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Benzodiazepine derivative methanindiazenone modulates lipid metabolism in the liver of rats with rotenone-induced Parkinson's syndrome

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Parkinson's disease (PD) is a neurodegenerative condition for which the exact causes remain elusive, and no effective treatments currently exist. The pathogenesis of PD is believed to involve oxidative stress, mitochondrial dysfunction, and lipid metabolism disorders. A benzodiazepine derivative JM-20 has demonstrated protective effects on mitochondria in both neurons and peripheral tissues of rats with rotenone-induced Parkinson's syndrome (PS). This study aimed to analyze bile composition and assess the impact of a new benzodiazepine derivative, methanindiazenone, on lipid metabolism in the liver of rats subjected to the rotenone model of PS. The results indicated that, compared to the control group, bile concentration of phospholipids, cholesterol, cholesterol esters, and triglycerides decreased by 24.3, 26.2, 25.8, and 27.5%, respectively. With methanindiazenone treatment at doses of 0.5 and 1.0 mg/kg, all these metrics reverted to the control level. However, in the rotenone+methanindiazenone 2.0 mg/kg group, the levels of phospholipids, cholesterol, and cholesterol esters (except for triglycerides) surpassed the control values by 33, 28.1, 28.4 and 33.5%, respectively. Methanindiazenone positively impacted the motor behavior of rats with the rotenone model of PS and enhanced their survival rates. Therefore, at doses of 0.5 and 1.0 mg/kg, methanindiazenone not only improved lipid metabolism in the liver but also the overall well-being of rats with the rotenone model of PS. However, a 2 mg/kg dose of methanindiazenone displayed toxic effects, as seen from the increased content of phospholipids, cholesterol, and cholesterol esters in bile. Hence, methanindiazenone holds potential as a therapeutic agent for PS and possibly other neurodegenerative diseases related to lipid metabolism impairment, but its use should be limited to doses of 0.5 and 1.0 mg/kg.
Key words: Parkinson's syndrome; rotenone model; methanindiazenone; liver; bile; lipids.

INTRODUCTION

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, leading to dopamine deficiency in the caudate nucleus and putamen [1]. Dopamine is a neurotransmitter responsible, among others, for balance, gait, and movements. The degeneration of dopaminergic neurons results in motor complications, such as body bradykinesia, resting tremor, rigidity, and postural instability. Additionally, PD patients exhibit non-motor symptoms, including disturbances in the autonomic nervous system, dementia, apathy, depression, anxiety, neuropsychiatric disorders, cognitive dysfunction, sleep disorders, orthostatic hypotension, sexual dysfunction, and gastrointestinal complications [2, 3]. In the past decades, the incidences of PD has dramatically increased worldwide, rising from 2.5 million patients in 1990 to 6.1 million in 2016. Predictions suggest a continuous upward trajectory. Consequently, PD is emerging as a significant health concern, with affected individuals experiencing a higher mortality rate compared to the general population [4]. The exact triggers of the neurodegenerative processes in PD remain elusive. Potential

factors include age, heredity, environmental exposures, oxidative stress, and mitochondrial dysfunction, the latter being linked to the blockade of complex I in the respiratory chain [5]. Rotenone, a pesticide, is known to inhibit the mitochondrial electron transport chain at complex I, leading to the production of reactive oxygen species and consequent cell damage [6]. Prolonged rotenone exposure in rats induces neuropathological and behavioral PD-like symptoms, this rotenone model effectively mimics the disease progression in human. Rotenone-mediated systemic mitochondrial inhibition results in selective nigrostriatal degeneration, oxidative stress, and apoptosis of dopaminergic neurons [7]. Recent hypotheses emphasize altered lipid metabolism and, especially, concerning cholesterol, in PD's pathogenesis. However, study findings have been inconsistent. Some data indicate that individuals with higher cholesterol levels have a reduced PD risk, suggesting a potential correlation with statins [8]. Other data indicate that hypercholesterolemia in experimental model of Parkinson's syndrome (PS) potentiated dopaminergic neurons loss in substantia nigra by disrupting mitochondrial functions and antioxidant homeostasis with subsequent reduction in striatal dopamine levels producing motor impairment [9]. Current pharmacological treatments for PD primarily involve drugs that either supplement or enhance natural dopamine effects. These medications predominantly address motor symptoms, leaving many non-motor complications unresolved [10]. Some believe that antipsychotic medications, specifically benzodiazepine derivatives, could mitigate non-motor symptoms in PD patients [11]. Notably, Fonseca-Fonseca, et al. [12] demonstrated that benzodiazepine derivatives protect the mitochondria of both rat neurons and liver from rotenone-induced damage. In our prior research, we documented lipid level alterations in the blood of rotenone-induced PS rats and identified changes in bile lipid fractions, pointing to suppressed hepatic metabolic processes in PS [13]. Thus, this study aims to investigate the potential protective effects of a new benzodiazepine derivative, methanediazenone, on the lipid metabolism in the liver of rotenone-induced PS rats.

