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PENTYLENETETRAZOL (PTZ)-INDUCED CHRONIC EPILEPTIC SYNDROME AS A MODEL FOR LIPID METABOLISM IMPAIRMENT AND STEATOHEPATITIS

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Background. The pathogenesis of chronic epilepsy is associated with the impairment of lipid metabolism and affects the liver.

The study aimed at investigating the serum lipid profile and liver histomorphology in a rat model of PTZ-induced kindling following the administration of rapamycin and pioglitazone.

Material and methods. Kindling was induced by repeated PTZ administration for three weeks; pioglitazone and rapamycin were administered during the last ten days. Total cholesterol, triglycerides, HDL and LDL levels were measured colorimetrically.

Results and discussion. PTZ kindling caused dyslipidemia (elevated cholesterol, triglycerides, LDL; lowered HDL) and histological signs of steatohepatitis, including activated Kupffer cells.

Combined treatment with pioglitazone and rapamycin was most effective in correcting the lipid profile and reducing heightened levels of cholesterol. The combination's effect on cholesterol reduction significantly exceeded that of either drug administered separately (by 14.8% and 22.5%, respectively). Compared to untreated kindled animals, the combined therapy reduced triglycerides by 18.7% and LDL by 18.1%, while increasing HDL levels by 39.1%.

While the density of Kupffer cells exceeded that of the control group by 24.5% it was diminished by 20.3% compared with kindled animals after treatment with rapamycin and pioglitazone.

Conclusion. Fully developed PTZ kindling in rats leads to dyslipidemia and histological signs of steatohepatitis. Combined treatment with pioglitazone and rapamycin effectively prevented these disturbances while retarding seizure development, suggesting the model's relevance for studying the pathogenesis of steatohepatitis and metabolic syndrome.

Keywords: chronic epileptic syndrome, dyslipidemia, steatohepatitis, metabolic syndrome, morphological changes.

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ПЕНТИЛЕНЕТЕТРАЗОЛ (ПТЗ)-ІНДУКОВАНИЙ ХРОНІЧНИЙ ЕПІЛЕПТИЧНИЙ СИНДРОМ ЯК МОДЕЛЬ ПОРУШЕНЬ МЕТАБОЛІЗМУ ЛІПІДІВ ТА РОЗВИТКУ СТЕАТОГЕПАТИТУ
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Метою дослідження було вивчення вмісту ліпідів та гістоморфологічних характеристик печінки щурів на моделі пентиленететразол(ПТЗ)-індукованого кіндлінгу за умов застосування рапаміцину та піоглітазону. Встановлено, що розвинений ПТЗ-провокований судомний синдром супроводжується дисліпідемією: зростанням вмісту холестерину, тригліцеридів, ЛПНЩ та зниженням рівня ЛПВЩ у сироватці крові. Гістоморфологічно виявлено активацію клітин Купфера та накопичення мікровезикул у цитоплазмі гепатоцитів, що є свідченням розвитку стеатогепатиту. Застосування піоглітазону та рапаміцину попереджало розвиток розладів ліпідного обміну та гістоморфологічних порушень у печінці. Ці ефекти супроводжувалися гальмуванням динаміки формування розвинених кіндлінгових проявів.

Ключові слова: хронічний епілептичний синдром, дисліпідемія, стеатогепатит, метаболічний синдром, морфологічні зміни.

Introduction

Epilepsy represents one of the most debilitating neurological disorders. Its pathogenesis involves complex disruptions across all metabolic pathways supporting the nervous system, as well as systemic effects on various organs. Notably, lipid metabolism plays a pivotal role in this process, as its dysregulation is known to significantly enhance seizure susceptibility [1; 2].

