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Effect of the PPARγ Agonist Pioglitazone on Rat Behavior and Expression of Epileptogenesis-Related Genes during the Latent Phase of the Lithium-Pilocarpine Model

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Abstract—Epilepsy is a severe chronic condition that remains pharmacoresistant in approximately 30% of the patients, which necessitates the search for new treatment approaches. Epileptogenesis involves disruption in the interaction between metabolic pathways and neuronal signaling. A promising therapeutic target is the peroxisome proliferator-activated receptors (PPARs), which integrate metabolic and anti-inflammatory signals. The aim of this work was to evaluate effects of the PPARγ agonist pioglitazone on the complex of epileptogenesis manifestations: behavior and expression of the genes encoding glial markers, cytokines, neurotrophic factors, and glutamate receptor subunits during the latent phase of the lithium-pilocarpine model in rats. The study was conducted with 8-week-old male Wistar rats divided into control and experimental groups. Pioglitazone was administered at low doses (7 mg/kg after status epilepticus, followed by 1 mg/kg/day for 7 days). On the days 8-9, locomotor and social activities were assessed using the Open Field and Social Interaction tests. On the day 10, expression of the genes encoding markers for activation and various states of astro- and microglia, cytokines, neurotrophic factors, and glutamate receptor subunits was analyzed in the dorsal hippocampus and temporal cortex using RT-qPCR. It was shown that pioglitazone partially alleviated the pilocarpine-induced social deficit. In the brain of rats with the epilepsy model, increased expression of the glial activation markers (*Gfap*, *Aif1*) and cytokines (*Il1b*, *Il1rn*) was found, which was weakly affected by administration of pioglitazone. At the same time, the drug completely prevented the pilocarpine-induced decrease in the expression of the glutamate receptor subunit gene *Grin2b*. The obtained data suggest that, at the applied doses, pioglitazone primarily modulates expression of the genes related to synaptic plasticity and does not exert a significant effect on expression of the genes associated with glial activation and inflammation. Thus, activation of PPARγ as a metabolic sensor during epileptogenesis could stabilize transcriptional programs that are important for maintaining synaptic homeostasis, which opens the possibilities for targeted modulation of metabolic pathways in epilepsy therapy.

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INTRODUCTION

Epilepsy is a severe chronic disorder characterized by the development of spontaneous recurrent seizures and associated behavioral disturbances. Up to 30% of the patients with epilepsy are resistant to current therapies, necessitating the search for novel treatment approaches [1]. The underlying basis of this process is pathological interaction between the disrupted neuronal signaling (primarily imbalance between the glutamatergic and

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GABAergic systems) and severe metabolic remodeling [2, 3].

Glial cells play a key role in mediating this interplay, as they not only maintain homeostasis but also actively regulate neuroinflammation and cerebral energy metabolism [3, 4].

Dysfunction of astrocytes and microglia, often described as their shift toward pro-inflammatory phenotypes (M1/A1), is accompanied by metabolic reprogramming [5]. These phenotypes support neuroinflammation and create energy deficit in neurons, thus reducing the seizure threshold [6]. Glial cells could also exert protective functions by shifting toward anti-inflammatory phenotypes (M2/A2) that promote neural tissue repair [7, 8]. Therefore, a promising therapeutic approach lies in identifying drugs that could shift glial activity from a pro-inflammatory to a protective phenotype via concurrent modulation of both the glial metabolic state and neuroinflammation.

Agonists of the peroxisome proliferator-activated receptors (PPARs α, β/δ, and γ) – a family of nuclear transcription factors that function as key metabolic sensors – exhibit precisely these properties. PPARs coordinately regulate lipid and energy metabolism, as well as inflammatory and oxidative stress signaling cascades [9]. PPAR activation is considered one of the key mechanisms underlying efficacy of ketogenic diet in the drug-resistant epilepsy [10]. Antiepileptic properties of the PPAR agonists have been demonstrated in the pentylenetetrazole- and pilocarpine-induced seizure models [11, 12]. Their neuroprotective effects are thought to be mediated through regulation of the glial energy metabolism [5], reversal of the mitochondrial dysfunction [13], suppression of neuroinflammation (including inhibition of the transcription factor NF-κB) [14], and attenuation of oxidative stress [15].

Pleiotropic neuroprotective and anti-inflammatory properties in the acute seizure models have been demonstrated for the selective PPARγ agonist pioglitazone (PG) [11], a drug used in clinical practice for treatment of the type 2 diabetes. PG affects functional activity of the NMDA-type glutamate receptors [16], which play a key role in epileptogenesis [2]. However, impact of PG on expression of the genes of glutamate receptor and glial proteins during epileptogenesis remains largely unexplored.