METHODS

The experiments were carried out according to the current international requirements and norms of humane treatment of animals (Strasbourg, 1986, Law of Ukraine dated February 21, 2006 No. 3447-IV) and following the decision of the Biological Ethics Committee of the Scientific Center «Institute of Biology and Medicine» Taras Shevchenko Kyiv National University (protocol No. 3 dated April 9, 2009).

The following materials were used in the research: rotenone and dimethylsulfoxide manufactured by "Sigma" (USA); methanindiazenone, whose formula is as follows: 4-(4-methoxy-3-methylphenyl)-2,5-dihydro-1H-benzo[d][1,2]-diazepin-1-one4-(4-methoxy3-methylphenyl)-2,5-dihydro-1H-benzo[d][1,2]-diazepin-1-one, was synthesized in our laboratory. The elemental analysis of methanindiazenone was conducted at V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the National Academy of Sciences of Ukraine [14]. Sodium thiopental ("Kyivmedpreparat") was used to anesthetize experimental animals. The research was carried out in acute experiments on 60 mature male Wistar rats (obtained from Institute of Pharmacology and Toxicology, Academy of Medical Sciences of Ukraine).

Experimental design. The animals' weight was in the range of 300-350 g, age – 14 weeks. During the experimental period, the animals were housed in standard vivarium conditions, such as environmental humidity of 55-60%, controlled air temperature of 22 ± 2°C, 12-h light/dark cycle, and free access to tap water and commercial food. At the beginning of the experiment, animals were randomly divided into six experimental groups: I - control animals treated with refined sunflower

oil; II - animals treated with rotenone (2 mg/kg); III - animals treated with rotenone+1% dimethylsulfoxide (1 ml/kg); IV - animals treated with rotenone+methanindiazenone (0.5 mg/kg); V - animals treated with rotenone+methanindiazenone (1 mg/kg); VI - animals treated with rotenone+methanindiazenone (2 mg/kg); n = 10 in each experimental group. Rotenone was suspended in refined sunflower oil immediately before use and administered i.p. at a single dose (2 mg/kg) [15]. The administration of rotenone lasted for 4 weeks (28 days) and was carried out at the same time: from 10:00 to 12:00. After that, a suspension of methanindiazenone in a 1% dimethylsulfoxide solution was prepared immediately before use and was administered by single i.p. injections. The dosage of methanindiazenone was determined based on the lowest dose of other neuroprotective drugs found to be effective.

Behavioral analysis. In the rotenone-treated groups, rats showed reduced and slow movement, tremor, and an unstable gait, which were identified as PS-like symptoms; also, rat fur became yellow and dirty [16].

Locomotor activity. An open field test was used to evaluate the spontaneous activity of rats. Twenty-eight days following the treatment, rats were placed in an open field square box (100 cm long, 100 cm wide, and 40 cm high), inside of wich the test area was divided into squares and well illuminated. The experiments were carried out in a quiet environment. Before the test, 70% ethanol was used to thoroughly wipe the box's inner wall and bottom surface so as not to affect results of the next test. An animal was placed at the center of the box bottom and observed with a video camera (Fotocam, Canon) for 6 min: 1 min for habituation and 5 min for behavioral analyzes. Two motor parameters were quantified throughout this test, namely locomotion frequency (number of squares crossings, defined as the number of quadrant crossings with four paws) and rearing frequency (times an animal rise for at least 2 sec on their rear paws in the air or against the walls). The animal was then replaced, and the experiment was repeated [17].