Current evidence suggests that circulating blood cholesterol critically influences the balance of cholesterol synthesis and metabolism within brain tissue, thereby modulating neuronal excitability [3]. The primary enzyme responsible for cholesterol metabolism in the brain is cholesterol 24-hydroxylase (CH24H). It converts cholesterol into 24S-hydroxycholesterol (24HC), a potent allosteric modulator of N-methyl-D-aspartate (NMDA) receptors. Furthermore, 24HC can stimulate glutamate release via tumor necrosis factor-alpha (TNF-α). Dysregulation of this pathway may lead to the accumulation of excitatory amino acids, pathological neuronal hyperexcitability, and subsequent epileptogenesis. Consequently, CH24H inhibitors are being investigated as a novel class of antiepileptic agents [4]. Statins, which lower systemic cholesterol [5], have also demonstrated anticonvulsant properties. Specifically, in the pentylenetetrazol (PTZ)-induced kindling model, atorvastatin has been shown to

delay the development of kindled seizure reactions [5]. The functional state of the liver parenchyma is critical in regulating lipid metabolism. Liver dysfunction is often accompanied by oxidative stress-induced inflammation and hepatocyte degeneration. In rats with developed PTZ-induced kindling, a significant (more than fourfold) increase in serum alanine and aspartate aminotransferase levels has been observed alongside elevated TNF-α concentrations [6].

Pharmacological agents that modulate lipid metabolism, such as the mTOR receptors inhibitor rapamycin, also exhibit anticonvulsant effects [7]. Prolonged administration of rapamycin (0.8 mg/kg daily) has shown hepatoprotective activity in non-alcoholic fatty liver disease models induced by high-calorie diets, likely through the regulation of bile secretion and glycerophospholipid metabolism [8]. Similarly, pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist, effectively corrects lipid profiles [9]. Recent studies have indicated a synergistic effect of pioglitazone and rapamycin in alleviating comorbid behavioral disorders, such as anxiety and depression, in PTZ-kindled rats [10], as well as reducing seizure manifestations [7].

Despite these findings, the roles of mTOR- and PPAR-γ-dependent mechanisms in the pathogenesis of hepatic dysfunction and the potential for pharmacological correction of lipid metabolism in chronic epileptic syndromes remain insufficiently explored.

The aim of this study was to investigate the lipid profile – cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL), and the histomorphological characteristics of the liver in rats with developed PTZ-induced kindling under conditions of rapamycin and pioglitazone administration.

Materials and Methods

The study was conducted on 38 sexually mature Wistar rats (three months old). The animals were housed in the standard vivarium conditions of Odesa National Medical University at a constant temperature of 23 °C, 60% humidity, and a 12-hour light/dark cycle, with ad libitum access to water and a standard diet.

All procedures were performed in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals and the Helsinki Declaration (Directive 86/609/EEC). The study protocol was approved by the Bioethics Committee of Odesa National Medical University (Protocol No. 1, 14.03.2022).

Chronic epilepsy model was induced via the PTZ-kindling model as previously described [11]. Pentylenetetrazol (P6500, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 0.9% NaCl freshly prepared and administered intraperitoneally (i.p.) at a dose of 35.0 mg/kg for 21 consecutive days.

Control rats received i.p. injections of 0.9% saline. After each injection, rats were placed alone in an isolated transparent cage and the severity of seizures was assessed for 30 minutes using a six-point scale [11].

The experimental groups were formed as follows:

– Intact Control (n = 8);

– PTZ-Kindling (35.0 mg/kg i.p., 21 days; n = 9);

– PTZ + Pioglitazone (Lilly S.A., Spain, 50.0 mg/kg i.p.; n = 7);

– PTZ + Rapamycin (Pfizer, USA, 1.0 mg/kg i.p.; n = 7);

– PTZ + Pioglitazone + Rapamycin (n = 7).

The test drugs, dissolved in dimethyl sulfoxide (DMSO) (volume 0.2–0.3 ml), were administered from day 10 to day 21, 60 minutes prior to PTZ injection.

