance administration, during the habituation of animals to subcutaneous injections); C — dependence of body weight on the dose of administered drugs. BW — body weight.

Table 1 – Data of variance analysis and subsequent pairwise comparisons of body weight change

Factor	df1	df2	F-value	*p*-value
Term × Group (Interaction)	48	792	52.70	< 0.0001
Term (Time)	24	792	218.4	< 0.0001
Group	2	33	81.47	< 0.0001

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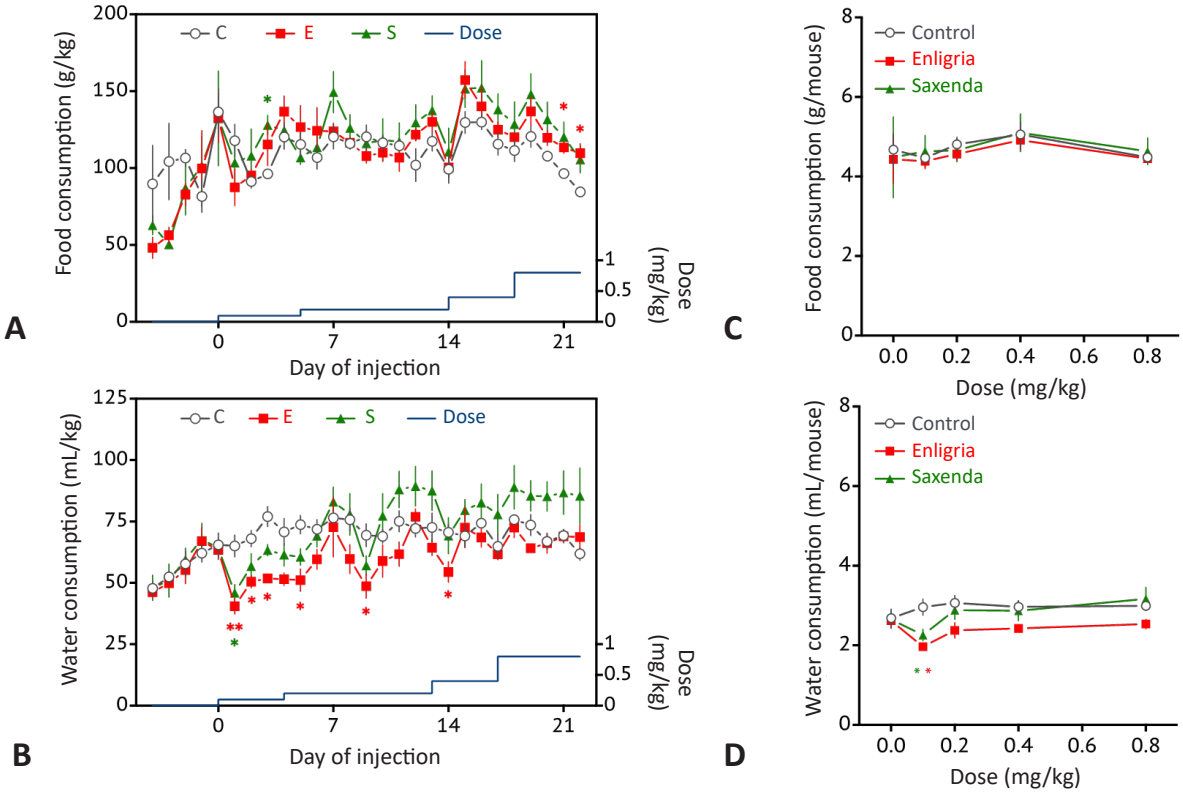

Figure 3 – Change in the amount of food and water consumption by animals

Note: Feed (A) and water (B) consumption depending on and the time of the study. Dependence of feed (C) and water (D) consumption the dose of the administered drug. * — $p < 0.05$, ** — $p < 0.01$ (Tukey test). E — Enligria®; S — Saxenda®; C — control.