Determination of lipids level in bile samples. According to the set goal, we determined the bile concentration of the following compounds (mg%): phospholipids, cholesterol, cholesterol esters, free fatty acids and triglycerides. Previously, rats were anesthetized with sodium thiopental (60 mg/kg), and laparotomy was performed. The common bile duct was then cannulated with a polyethylene catheter. Secreted bile was collected every 30 min during 1 h of the experiment by a graduated micropipette connected to a cannula located in the bile duct. Bile collected during the first 30 min was not taken into account (equilibrium period to stabilize the rate of bile outflow). Then the bile was subjected to chemical treatment according to a chosen methodology. Bile lipids were divided by the method of thin-layer chromatography that has been described by Veselsky, et al. [18]. For this purpose, 0.1 ml of bile was added to a 2.4 µl mixture of chloroform-methanol (2:1) and 0.5 ml acidified water (0.5 ml of concentrated sulfuric acid per 1 liter of double-distilled water) was added in 5 min. Samples were kept overnight for complete separation into two phases. The lower phase contained lipids. The extract was dried at +70°C. The dry residue was dissolved in 40 µl of a chloroform-methanol mixture (3:1) and put on a plate as a thin strip. Chromatography was performed in a chamber saturated by solvent vapor. The system of eluents included petroleum ether, diethyl ether, ether, glacial acetic acid (30:10:0.2). Fractions of biliary lipids were stained with 5% phosphomolybdic acid in 96% ethanol, followed by heating at 100°C for 5 min. Identification of the major lipid fractions was performed using standards and color of the spots, considering the relative mobility of fractions. For quantitative evaluation of individual fractions of lipids in bile, solutions of their main components (1 mg of substance per 1 ml of solvent), both individually and in a mixture with specimens of other fractions, were prepared. This mixture of standards is quantitatively (from 1 µl to 2; 5; 10; 15; 20; 25

and 30 µl) adsorbed on chromatographic paper. After extraction and concentration of bile at the bottom of a cone tube, it should be dissolved in 50 µl of solvent and dropped a few times with a micropipette (5 µl) on the surface of a prepared and marked chromatographic plate. Chromatographic separation of lipid components of bile is carried out on "Silufol" plates. After treatment with an aqueous solution of phosphomolybdic acid, a quantitative assessment of the color intensity of each fraction was performed using a densitometer DO-1M ("Shimadzu", Japan, λ 620 nm). The area of the spot was also measured. The value of the combined test was deposited on the y axis in the calibration graph, and the x axis was marked with the known amount of a corresponding standard – a witness of this lipid fraction's presence. These parameters were evaluated for lipid fractions from bile samples. The amount of the corresponding lipid was determined in µg based on the calibration curve. Finally, taking into account the dilution and the part of the extract, we determined the amount of lipids in mg per 100 ml of bile.

The results were assessed by: the parametric one-way ANOVA method combined with the Tukey test for pairwise comparison, and p values less than 0.05 were considered significant; the nonparametric Kruskal Wallis ANOVA method combined with the Mann-Whitney test for pairwise comparison with Bonferroni correction, and p values less than 0.01 were considered significant. Statistical analysis was conducted with Origin Pro 8.0, and graphical representations were crafted using Excel software.

RESULTS AND DISCUSSION

The effect of methanindiazenone on the concentration of lipids in the bile of rats with PS. In this study, changes in the concentrations of various bile lipids were observed, with the exception of free fatty acids. In particular, the bile phospholipids level in control rats was 102.9 ± 3.5 mg%. After administration of rotenone, the phospholipids concentration decreased to 77.9 ± 2.2 mg%, or by 24.3% ($P < 0.001$) compared to the control. In the rotenone+1% dimethylsulfoxide group, the phospholipids content was at the control level. In rats treated with methanindiazenone at doses of 0.5 mg/kg and 1.0 mg/kg, the bile phospholipids concentration was consistent with control values. Notably, a dose of 2 mg/kg of methanindiazenone elevated the bile phospholipids levels by 33% relative to the control (Fig. 1).