Biochemical Analysis

Twelve hours after the final PTZ administration, rats were anesthetized with thiopental (60.0 mg/kg i.p.), and blood was collected via cardiac puncture. Serum levels of total cholesterol, triglycerides, HDL, and LDL were measured colorimetrically at a wavelength of 520 nm [12]. LDL and HDL fractions were determined using polyethylene glycol precipitation and expressed in mg/dL [12].

Histomorphological Examination

Liver tissue was collected immediately after exsanguination and fixed in a 10.0% formalin solution. After three weeks, paraffin blocks were prepared, and 5 μm sections were stained with hematoxylin and eosin (H&E).

Images were captured using an Olympus BX53 light microscope and the EVOS® FL Auto Imaging System (Life Technologies, Ltd.) and were analyzed visually. Image segmentation and quantitative cytomorphological assessment were performed using open options of Image-J and HALO® (Indica Lab., USA) software.

Statistical Analysis. Data were analyzed using SPSS v. 21.0 (Chicago, IL, USA). Seizure severity was compared using the Kruskal-Wallis test followed by Dunn's post-hoc test. Biochemical parameters were analyzed via one-way ANOVA and the Newman-Keuls test. Differences in Kupffer cell count were assessed using an unpaired Student's t-test. Statistical significance was set at $P < 0.05$. Results are presented as Mean ± Standard Deviation (M ± SD) or Mean ± Standard Error (M ± SEM).

Research results and their discussion

Seizure activity in the groups treated with pioglitazone and rapamycin was significantly lower than in untreated PTZ-kindled rats ($H(4.37) = 10.74$, $P = 0.013$; Fig. 1).

Specifically, in the rapamycin group (1.0 mg/kg, i.p.), generalized seizures were prevented in 3 out of 7 rats, with a significant reduction in overall seizure severity compared with the kindled control ($P = 0.036$). Combined treatment with pioglitazone (50.0 mg/kg, i.p.) and rapamycin (1.0 mg/kg i.p.) was even more effective, preventing generalized seizures in 5 out of 7 rats ($P = 0.0015$).

Serum cholesterol levels varied significantly across the experimental groups $F(4.37) = 18.66$, $P < 0.0001$ (Table 1). In PTZ-kindled rats, cholesterol levels were 38.7% higher than in the intact control ($P < 0.05$), and statistically higher cholesterol levels were determined in all groups using pharmacological agents. Pioglitazone monotherapy reduced cholesterol levels by 15.2% compared with kindled rats ($P < 0.05$), while the combination of pioglitazone and rapamycin resulted in a 27.7% reduction ($P < 0.05$). Notably, the combined therapy showed superior efficacy compared with either pioglitazone or rapamycin monotherapy, with additional reductions of 14.8% ($P < 0.05$) and 22.5% ($P < 0.05$), respectively.