The aim of this study was to evaluate the effect of the PPARγ agonist pioglitazone on behavioral and molecular alterations during the latent phase of the lithium-pilocarpine model in rats. We assessed behavioral responses and expression of the genes associated with glial activation and neuroinflammation, neurotrophic factors, and glutamate receptor subunits in the brain tissue. This model was selected because it reliably reproduces the key features of temporal lobe epilepsy, including neuroinflammation at this stage [17].

MATERIALS AND METHODS

Animals and work with them. Forty-one (41) 8-week-old male Wistar rats weighing 200-230 g, obtained from the vivarium of the Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences (IEPhB RAS) were used in the study, animals were housed under standard laboratory conditions. The animals were randomly assigned to four groups: (1) control (Ctrl, n = 9); (2) control treated with PG (Ctrl + PG, n = 6); (3) lithium-pilocarpine model of epilepsy (Pilo, initial n = 12, final n = 9); (4) lithium-pilocarpine model of epilepsy treated with PG (Pilo + PG, initial n = 14, final n = 11).

Lithium-pilocarpine model of temporal lobe epilepsy. Rats were injected with LiCl (127 mg/kg, i.p.). Twenty-four hours later, premedication with scopolamine methyl bromide (1 mg/kg, i.p.) was administered to prevent peripheral effects of pilocarpine. One hour later, status epilepticus (SE) was induced by repeated injections of pilocarpine (initial dose 10 mg/kg, i.p., at 30-min intervals) until stage 4 seizures according to the Racine scale were achieved [18]. SE was terminated with diazepam (10 mg/kg, i.p.) 90 min after onset of the stage 4 seizures. Animals that failed to develop seizures after a cumulative pilocarpine dose of 40 mg/kg were excluded from the experiment (<5%). Control rats received LiCl only. This protocol has previously been shown to lead to the development of spontaneous recurrent seizures in the chronic phase [19].

PG (TCI, Japan) was dissolved in DMSO and administered intraperitoneally (i.p.) at a volume of 0.1 mL per 100 g body weight. The PG dosing regimen was as follows: a loading dose of 7 mg/kg at 2 h after SE termination, followed by a maintenance dose of 1 mg/kg/day for 7 days. The control group received an equivalent volume of DMSO. During the first 24 h after pilocarpine administration, mortality was up to 30%. To support recovery, animals were provided with moist chow.

Unlike the prophylactic administration of PPARγ agonists prior to pilocarpine [20], we administered PG after SE termination to model therapeutic intervention during the latent period of epileptogenesis. The 7-day treatment course was chosen because the peak of glial activation occurs during the first week following induction of the lithium-pilocarpine model [21]. The maintenance dose of 1 mg/kg/day was based on evidence of an elevated seizure threshold in mice following its chronic administration [22]. Loading dose of 7 mg/kg administered as the first injection was aimed at suppressing the peak of neuroinflammation (IL-1β and TNF release) in the first hours after SE to maximize therapeutic effect within the "therapeutic window".

Behavioral testing. On days 8-9 after SE, during the dark phase of the light-dark cycle (20:00-23:00 h), behavior was assessed using the Open Field Test and the Social Interaction Test. These tests are sensitive to epileptic disturbances and neuroinflammation [19]. Video recordings were analyzed by a researcher blinded to group assignment using Field4 and Pole_Krest software (Institute of Experimental Medicine, St. Petersburg, Russia). In the Open Field Test (circular arena, 1 m in diameter, illumination 8 lux, 5-min recording), the following parameters were assessed: locomotor activity (distance traveled, duration of movement), exploratory activity (supported rears), and anxiety-related behavior (time spent in the central zone, duration of grooming, freezing, and unsupported rears). In the Social Interaction Test (a cage 60×30×40 cm, 24-h habituation of the resident to the setup, 5-min interaction with an unfamiliar intact male), the following resident behaviors were analyzed: aggressive (attacks, threats), communicative (sniffing, partner grooming), defensive, and anxiety-related (grooming).

Real-time reverse transcription polymerase chain reaction (RT-qPCR). On day 10 after SE, rats were decapitated, and brains were rapidly removed, frozen, and stored at −80°C. For molecular analysis, dorsal hippocampus and temporal cortex were dissected using an OTF5000 cryostat (Bright Instrument, UK) according to the stereotaxic atlas [23].