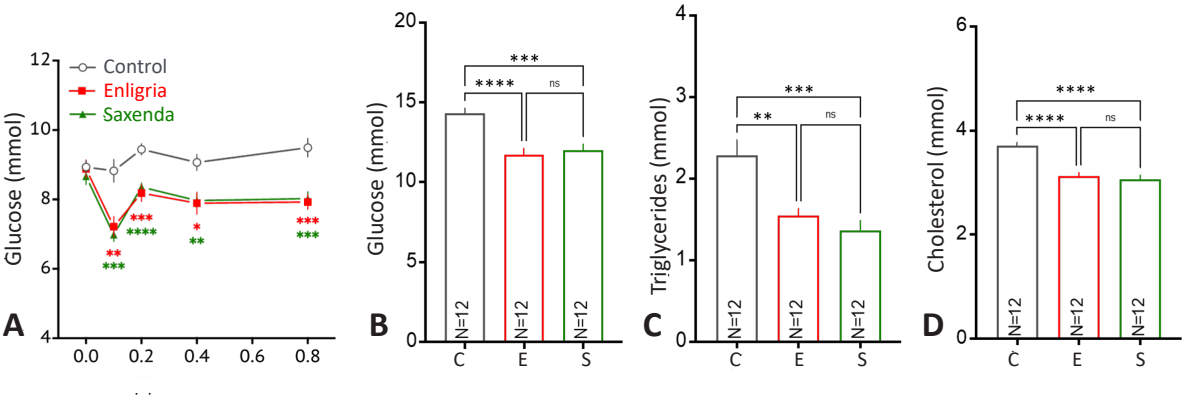

Figure 4 – Dynamics of changes in blood parameters in animals

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant (Tukey test).

Table 2 – Data of variance analysis and subsequent pairwise comparisons of changes in water and food consumption

Data block	df1	df2	F	*p*-value
Food consumption — dynamics over time, intergroup analysis	2	9	0.50	0.6224
Food consumption — dose dependence, intergroup analysis	2	9	0.08	0.9219
Water consumption — dynamics over time, intergroup analysis	2	9	2.94	0.1041
Water consumption — dose dependence, intergroup analysis	2	9	2.97	0.1021

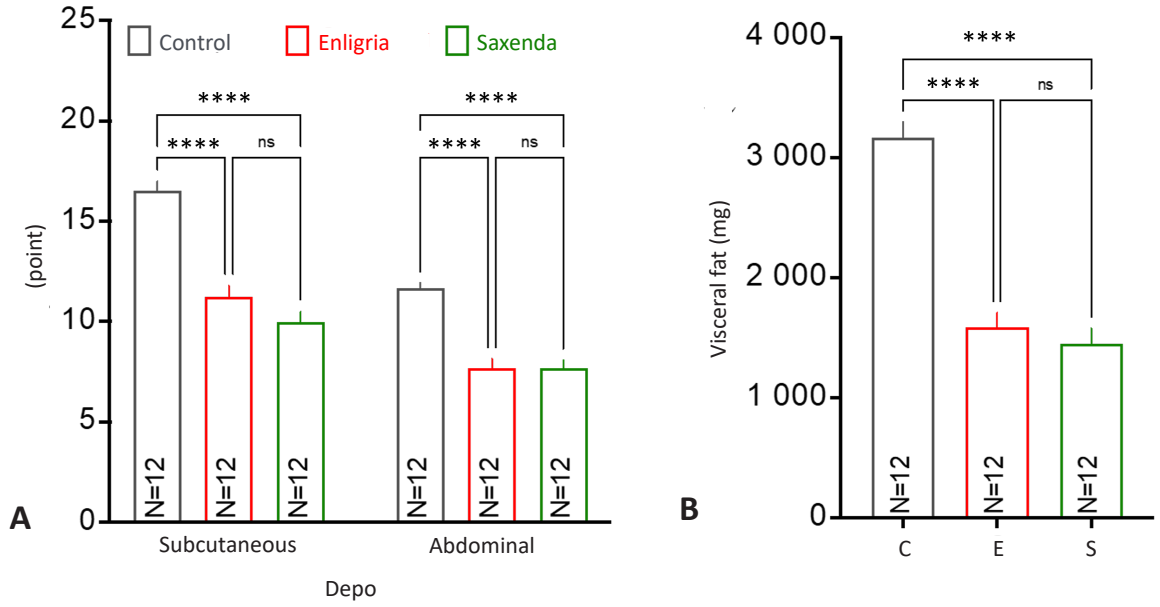

Figure 5 – Severity of fat depots according to visual assessment data (A) and visceral fat mass (B)
Note: **** — p <0.0001, ns — not significant (Tukey test).