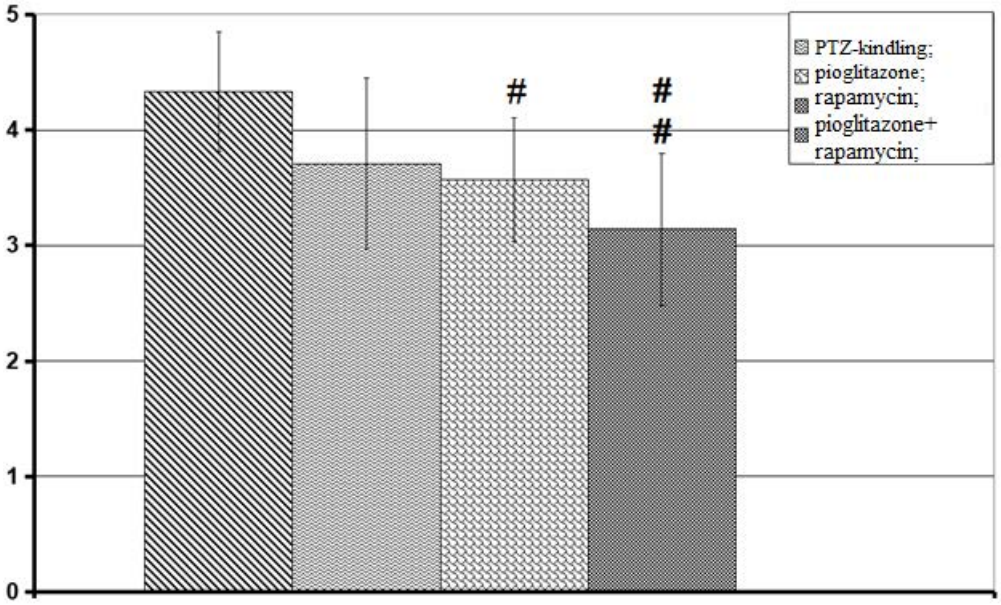

Fig. 1. Seizure severity during course administration of pioglitazone and rapamycin in kindled rats

Notes: on the ordinate axis – seizures severity (scores). # – P < 0.05; ## – P < 0.01 (Kruskal Wallis + Dunn`s test) compared with the group of kindled rats.

Table 1

Effect of pioglitazone and rapamycin on serum lipid levels in rats with PTZ-induced kindling (M + SD)

	Control (n = 8)	PTZ kindling (n = 9)	Pioglitazone (50.0 mg/kg, i.p.) (n = 7)	Rapamycin (1.0 mg/kg, i.p.) (n = 7)	Pioglitazone + rapamycin (n = 7)
Cholesterol (mg/dL)	97.70 ± 11.24	159.44 ± 20.2*	135.3 ± 15.39*#	148.85 ± 18.64*	115.3 ± 14.6*#
Triglycerides (mg/dL)	102.60 ± 8.33	130.37 ± 13.03*	119.02 ± 10.69*	113.3 ± 13.75#	106.01 ± 9.1#
HDL (mg/dL)	46.02 ± 5.18	29.37 ± 3.95*	33.65 ± 5.63*	35.69 ± 4.97*	40.86 ± 6.77#
LDL (mg/dL)	28.77 ± 2.80	42.44 ± 6.88*	38.07 ± 4.94*	36.34 ± 5.78*	34.75 ± 5.54*#

Notes: * – P < 0.05 compared with the control group; # – P < 0.05 compared with the PTZ-induced kindling group (one-way ANOVA followed by the Newman–Keuls test).

Differences in triglyceride content in the groups were significant at F(4.37) = 8.04, P < 0.0001. In rats with PTZ-kindling, their level exceeded the control value by 21.3% (P < 0.05). Rapamycin monotherapy lowered these levels by 13.1% (P < 0.05), while combined administration with pioglitazone led to an 18.7% reduction (P < 0.05).

HDL levels showed marked variations in groups at F(4.37) = 12.18, P < 0.0001. Kindled rats exhibited a 36.2% decrease in HDL compared with the control (P < 0.05). Combined treatment significantly restored HDL levels, showing a 39.1% increase over kindled rats (P < 0.05) and there were no significant differences from the control (P > 0.05). Furthermore, this effect was 28.1% greater than that observed with pioglitazone alone (P < 0.05).

LDL levels were significantly higher in kindled rats (by 32.2%) compared with the control (F(4.37) = 7.11, P < 0.0001). Combination therapy of pioglitazone and rapamycin reduced LDL levels by 18.1% compared with untreated kindled animals (P < 0.05), though they remained 17.2% higher than in the intact control (P < 0.05) (Table 1).

The control group showed preserved hepatic cord structure with no signs of dystrophy or focal infiltration (Fig. 2 A, B). Conversely, PTZ-kindled rats displayed activated Kupffer cells forming infiltrates without typical perivenular localization (Fig. 2 C, D, E). The cytoplasm of hepatocytes exhibited acidophilic properties with poorly defined cord structures and the presence of oval, unstained microvesicles.

Kupffer cell count in kindled rats was 24.5% higher than in the control (F(4.37) = 16.10, P = 0.0025; Fig. 2 F).