Real-time RT-qPCR was used to analyze gene expression at the mRNA level. All steps of sample preparation were described in detail previously [24]. PCR was performed using a C1000 Touch thermal cycler with a CFX384 Touch™ detection system (Bio-Rad, USA) in a total volume of 6 μL, containing 0.8 μL of cDNA, 0.5 units of TaqM polymerase (Alkor Bio, Russia), 3.5 mM $MgCl_2$, and gene-specific forward and reverse primers, and probes (the primer and probe sequences are listed in Online Resource 1), manufactured by DNA-Synthesis LLC (Russia). All samples were analyzed in quadruplicate. In the present study, we performed a comprehensive assessment of the effect of PG on the expression of a broad panel of genes involved in the regulation of epileptogenesis: (1) markers of astroglial (*Gfap*) and microglial (*Aif1*) activation; (2) pro-inflammatory (*Il1b*, *Tnfa*) and anti-inflammatory (*Il1rn*) cytokines; (3) genes associated with reactive glial and macrophage phenotypes (*Lcn2*, *S100a10*, *Nos2*, *Nlrp3*, *Arg1*). *Lcn2* was considered as a marker of the neurotoxic response, expressed in astrocytes and microglia/infiltrating cells; *S100a10* – as a marker of the neuroprotective astroglial phenotype; *Nos2* and *Nlrp3* – as markers of pro-inflammatory (M1-like), and *Arg1* – as a marker of anti-inflammatory (M2-like) microglial/macrophage activation; (4) neurotrophic factors *Fgf2*, *Bdnf*, *Tgfb1*; (5) subunits of glutamate NMDA receptors (*Grin1*, *Grin2a*, *Grin2b*) and AMPA receptors (*Gria1*, *Gria2*). Gene name abbreviations are provided in Online Resource 1.

Relative expression of the genes of interest was calculated using the $2^{-\Delta\Delta Ct}$ method [25]. Data were normalized to the geometric mean of the expression of the three most stable reference genes, selected under conditions of the present experiment from nine housekeeping genes (*Gapdh*, *Actb*, *Rpl13a*, *B2m*, *Pgk1*, *Ppia*, *Hprt1*, *Ywhaz*, *Sdha*) using the online tool RefFinder® (https://ciidirsinaloa.com.mx/RefFinder-master/): *Actb*, *Hprt1*, *Pgk1* for the dorsal hippocampus; *Rpl13a*, *Sdha*, *Ppia* for the temporal cortex.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics 23.0 and GraphPad Prism 9.0 software. Normality of data distribution was assessed using the Kolmogorov–Smirnov test; outliers were identified using the interquartile range method, and homogeneity of variances across groups was verified by the Levene's test. The required sample size was estimated *a priori* using G*Power 3.1 software with a significance level of $\alpha = 0.05$ and power of 80%.

Changes in body weight over time were analyzed using three-way mixed-design analysis of variance (Mixed ANOVA) with the factors "Model," "Treatment", and "Day of testing." Survival analysis was performed using the Kaplan–Meier method and the log-rank test. To test the hypothesis regarding the effect of PG on behavioral and molecular alterations in experimental and control rats, two-way analysis of variance (two-way ANOVA) with the fixed factors "Model" and "Treatment" was applied. When a significant interaction between the factors was detected, *post hoc* pairwise comparisons were performed using the Sidak test.

Since we hypothesized that alterations could be present in the untreated rats but not in treated animals, we additionally used the method of planned contrasts alongside the two-way ANOVA. Two comparisons were performed: (Ctrl vs. Pilo) in the untreated groups and (Ctrl+PG vs. Pilo+PG) in the treated groups. Unlike the *post hoc* tests, planned contrasts were performed regardless of the significance of the interaction between the factors. To control for type I error in multiple comparisons, the Bonferroni correction was applied (adjusted significance level $\alpha = 0.025$). Data in the graphs are presented as a mean ± standard deviation. Individual data points represent values for individual animals.

RESULTS

Body weight dynamics and survival. Initial body weight did not differ between the groups.