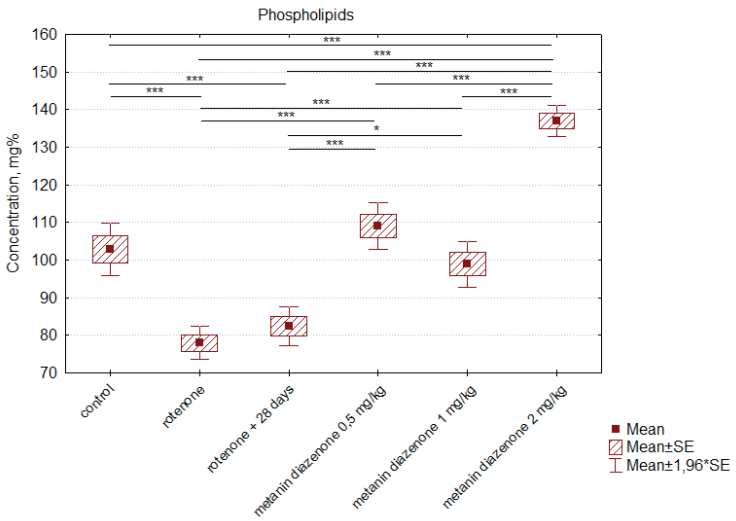

Fig. 1. Effect of methanediazenone on the amount of phospholipids in bile of rats with rotenone-induced PS, mg%. Secreted bile was collected each half-hour during 1 h of the experiment. Kruskal-Wallis test. *$P < 0.05$, ***$P < 0.001$

We also determined that compared to control values (33.75 ± 0.9 mg%), long-term rotenone administration led to a 28.3% decrease in bile cholesterol concentration (24.2 ± 0.9 mg%) ($P < 0.001$). In the rotenone+1% dimethylsulfoxide group (24.6 ± 0.9 mg%), cholesterol levels were 27.1% below control values ($P < 0.001$). In contrast, there was no significant difference from the control in the rotenone+ methanindiazenone 0.5 mg/kg (29.6 ± 1.1 mg%) and rotenone+methanindiazenone 1.0 mg/kg groups (33.6 ± 1.1 mg%). However, for the rotenone +methanindiazenone 2.0 mg/kg group, cholesterol levels were 29.5% above control values ($P < 0.001$) (Fig. 2).

The presented data revealed that under the effect of rotenone, the content of cholesterol esters in groups of rotenone and rotenone+1% dimethylsulfoxide decreased by 29.3% ($P < 0.001$) and by 22.4% ($P < 0,01$, respectively in comparison with the control group. Administering methanindiazenone at doses of 0.5 and 1 mg/kg normalized the cholesterol esters content in bile to control values. However, the rotenone+methanindiazenone 2.0 mg/kg group exhibited cholesterol esters levels 27.6% above control values ($P < 0.001$) (Fig. 3).

As demonstrated in Fig. 4, rotenone exposure did not alter the bile free fatty acids levels across all the studied groups (Fig. 4).

Fig. 5 reveals that rotenone-only treatments led to a 33.3% reduction in plasma triglycerides ($P < 0.05$). However, methanindiazenone doses of 0.5, 1.0, and 2 mg/kg restored all markers to the control levels.

Utilizing the open field method, we assessed the locomotor behavior of rats across all groups. We observed that rotenone induced a significant decrease in the motor activity of animals. Methanindiazenone treatment considerably enhanced motor activity in rats with Parkinson's-like symptoms, with behaviors aligning closely with healthy controls. Our prior study, which is part of this experiment, detailed these motor behavior test results [19].