A characteristic feature of the fully developed kindling state was the perivenular distribution of a significant Kupffer cell population (Fig. 3 A, B). Following the administration of pioglitazone and rapamycin, a 20.3% reduction in the Kupffer cell population was observed compared with untreated kindled rats (F(4.37) = 10.49, P = 0.009;) (Fig. 3 C). Notably, under these treatment conditions, a higher prevalence of Kupffer cells persisted specifically within the perivenular zone (Fig. 3 D, E).

In summary, our results demonstrate that fully developed PTZ-induced kindling in rats is characterized by a significant increase in serum cholesterol, triglycerides, and LDL levels, alongside a marked reduction in HDL content. A 10-day course of combined pioglitazone and rapamycin therapy effectively attenuated these metabolic disturbances. Notably, pioglitazone induced a more

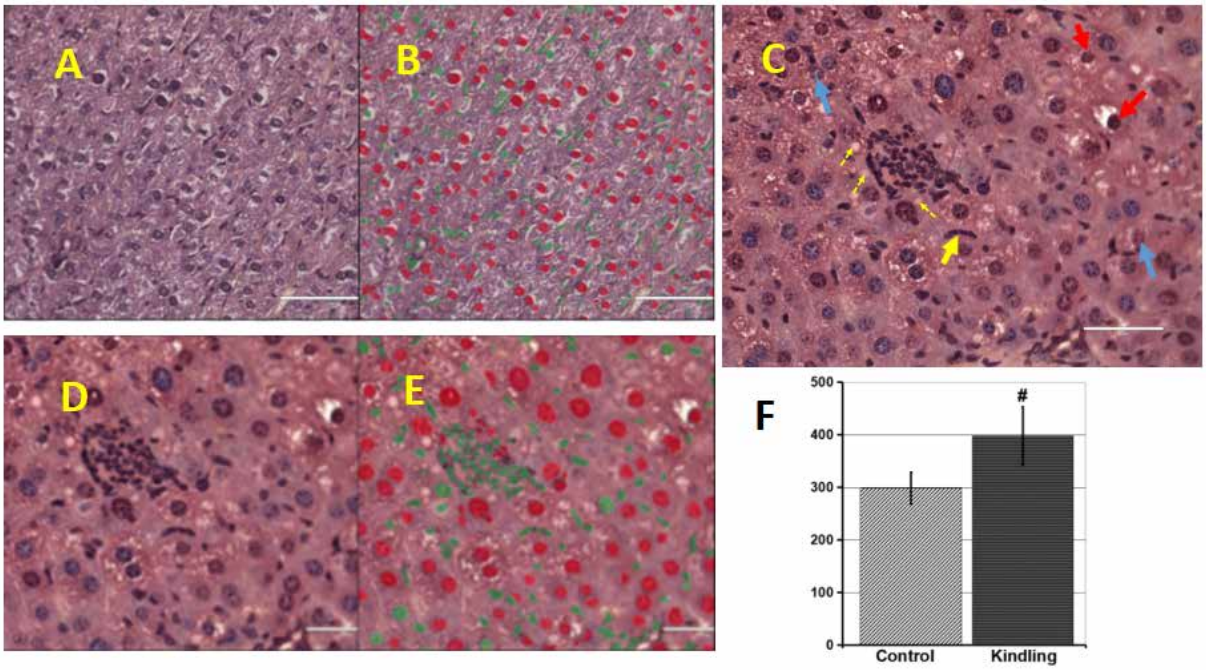

Fig. 2. Histomorphological features of liver tissue in rats with PTZ-induced kindling