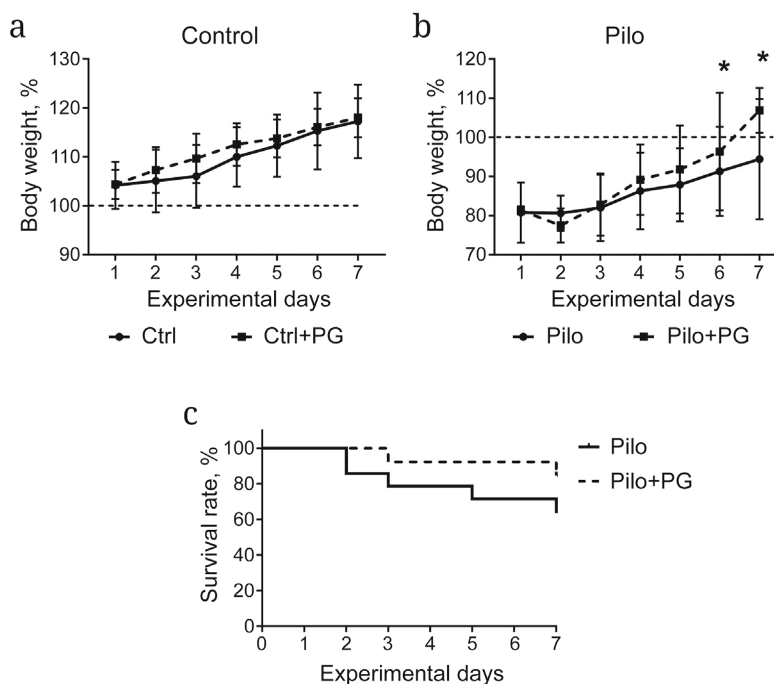

Fig. 1. Body weight dynamics in the control (Ctrl) (a) and experimental (Pilo) (b) animals, and survival curves of the rats with lithium-pilocarpine model of epilepsy untreated (Pilo) and treated with pioglitazone (Pilo+PG) (c). Ctrl – control, PG – pioglitazone; * $p < 0.05$, Sidak *post hoc* test.

Following SE induction, animals with the epilepsy model showed a 12-29% decrease in body weight compared to the baseline values (Fig. 1, a, b). Three-way mixed ANOVA revealed a significant main effect of the factor "Model" ($F_{2,6;\ 76,8} = 5.3$; $p = 0.003$), the factor "Treatment" ($F_{2,6;\ 76,8} = 3.2$; $p = 0.032$), and significant "Day × Model × Treatment" interaction ($F_{2,6;\ 76,8} = 5.2$; $p = 0.002$). In the control groups, PG had no effect on body weight. In the experimental animals, on days 6-7 after SE, body weight was significantly higher in the Pilo+PG group than in the Pilo group ($p < 0.05$). During the first 72 h after SE, mortality was 25% (3/12) in the Pilo group and 21.4% (3/14) in the Pilo+PG group. Kaplan–Meier survival analysis revealed no significant differences between the groups (Fig. 1c, $\chi^2 = 1.6$; $p = 0.21$).

Behavioral analysis. In the Open Field Test (Fig. 2, a-e), the rats with the lithium-pilocarpine model showed increased locomotor activity as measured by locomotion time (factor "Model": $F_{1,32} = 9$; $p < 0.01$; factor "Treatment": $F_{1,32} = 4,0$; $p = 0.06$; "Model" × "Treatment" interaction: $F_{1,32} = 0,5$; $p = 0.49$), planned contrasts revealed a significant difference between the Ctrl and Pilo groups ($p = 0.01$). A similar trend was observed for another measure of locomotor activity – distance traveled; however, the differences did not reach statistical significance (factor "Model": $F_{1,30} = 3.1$; $p = 0.09$).

Two-way ANOVA revealed a statistically significant main effect of the factor "Model" on the time spent in the center ($F_{1,31} = 4.8$; $p = 0.04$) and duration of grooming ($F_{1,31} = 9.9$; $p = 0.004$), which may be interpreted as an alteration in anxiety levels. The effect of the factor "Treatment" and interaction between the factors did not reach statistical significance ($p > 0.05$ for all cases). Planned contrasts revealed that, among the PG-treated animals, grooming time was significantly lower in the epilepsy model group compared to the control group (Ctrl+PG vs. Pilo+PG; $p < 0.01$; Fig. 2e).

In the Social Interaction Test (Fig. 2, f, g), the rats with the epilepsy model exhibited reduced communicative activity: interaction time was reduced by a factor of 10 ($F_{1,30} = 61.9$; $p < 0.001$), and the number of social contacts was reduced by a factor of 4.8 ($F_{1,31} = 26.9$; $p < 0.001$). For the number of contacts, a significant "Model × Treatment" interaction was revealed ($F_{1,30} = 4.3$; $p < 0.05$). *Post hoc* analysis revealed differences between the Ctrl and Pilo groups ($p < 0.0001$), but not between the Ctrl+PG and Pilo+PG groups, suggesting a corrective effect of pioglitazone on social behavior. Aggressive and defensive behaviors did not differ significantly between the groups.