Table 3 – Indicators of the mass of internal organs of mice (in mg) receiving liraglutide drugs 0.1–0.8 mg/kg or saline

Organ / tissue	Control	Enligria	Saxenda	Statistical data
Brain	496 ± 3	490 ± 2	491 ± 4	$F_{(2, 33)}$ = 0.94; p = 0.4019
Heart	173 ± 3	149 ± 4**** (-14 ± 2 %)	151 ± 3*** (-13 ± 2 %)	$F_{(2, 33)}$ = 15.43; p < 0.0001
Lungs	171 ± 4	169 ± 4	167 ± 3	$F_{(2, 33)}$ = 0.26; p = 0.7758
Kidneys	274 ± 6	256 ± 6	263 ± 4	$F_{(2, 33)}$ = 2.65; p = 0.0855
Liver	1890 ± 61	1565 ± 52*** (-17 ± 3%)	1469 ± 54**** (-22 ± 3%)	$F_{(2, 33)}$ = 15.72; p < 0.0001
Pancreas	239 ± 6	262 ± 10	261 ± 9	$F_{(2, 33)}$ = 2.13; p = 0.1347
Spleen	78,8 ± 1,6	72,8 ± 1,3* (-8 ± 2%)	71,6 ± 1,9** (-9 ± 2%)	$F_{(2, 33)}$ = 5.69; p = 0.0076
Triceps muscle of the lower leg	223 ± 3	211 ± 3* (-6 ± 1%)	206 ± 4** (-8 ± 2%)	$F_{(2, 33)}$ = 6.19, p = 0.0052
Testicle	113 ± 1	116 ± 2	115 ± 2	$F_{(2, 33)}$ = 0.89; p = 0.4207

Note: * — p <0.05; ** — p <0.01; *** — p <0.001; **** — p <0.0001, ns — not significant (Tukey test). For significant differences, the value of the change in organ mass in percent relative to the control group is given in parentheses. Data are presented as M±SD.

To analyze the dependence of the effect of medicines on the BW of mice on the dose, half maximal effective concentrations — EC_{50} were calculated (Fig. 2B). The half maximal effective concentration for the study drug was 0.179 mg/kg (95% CI = 0.152–0.235), for the comparison drug — 0.156 mg/kg (95% CI = 0.123–0.208). The EC_{50} values for the two medicines did not differ significantly ($F_{(1, 114)}$ = 0.92, p = 0.3406). Dose-effect curves were satisfactorily ($R^2 \approx 0.8$) described by a 4-parameter logistic function. Table 1 presents the data of statistical analysis.

Food and water consumption

The amount of food and water consumed by animals in the experimental groups did not differ significantly (Table 2). During the experiment, at the initial stage of drug administration, a decrease in water consumption was noted in the groups of animals receiving liraglutide, which was established in almost all toxicological and pharmacological studies (OECD 407/408/409, ICH M3[R2]). The fact that during the experiment the amount of water consumed by the control and experimental groups had similar values indicates the absence of a systemic effect.

The difference in BW changes between the comparison and control groups during the experiment was also not observed (Fig. 3). Table 2 presents the data of statistical analysis.

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Blood parameters

The concentration of glucose in the blood (not fasting) decreased after the start of administration of liraglutide, while the severity of the decrease did not depend on the study drug and dose (Fig. 4A). The concentration of glucose in the blood of mice receiving drugs T and R was reduced compared to mice in the control group by 18 ± 3% ($p < 0.0001$) and 16 ± 9% ($p < 0.001$), respectively. The concentrations of triglycerides in mice receiving drugs T and R decreased by the end of the experiment by 32±13% (p <0.01) and 33±18% (p <0.001), respectively (Fig. 4 B, C). When the study drugs were administered, a decrease in cholesterol concentration relative to the control group was observed ($p < 0.0001$). Thus, for the liraglutide drug (T), this indicator was 17.7 ± 6.8%, for R — 16.6 ± 8.6% (Fig. 2D). Biochemical blood parameters of mice receiving liraglutide drugs did not differ between themselves.

Assessment of the amount of adipose tissue

The severity of the decrease in the amount of adipose tissue in mice receiving liraglutide was indistinguishable both according to visual assessment data and according to indicators of visceral fat mass.

The severity of subcutaneous and visceral fat depots during visual assessment significantly decreased in animals receiving drugs T and R (Fig. 5A). Thus, in mice receiving the study drug, subcutaneous fat depots were 32 ± 3% ($p < 0.0001$), visceral fat depots were 34 ± 4% ($p < 0.0001$) less pronounced than in control individuals. In animals receiving the reference drug, these values decreased, respectively, by 39 ± 3% ($p < 0.0001$) and 34 ± 4% ($p < 0.0001$) than in mice that were injected with SS.

During necropsy, visceral fat (epididymal, perirenal) was excised from mice and its mass was determined. The mass of adipose tissue in mice receiving liraglutide drugs was sharply reduced compared to control individuals (Fig. 5 B). In mice that were injected with the study drug, the decrease in adipose tissue mass was 50 ± 14% ($p < 0.0001$), in animals receiving the reference drug — 54 ± 14% ($p < 0.0001$).