Notes: A – control (H&E staining), B – segmentation – hepatocytes are stained in red, Kupffer cells in green (HALO, Indica Lab., USA). C 0 liver tissue of kindled rats demonstrating ill-defined sinuses and hepatic cords, alongside the diffuse presence of oval microvesicles within the hepatocyte cytoplasm (indicated by thin dashed arrows); mitotic hepatocytes (blue arrows), activated Kupffer cells (yellow arrows), and degenerative cells (red arrows) are observed. Kupffer cell infiltration is visible within the central zone of the section. D and E – cell segmentation performed for quantitative analysis. F – statistical evaluation of Kupffer cell population: # – $P < 0.01$ compared with the control group (one-way ANOVA followed by Tukey's HSD test). The white scale bar in the lower right corner represents 100 μm for A and B, and 50 μm for C–E.

pronounced reduction in cholesterol levels, whereas rapamycin was more effective in lowering triglycerides. The synergistic corrective effect of the combined therapy significantly exceeded the efficacy observed with either drug administered as monotherapy.

These abnormalities occurred against a background of systemic immune activation, specifically the proliferation and infiltration of the liver tissue by resident immunocompetent Kupffer cells. Furthermore, histological analysis of hepatocytes revealed microvesicular inclusions and degenerative forms of hepatocytes, which are hallmark features of steatohepatitis [6; 13–15]. Such morphological alterations likely indicate the involvement of mitochondria in the development of the pathological process and activation of β-oxidation [13].

A pivotal element in the pathogenesis of steatohepatitis is the activation of Kupffer cells, the release of reactive oxygen species and pro-inflammatory cytokines, specifically TNF-α, and hepatocyte injury [15]. It should be noted that TNF-α activates hepatic stellate cells, promoting their proliferation and transformation into myofibroblasts. These cells synthesize components of connective tissue, facilitating the development of fibrotic lesions [6]. These processes histomorphologically align with our findings, specifically the pronounced acidophilic properties of the hepatocyte cytoplasm and evidence of apoptosis.

Combined administration of rapamycin and pioglitazone induced a pronounced reduction in cholesterol levels, which were significantly lower than those observed with either drug administered as monotherapy, thereby evidencing a synergistic corrective effect. Furthermore, LDL levels in the combination therapy group were significantly lower compared with those receiving pioglitazone alone. Administration of combined therapy effectively mitigated histomorphological impairment within the liver parenchyma.

The fundamental mechanism underlying the synergistic corrective effect of these agents is the interaction of regulatory pathways governing lipid metabolism via mTOR inhibition and PPAR-γ receptor activation. Given the multifaceted nature of these signaling networks, a synergistic interplay is highly probable, particularly regarding concomitant anti-inflammatory effects. For instance, Zhao et al. [8] demonstrated that rapamycin modulates 579 metabolites in rats with hepatic steatosis, affecting primary classes of amino acids, peptides, aromatic hydrocarbons, lipids, and fatty acids. Similarly, the metabolic consequences of PPAR-γ agonists are extensive [9]. Such a broad metabolic spectrum likely facilitates the synergistic corrective impact observed with rapamycin combined with resveratrol (a PPAR-γ agonist) on insulin resistance in high-calorie diet models [13], as well as the effects of rapamycin and pioglitazone on seizure activity and comorbid behavioral manifestations – specifically aggression and depression – in PTZ-kindled rats [10].

It is important to emphasize that the identified disruptions in lipid metabolism and the functional-morphological