Analysis of expression of the genes involved in regulation of epileptogenesis. *Genes of astroglial and microglial/macrophage proteins.* In the temporal cortex, the lithium-pilocarpine model induced a sharp increase in the expression of the astrocyte activation marker gene (*Gfap*) and the microglial activation marker gene (*Aif1*) (Fig. 3, b, d; effect of the model – $F_{1,21} = 90.6$; $p < 0.001$ and $F_{1,19} = 46.8$; $p < 0.0001$, re-

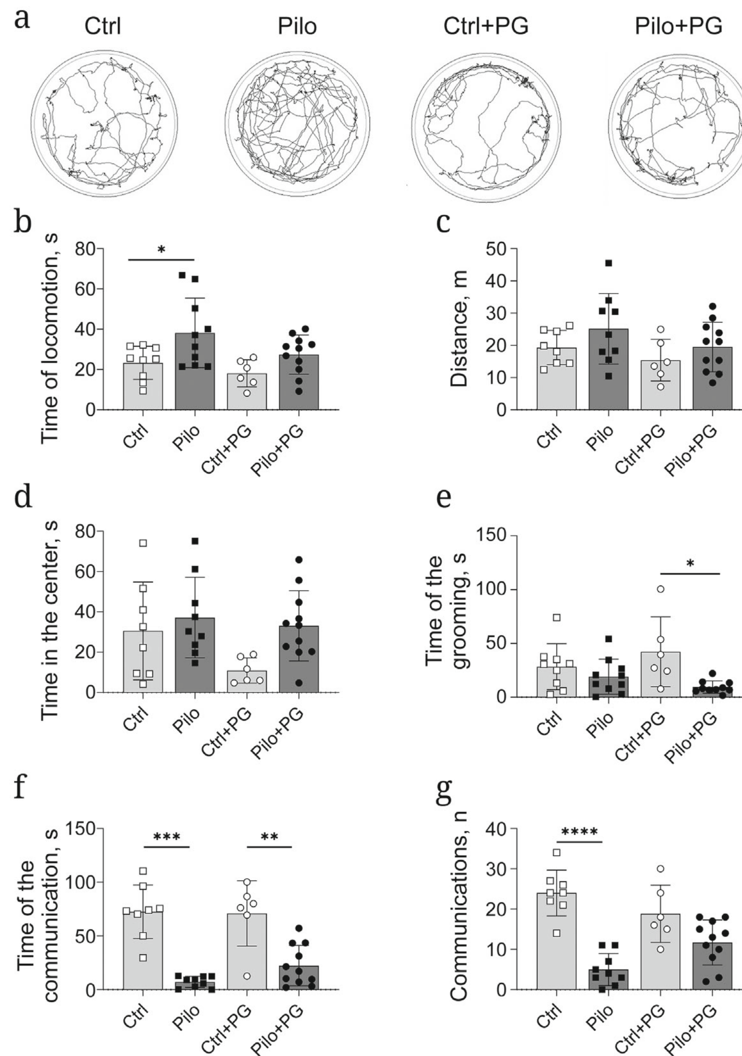

Fig. 2. Behavior of control (Ctrl) rats and rats with temporal lobe epilepsy model (Pilo) in the Open Field Test (a-e) and the Social Interaction Test (f, g). a) Representative tracks in the Open Field. Ctrl – control, PG – pioglitazone; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, Sidak *post hoc* test (f) or planned contrasts within the analysis of variance (g).

spectively). PG administration did not prevent this increase. In the dorsal hippocampus, two-way ANOVA revealed a statistically significant main effect of the factor "Treatment" on the mRNA levels of *Gfap* and *Aif1* (Fig. 3, a, c; $F_{1,23} = 5.9$; $p = 0.02$ and $F_{1,23} = 5$; $p = 0.04$, respectively), however, pairwise comparisons revealed no significant differences between the individual groups.

In the animals with lithium-pilocarpine model of epilepsy, expression of the pro-inflammatory gene *Il1b* was unchanged in the dorsal hippocampus but was increased in the temporal cortex (Fig. 4, a, b; factor "Model": $F_{1,20} = 16.8$; $p < 0.001$); PG administration did not prevent this increase. Expression of the anti-inflammatory gene *Il1rn* was increased in both brain regions examined: in the dorsal hippocampus (Fig. 4c; factor "Model": $F_{1,24} = 45.3$; $p < 0.001$) and in the temporal cortex (Fig. 4d; factor "Model": $F_{1,22} = 11.6$; $p < 0.01$). In the temporal cortex, two-way ANOVA also revealed a statistically significant main effect of the factor "Treatment" on the *Il1rn* expression ($F_{1,22} = 5.8$; $p = 0.03$).

Expression of the *Tnfa* gene did not depend on the factor "Model"; however, in the dorsal hippocampus, a statistically significant main effect of the factor "Treatment" was revealed (Fig. 4e; PG: $F_{1,19} = 8.2$; $p = 0.01$).