Mass of internal organs

During necropsy, the main organs and tissues were excised and examined. Given the significant differences in the mass of animals, as well as the fact that the mass of most internal organs are allometrically proportional to lean (without adipose tissue), and not total BW. Data on absolute mass, and not mass coefficients, were used to analyze the mass of internal organs. The mass of the brain, lungs, pancreas, testicles, adrenal glands in mice receiving liraglutide preparations did not differ from the values of the control group, which indicates the safety of therapy (Table 3). The mass of the liver, heart, spleen and triceps muscle of the lower leg in groups of animals receiving medicines T and R were less than in control individuals, which indicates a positive effect of the medicine in relation to reducing the amount of visceral fat associated with the development of complications.

DISCUSSION

GLP-1 is one of the most important and studied incretin hormones responsible for glucose homeostasis when it enters the body with food [10–12]. It has been established that up to 70% of glucose-dependent insulin secretion is due to the incretin effect. Normally, endogenous GLP-1s are synthesized in the L-cells of the intestine in response to food intake.

It is known that in T2DM, the incretin effect is reduced, which determines the therapeutic potential of hypoglycemic agents that restore the incretin effect [1]. It is important to note that GLP-1 produced by intestinal cells activates receptors located on sensory neurons of the *vagus* nerve, thereby regulating the activity of various areas of the brain. In addition, GLP-1 receptors are expressed in different areas of the brain, where GLP-1 behaves as a neuropeptide involved in various specific effects, including appetite control, water consumption and stress response [3].

In clinical studies in patients with T2DM, the beneficial effects of native GLP-1 were limited by a short half-life, which is approximately 2–5 min, due to their degradation by the enzyme dipeptidyl peptidase 4 (DPP-4). To reduce the effect of the enzyme, DPP-4-resistant GLP-1 agonists conjugated with a lipid, such as liraglutide, have been developed [7, 10–13]. Liraglutide is a peptide 97% homologous to the native hormone in terms of amino acid composition, and modified with a 16-carbon fatty acid residue by attaching it through a glutamic spacer to the ε-amino group of lysine (ε-Lys26). This structure provides protection against DPP-4, and, as a result, prolongs activity [14, 15].

In this *in vivo* study, the efficacy of the Russian liraglutide drug (Enligria®), the active ingredient of which is obtained by chemical synthesis, and a commercially available foreign analogue (Saxenda®), the active ingredient of which is obtained by biotechnological synthesis, was studied.

The results of the study showed that mice with excess BW receiving liraglutide had a pronounced decrease in BW compared to the control group. The decrease in the level of adipose tissue was statistically significant, with comparable results for both the original and the Russian drug. Blood glucose levels also decreased, indicating improved glycemic control. In addition, triglyceride and total cholesterol levels in the blood showed a noticeable decrease. These study data confirm the efficacy of liraglutide both in the original and in the Russian version in the context of treating excess BW and metabolic disorders. Since the severity of the effect was similar for both forms of medicines, this may indicate the high quality of the Russian analogue, which is an important aspect for clinical use in practice. Comparison of half maximal effective doses indicates identical mechanisms of action and equivalent bioavailability of both drugs.

In contrast to the appetite suppression in humans well described in the work of C. Verdich et al. for liraglutide, in our in vivo work, suppression of feed consumption was not observed, which is probably based on species differences between mice and the human body [16]. It has previously been shown that one of the leading mechanisms mediating the decrease in BW in mice when GLP-1 receptors are activated is stimulation of the sympathetic nervous system [17, 18] and β3-adrenoreceptor-mediated decrease in fat deposition by white adipose tissue adipocytes [2, 19], as well as induction of thermogenic expression, “browning” of adipose tissue [14, 20]. These observations are in good agreement with our data on a significant decrease in the mass of fat depots in animals receiving liraglutide preparations. It is important that the central effects of GLP-1 agonists on adipocyte metabolism were manifested with a normal diet [19, 21].

A pronounced hypoglycemic effect was found for the studied drugs, which was observed even at the smallest of the doses we studied — 0.1 mg/kg. Increasing the dose of liraglutide was not accompanied by an increase in the hypoglycemic effect. It can be assumed that already 0.1 mg/kg of the peptide was a saturating concentration for peripheral (in the pancreas) GLP-1 receptors, while the lower bioavailability of liraglutide for central receptors due to low penetration through the blood-brain barrier [22, 23] led to a gradual increase in the central action of liraglutides with increasing dose and a progressive decrease in BW.