The liver ensures the body lipid homeostasis, which are crucial for membrane fluidity and permeability, serving as an energy reservoir, and mediating inflammatory processes and apoptosis signals. The ratio of lipid fractions of bile to a certain extent reflects the features of lipid metabolism in the liver. It has an important physiological significance, and its disturbance is a necessary prerequisite for disorders of bile formation and the pathogenesis of gallstone disease. Hepatocytes obtain bile lipids in

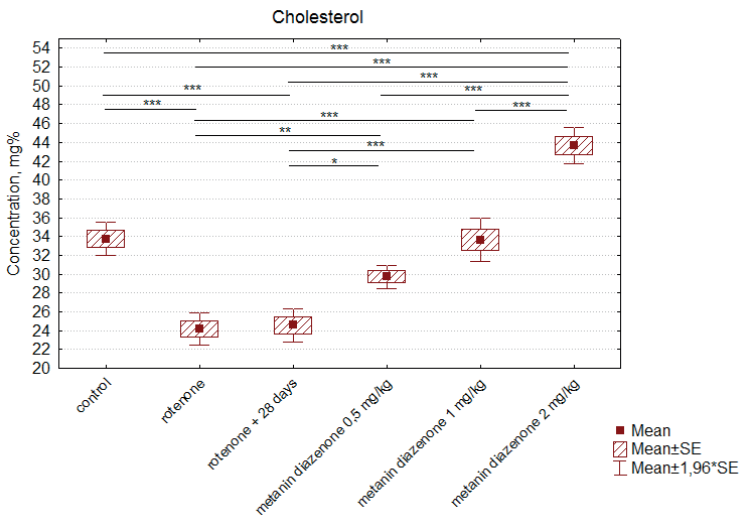

Fig. 2. Cholesterol level in bile of rats with PS induced by rotenone, before and after administration of methanediazenone in different doses. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

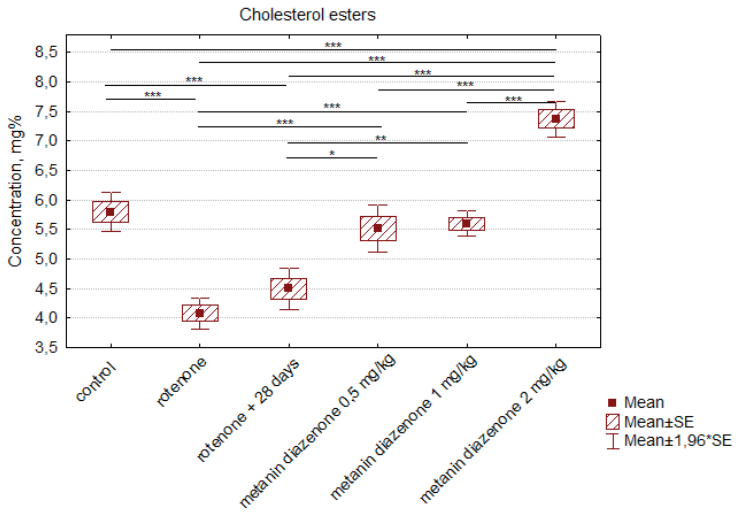

Fig. 3. Cholesterol esters concentration in bile of rats with PS induced by rotenone, before and after methanediazenone administration. *P < 0.05, **P < 0.01, ***P < 0.001

three ways: biosynthesis, lipoproteins, and existing molecules derived from intracellular membranes. At the same time, newly synthesized lipids account for about 20% of the total bile lipids.

Phospholipids are important for maintaining the colloid resistance of bile, because together with bile acids, which are a product of cholesterol catabolism, and other hydrophobic compounds, they form mixed micelles. The latter are extremely important for the removal of water-insoluble compounds from the body, such as cholesterol and others, and phospholipids is the most important component of the formation of micelles [20]. Micelle formation is a classical characteristic of surfactants. A decrease in the amount of phospholipids in the liver reduces their accumulation in bile. This may cause a disturbance of its colloid stability. Micelles formed by phospholipids and bile acids have a 1 million times greater ability to absorb cholesterol than micelles without phospholipids.