Next, we analyzed expression of the genes associated with pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes of microglia/macrophages: *Nlrp3* and *Nos2* (M1 markers) and *Arg1* (M2 marker) (Fig. 5). Two-way ANOVA revealed a statistically significant main effect of the factor "Model" on the *Nlrp3* gene expression in the temporal cortex ($F_{1,20} = 11.7$; $p = 0.003$), however, *post hoc* comparisons did not reach statistical significance (Fig. 5f).

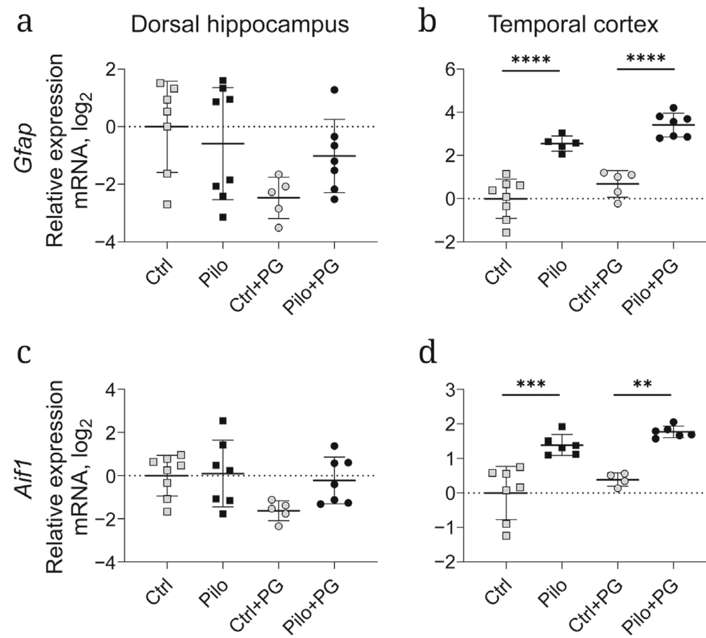

Fig. 3. Relative expression of the astrocyte activation marker gene *Gfap* (a, b) and the microglial activation marker gene *Aif1* (c, d) in the dorsal hippocampus and temporal cortex of experimental (Pilo) and control (Ctrl) rats. PG – pioglitazone; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$, planned contrasts within the analysis of variance.

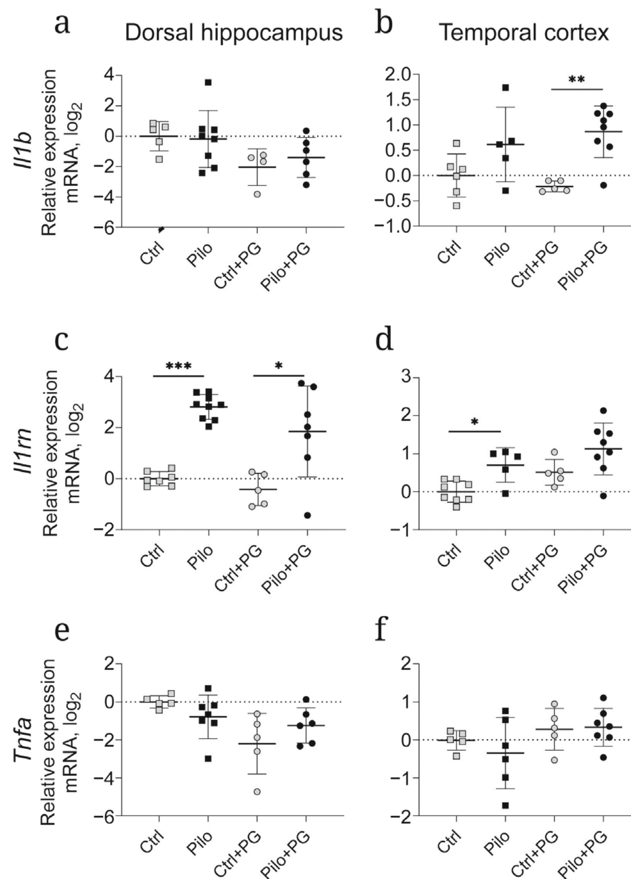

Fig. 4. a-f) Relative expression of pro- and anti-inflammatory cytokine genes in the dorsal hippocampus and temporal cortex of experimental (Pilo) and control (Ctrl) rats. PG – pioglitazone; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, planned contrasts within the analysis of variance.