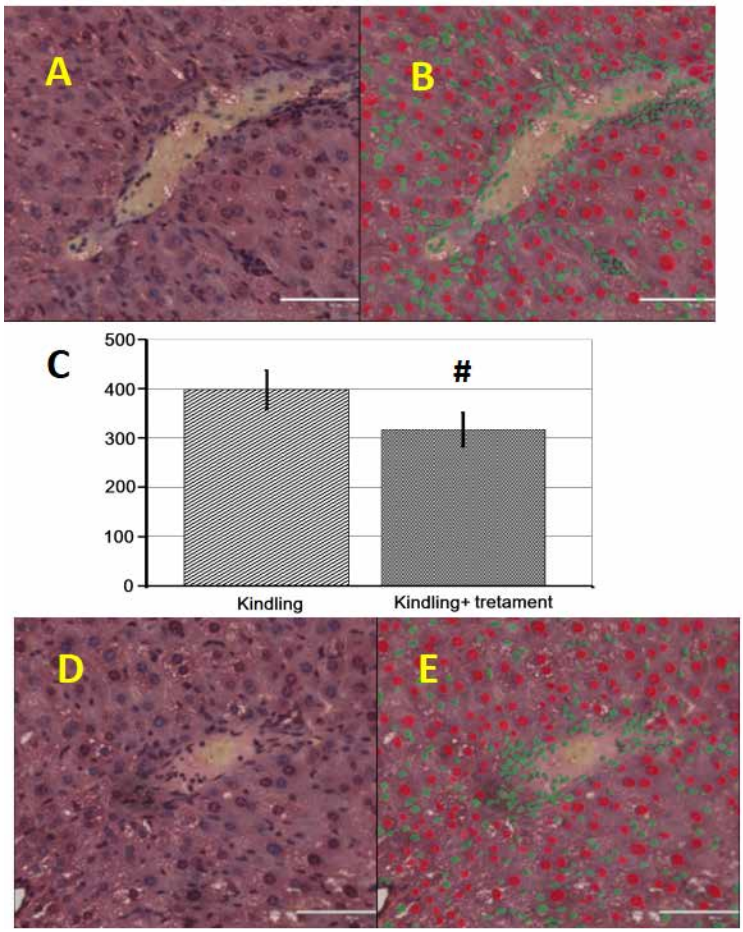

Fig. 3. Kupffer cell population in the liver parenchyma of PTZ-kindled rats following pioglitazone and rapamycin administration

Notes: Perivenular distribution of Kupffer cells in PTZ-kindled rats (A and B), and in kindled rats treated with pioglitazone and rapamycin (D and E); quantitative assessment – fragment C. # – $P < 0.01$ – compared with the kindled group (one-way ANOVA followed by Tukey's HSD test). The white scale bar in the lower right corner represents 50 μm.

state of the liver are hallmark manifestations of metabolic syndrome [2]. Pioglitazone is established as an effective pharmacological intervention for diabetes mellitus, a condition whose pathogenesis is intrinsically linked to the development of metabolic syndrome. Consequently, our findings suggest a shared pathogenic substrate between chronic epileptogenesis and metabolic syndrome as a comorbid state. In this regard, future investigations focusing on carbohydrate metabolism and insulin resistance in PTZ-kindled rats are warranted to further elucidate these cross-pathological links and the potential for multi-target therapeutic strategies.

In conclusion, the demonstrated synergistic effects of rapamycin and pioglitazone on serum lipid profiles and hepatic histomorphology in rats with developed PTZ-induced seizures underscore the critical role of lipid metabolism disturbances. Furthermore, these findings highlight the potential significance of steatohepatitis as a key comorbid condition in the pathogenesis of chronic epileptic syndrome.

Conclusions

Rats with pentylenetetrazol (PTZ)-induced chronic epileptic syndrome exhibit profound disruptions in lipid metabolism, characterized by elevated serum levels of total cholesterol, triglycerides, and low-density lipoproteins (LDL), concurrent with a marked reduction in high-density lipoproteins (HDL).

The liver parenchyma in PTZ-kindled rats demonstrates marked Kupffer cell activation and focal infiltration, alongside the accumulation of microvesicles within the hepatocyte cytoplasm. These histomorphological alterations are indicative of the development of steatohepatitis.

The observed metabolic and histomorphological pathological manifestations are effectively attenuated by a treatment course with rapamycin and pioglitazone. When administered in combination, these agents exert a pronounced synergistic corrective effect.

Disruptions in mTOR- and PPAR-γ-dependent signaling pathways play a pivotal role in the pathogenesis of PTZ-induced kindling and may constitute the mechanistic basis for shared pathogenic elements between chronic epilepsy and metabolic syndrome.

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