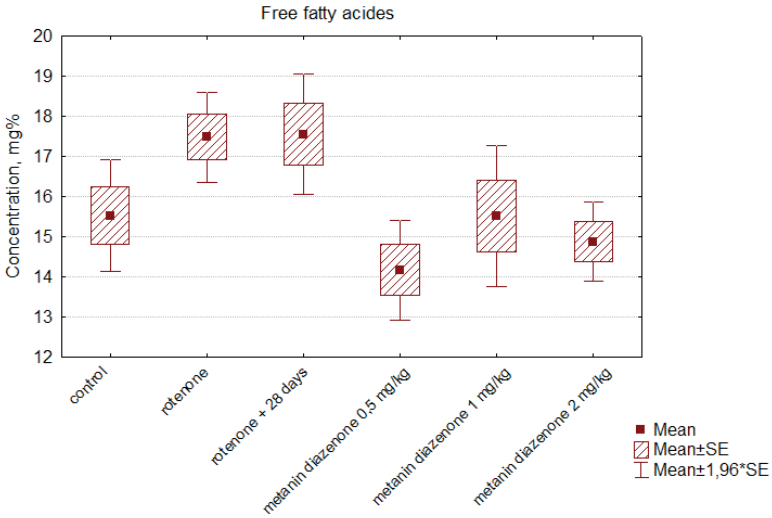

Fig. 4. The amount of free fatty acids in bile of rats with PS induced by rotenone, before and after administration of methanediazenone in different doses

This possibility is provided by the presence of a hydrophilic residue of phosphoric acid in phospholipids molecules, so these compounds are good solvents not only for cholesterol, but also for other hydrophobic substances [21]. Free fatty acids and cholesterol are the fundamental building blocks of lipids that control important metabolic processes. The liver's free fatty acids pool mainly depends on the absorption of non-esterified fatty acids into the blood from food sources (in the fed state) or the lipolysis of adipose tissue (in the fasting state). In the liver these compounds are accumulated through their absorption by hepatocytes from the plasma and de novo biosynthesis. As a result of the synthesis in the liver, up to 15-25% of all free fatty acids accumulates [22]. Neutral storage of free fatty acids in a healthy liver is carried out in the form of triglycerides. Neutral lipids are stored in lipid droplets, typically not exceeding 5% in a healthy liver. Stored free fatty acids can be oxidized to generate energy (ATP) or transported as very low-density lipoproteins. Free fatty acids and triglycerides metabolism is closely linked. In hepatocytes, free fatty acids are activated via acyl-CoA and transported to the mitochondria for conversion to ATP and warm as a form of energy, and free fatty acids synthesis also requires energy. Contrarily, most of the body's cholesterol (80%) is synthesized, with the liver controlling almost half of this synthesis. The human body contains about 100 g of cholesterol with a synthesis rate of 1.2 g per day at a body weight of 70 kg. While sufficient amounts of cholesterol may be synthesized, dietary intake can vary from 300 to 500 mg per day [23]. Bile contains not only cholesterol but also cholesterol esters. Cholesterol esters aids cholesterol molecule esterified with fatty acids, which is a form of cholesterol transport, since the excretion of cholesterol in the form of bile acids is not sufficient to completely neutralize its excessive intake with food. In general, up to 75% of cholesterol in the body is in the form of cholesterol esters. It is an intermediate product in metabolism. Cholesterol esters, as an ether, is more easily broken down in the liver. In our work, in rats of the 2 mg/kg rotenone group, we found a decrease in the bile levels of both phospholipids and triglycerides as well as cholesterol and cholesterol esters. This proves a disorder of the synthesis and accumulation of these compounds in the liver. In our previous study, we showed that long-term administration of rotenone to experimental rats is accompanied by inhibition of energy metabolism, which was manifested by a decrease in the amount of bile ATP by 38% [24]. In fact, such results can

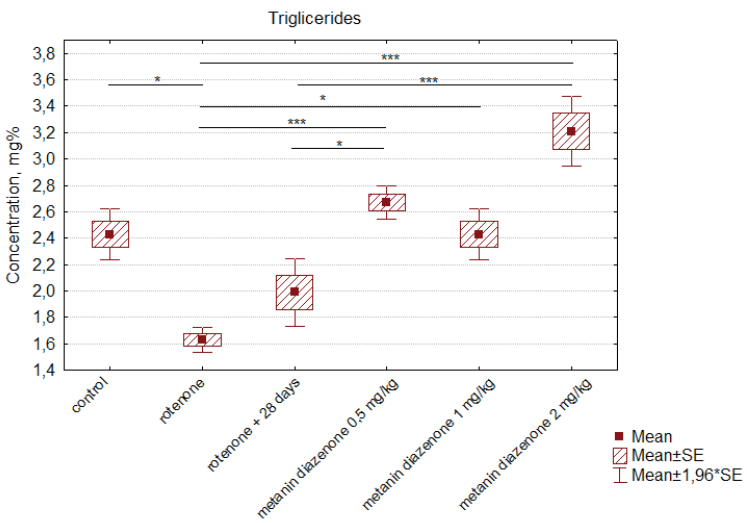

Fig. 5. Effects of methanediazenone in the different groups of rats on the bile level of triglycerides, mg%. *P < 0.05, ***P < 0.001