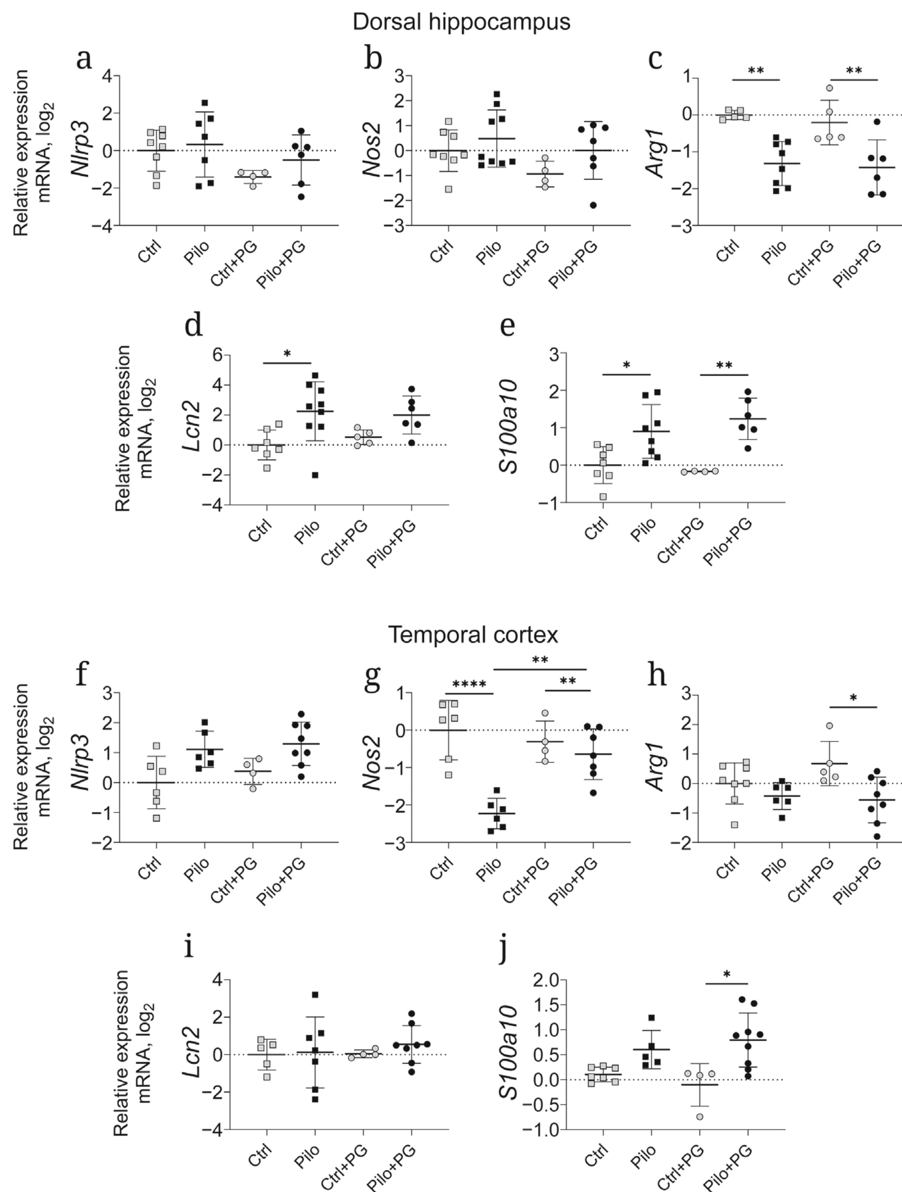

Fig. 5. a-j) Relative expression of microglial and astroglial protein genes in the dorsal hippocampus and temporal cortex of experimental (Pilo) and control (Ctrl) rats. PG – pioglitazone; * $p < 0.05$, ** $p < 0.01$, **** $p < 0.0001$, Sidak *post hoc* multiple comparisons test or planned contrasts within the analysis of variance.

For the *Nos2* gene in the temporal cortex, significant main effects of the factors “Model” ($F_{1,19} = 22.6$; $p < 0.001$) and “Treatment” ($F_{1,19} = 5.6$; $p = 0.03$) were observed, as well as their interaction ($F_{1,19} = 12.3$; $p = 0.002$; Fig. 5g). *Post hoc* analysis revealed that in the untreated animals with the epilepsy model, *Nos2* expression was reduced compared to the control ($p < 0.001$), whereas in the PG-treated animals this decrease was not observed (difference between the Pilo and Pilo+PG groups: $p < 0.01$).