When examining the internal organs of mice on day 21 of administration of liraglutide preparations, a significant decrease in liver mass was found. The liver of obese mice contains at least ≈10% fat (up to 30%) [24, 25]. Given the data on the enhancement of β-oxidation of fatty acids in a number of tissues when peripheral GLP-1 receptors are activated, it can be assumed that the decrease in liver mass was due to a decrease in fat content [12, 26]. The data obtained also confirm the high potential of GLP-1 agonists in the treatment of non-alcoholic fatty liver disease. Muscles contain significantly less adipose tissue, which is in good agreement with the less pronounced decrease in the mass of the triceps muscle of the lower leg we studied in animals receiving liraglutides. In this regard, it should be noted that GLP-1 receptor agonists prevent the loss of muscle mass by suppressing the expression of ubiquitin ligases and stimulating the differentiation of muscle cells [27].

For all the studied organs and tissues, there were no differences in the effects of liraglutide drugs obtained by biotechnological and synthetic methods of synthesis.

As a result of our previous studies, a sufficient amount of data has been collected confirming the similarity of the physicochemical and biological properties of these drugs [2]. Verification of the amino acid sequence of peptides in both drugs and determination of the intact mass were carried out by liquid chromatography mass spectrometry (LC-MS). The similarity of the profiles of the active substance, high-molecular compounds and related impurities contained in the drugs was confirmed by reversed-phase and size-exclusion HPLC techniques. At the same time, the content of impurities in liraglutide obtained by chemical synthesis was 3.5 times lower than in the original medicine, which confirms the advantages of the chosen technology for the production of the substance [2]. The comparability of the biological activity of the drugs was confirmed in in vitro studies on the CHO-K1 / GLP-1R cell type (GenScript, USA) [2]. In the conducted bioequivalence study, no adverse events were observed, and the tolerability of the test drugs was assessed as “good”. At the same time, it is important to note that no cases of immunogenicity were noted for the Russian drug, which confirms the reduction in the risk of lack of effectiveness of therapy and the high safety profile of the drug [2].

Thus, as a result of the studies carried out, it can be concluded that the drug Enligria® (INN: liraglutide), solution for subcutaneous administration, 6 mg/mL,

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PROMOMED RUS LLC, and Saxenda® (INN: liraglutide), solution for subcutaneous administration, 6 mg/mL, Novo Nordisk A/S, are bioequivalent.

Limitations of the study

Despite the fact that the use of an experimental model on CBA×C57BL/6 mice to study metabolic syndrome can provide valuable data, it is also important to be aware of the limitations that may affect the validity and generalizability of the results. For example, C57BL/6 mice are known to have a high risk of developing obesity and insulin resistance on a high-fat diet, which may not reflect the reactions of other animal strains [28]. This fact may lead to the fact that the results will not be applicable to a wider population of mammals, including humans. It is also important to consider possible combinations of diet and habitat that may affect the behavior and physiology of animals. For example, the presence of stressors, such as social interaction or housing conditions, can significantly affect the results, especially in studies related to metabolic disorders and obesity [29]. Finally, it should be noted that differences in methods for measuring fat mass, food consumption, and other biochemical parameters can affect the comparability of data. For example, differences in the biomarkers used to assess glucose and lipid levels can lead to differences in the interpretation of the data obtained [30].

Further studies using diverse models and increasing the sample size may help in a more accurate understanding of the mechanisms and effect of therapy.

CONCLUSION

A comparative study of the efficacy of liraglutide drugs obtained by biotechnological synthesis and by directed peptide synthesis showed the equivalence of their biological activity and safety. This study confirmed the efficacy of liraglutide both in the original and in the Russian version in the context of treating excess BW and metabolic disorders. Since the severity of the effect was similar for both forms of medicines, this may indicate the high quality of the Russian analogue, which is an important aspect for the clinical use of the drug. Comparison of half maximal effective doses indicates identical mechanisms of action and equivalent bioavailability for both drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Alexander A. Andreev-Andrievskiy — development of the preclinical research concept, analysis and description of the results, draft editing; Kira Ya. Zaslavskaya — analysis and selection of literary sources, writing the text of the article; Olga V. Fadeeva — discussion of the design and results of the study; Petr A. Bely — research design implementation, research data processing; Victoria S. Scherbakova, Ekaterina A. Rogozhina — discussion of the design and results of the study; Tatiana G. Bodrova — design development and research concepts; Denis V. Kurkin, Ksenia N. Koryanova, Ekaterina S. Mishchenko — writing and editing the text of an article; Yuri G. Kazaishvili — development of the design and concept of preclinical research; Alexey V. Taganov — search and analysis of literary sources; Majed Wannouss — analysis and description of the results; Mihail A. Mashkin – selection of literary sources, writing the text of the article. All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

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