explain a decrease in the intake of various lipids into bile, since the process of their synthesis and absorption from the blood requires a large amount of energy. Other authors found a low content of cholesterol and triglycerides but in the plasma of patients with PD, which is evidence of a disorder of these compounds metabolism in this pathology [25]. The presented results also showed that in parkinsonian rats administered methanindiazenone in the amount of 2.0 mg/kg, the biliary level of cholesterol, cholesterol esters, phospholipids significantly increased. This may be evidence of the accumulation of these compounds in the liver in excessive amounts, as a result of homeostasis disoder. Hepatic uptake of cholesterol released from peripheral cells can occur through the HDL, SR-BI, and LDL receptors. Hepatic lipase contributes to the selective absorption of cholesterol esters by hepatocytes, showing a lipolytic effect [26]. The increased esterification of cholesterol, which we observed in our work, is another important aspect of its abnormal metabolism. We consider such results to be a manifestation of the toxicity of the studied drug, applied in a dose of 2 mg/kg. In patients with PD, gallstone disease is oftenly detected. This is explained by impaired motility of the gallbladder [27]. The problem in the treatment of PD is complicated by the lack of a universally accepted definitive biomarker. The need to develop early diagnostic biomarkers has two reasons: to identify the initial stages of the disease and to monitor the course of therapeutic interventions that can slow or stop the development of the disease. In recent years, blood lipids have emerged as a biochemical blood marker that may be associated with PD in many clinical studies [28]. However, the research results are conflicting and therefore it is not clear whether a low or high blood lipid content should be considered as a marker of PD. Earlier, detailed bile lipid composition studies in PS animal models were scarce. Initially, rotenone application for PS modeling involved high-concentration brain injections, leading to complete dopaminergic neurons destruction [29]. In subsequent studies, the administration of rotenone systemically in very high doses led to peripheral toxicity and non-specific brain lesions. In contrast, at lower doses (2-3 mg/kg/day), approaching complex I inhibition in platelets from PD patients, rotenone induced highly selective nigrostriatal degeneration of dopaminergic neurons and α-synuclein inclusions were found in surviving neurons. In addition, the animals were hypokinetic and had postural instability [30]. Rotenone has lipophilic properties, so it freely penetrates into all cells, and the high sensitivity of dopaminergic neurons to it indicates that these neurons are primarily sensitive to inhibition of complex I. The rotenone model provided the first proof of concept that systemic mitochondrial dysfunction may play a role in neurodegenerative disorders. Impressively, the concentration and degree of inhibition of complex I were the same in the brain as in other organs [31]. That is, in PD, mitochondrial dysfunction is not limited to the brain. Most importantly, dysfunction can cause selective nigrostriatal degeneration. In addition, the rotenone model accurately reproduced many other features of human PD, including anatomical, neurochemical, behavioral, and neuropathological characteristics. Studies by Betarbet, et al., 2000 showed that chronic exposure to rotenone leads to the accumulation and aggregation of α-synuclein [30]. Rotenone, both in neurons and in hepatocytes, suppresses the functioning of mitochondria, causing energy deficiency in cells, which causes the inhibition of biosynthetic processes in the liver. This could be the reason for a decrease in the amount of lipids in bile, which we observed in our study. Fonseca- Fonseca L. and co-authors on the basis of benzodiazepine developed JM-20, a new drug that in an experimental model of PS protected mitochondria from rotenone-induced oxidative stress and disruption of membrane potential both in neurons and in liver cells. JM-20 prevented motor behavior disorders, body weight loss, and mortality caused by rotenone [12].

Mitochondria are cellular organelles with

a universal function crucial to all body cells. They supply over 90% of cellular ATP, ensuring cellular homeostasis and facilitating normal cell operations. Disruption in the structural and functional organization of the respiratory chain components results in an energy deficit within cells. This is due to the inhibited respiratory process and diminished efficiency of oxidative phosphorylation. Such changes consequently lead to a decrease in the cell's ATP concentration [32]. In in vitro experiments, drugs of the new family of 1,5-benzodiazepin-2(3H)-ones also protected neurons from oxidative stress, significantly reducing the level of reactive oxygen species and restoring the functional state of mitochondria by normalizing their membrane potential [33]. Similar studies open a new promising way for the synthesis and utilization of novel drugs derived from well-established benzodiazepine group for treating severe pathology like PS.

CONCLUSION

In rotenone-induced PS rats, there's a significant decrease in bile concentration of phospholipids, cholesterol, cholesterol esters, and triglycerides. This suggests a reduced lipid synthesis and accumulation in these animals' liver. Methanindiazenone, a new drug we synthesized, restores lipid homeostasis in the liver of rotenone-induced PS rats at doses of 0.5 and 1.0 mg/kg. However, at a dose of 2.0 mg/kg, methanindiazenone might disrupt lipid homeostasis in the liver, leading to a heightened release of various lipids into bile, surpassing control levels. As a result, methanediazenone is potentially suitable for clinical trials as a therapeutic agent for PS treatment when combined with other drugs. A substantial and prolonged decrease in bile lipids can serve as a diagnostic marker of Parkinson's syndrome.

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The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ПОХІДНЕ БЕНЗОДІАЗЕПІНУ – МЕТАНІНДІАЗЕНОН МОДУЛЮЄ ЛІПІДНИЙ ОБМІН У ПЕЧІНЦІ ЩУРІВ З ІНДУКОВАНИМ РОТЕНОНОМ СИНДРОМОМ ПАРКІНСОНІЗМУ

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Хвороба Паркінсона – це нейродегенеративна хвороба, причини якої не встановлені, а ефективних методів лікування не існує. Припускають, що в основі її патогенезу лежать окисний стрес, дисфункція мітохондрій та порушення обміну ліпідів. Похідні бензодіазепіну типу JM-20 захищають мітохондрії як в нейронах, так і в периферичних тканинах щурів з синдромом паркінсонізму (СП), викликаним дією ротенону. Метою роботи було, вивчаючи склад жовчі, дослідити дію нового похідного бензодіазепіну – метаніндіазенону на ліпідний метаболізм у печінці щурів з ротеноновою моделлю ПС. Одержані результати показали, що порівняно з контролем під впливом ротенону в жовчі зменшувалася концентрація фосфоліпідів, холестерину, ефірів холестерину і тригліцеридів на 24.3, 26.2, 25,8 і 27.5% відповідно. При дії метаніндіазенону в дозах 0.5 і 1.0 мг/кг усі вищеназвані показники повернулися до рівня контролю. На відміну від цього, у тварин з СП і введеним метаніндіазенону в дозі 2.0 мг/кг вміст фосфоліпідів, холестерину, ефірів холестерину (окрім тригліцеридів) перевищував контрольні значення на 33, 28.1, 28.4% відповідно. Метаніндіазенон позитивно впливав на рухову поведінку щурів з ротеноновою моделлю ПС, сприяв більшому їх виживанню. Таким чином, цей препарат у дозах 0.5 та 1.0 мг/кг покращує як обмін ліпідів у печінці, так і загальний

стан щурів з ротеноновою моделлю СП. При дозі метаніндіазенону 2.0 мг/кг спостерігалися ознаки його токсичної дії, що проявлялося в підвищенні вмісту фосфоліпідів, холестеролу, ефірів холестеролу у жовчі. Отже, метаніндіазенон можна рекомендувати як терапевтичний засіб для лікування СП та, можливо, інших нейродегенеративних захворювань, які пов'язані з порушенням обміну ліпідів в організмі, але лише в дозах 0.5 та 1.0 мг/кг.

Ключові слова: синдром паркінсонізму; ротенонова модель; метаніндіазенон; печінка; жовч; ліпіди.

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