In the animals with the epilepsy model, expression of the *Arg1* gene was reduced in both structures examined (Fig. 5, c, h; dorsal hippocampus: $F_{1,20} = 27.2$; $p < 0.0001$; temporal cortex: $F_{1,23} = 9.4$; $p = 0.006$). In the dorsal hippocampus, the changes were unidirectional in the Pilo and Pilo+PG groups, whereas in the temporal cortex, according to the planned contrasts analysis, reduction was more pronounced in the PG-treated animals ($p < 0,05$). In contrast to *Nos2*, no significant effect of the factor “Treatment” was detected by two-way ANOVA for the *Nlrp3* and *Arg1* genes.

Next, we analyzed expression levels of the *Lcn2* gene (marker of neurotoxic response in astrocytes and microglia/infiltrating cells) and of the *S100a10* gene (marker of the neuroprotective astroglial phenotype). In the animals with the epilepsy model, the *Lcn2* expression was increased in the dorsal

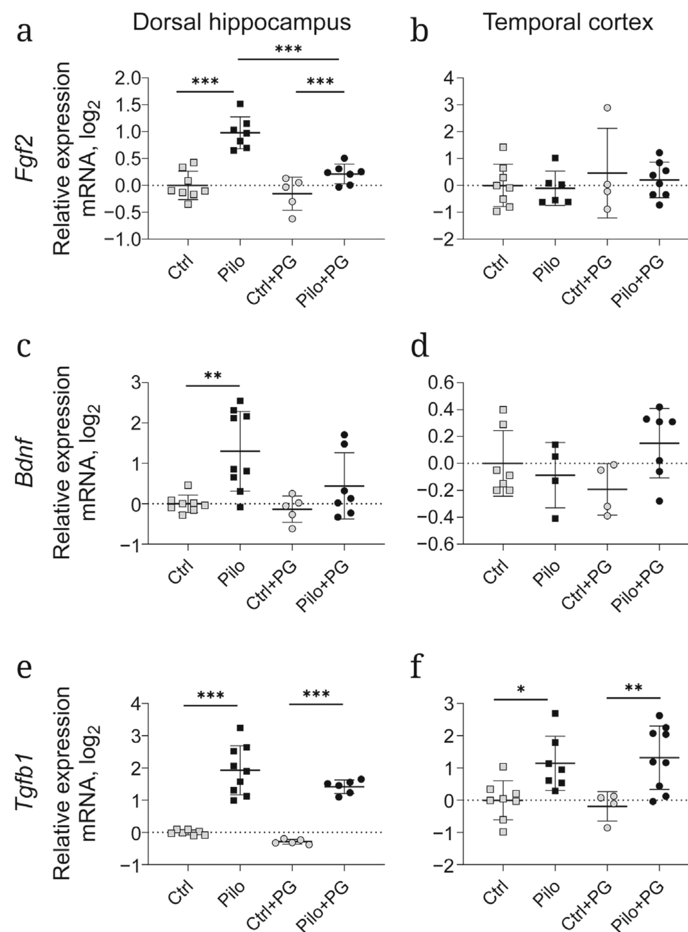

Fig. 6. a-f) Relative expression of growth factor and neurotrophic protein genes in the dorsal hippocampus and temporal cortex of experimental (Pilo) and control (Ctrl) rats. PG – pioglitazone; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, planned contrasts within the analysis of variance.

hippocampus (Fig. 5d; factor "Model": $F_{1,23} = 11.2$; $p < 0.01$). According to the planned contrasts analysis, a statistically significant increase was observed only in the Pilo group (without PG treatment). Expression of the neuroprotective gene *S100a10* was also increased in the dorsal hippocampus (Fig. 5e; factor "Model": $F_{1,21} = 24.7$; $p < 0.001$) and in the temporal cortex (Fig. 5j; factor "Model": $F_{1,24} = 15.6$; $p < 0.001$). The planned contrasts analysis revealed that in the hippocampus, increase in the *S100a10* expression was significant in both epilepsy model groups, whereas in the temporal cortex it reached statistical significance only in the PG-treated animals.

Overall, analysis of expression of the astroglial and microglial/macrophage marker genes revealed their substantial alterations during the latent phase of the lithium-pilocarpine model, with a more pronounced response to the model observed in the temporal cortex. PG administration did not prevent most of the identified alterations; however, in some cases (*Lcn2* in the hippocampus, *Nos2* in the cortex), a modulatory effect of the drug was observed.

Expression of growth factor and neurotrophic factor genes (Fig. 6). In the animals with the epilepsy model, expression of the *Fgf2* ($F_{1,23} = 42.7$; $p < 0.001$), *Bdnf* ($F_{1,25} = 12.1$; $p = 0.002$), and *Tgfb1* ($F_{1,22} = 140.8$; $p < 0.001$) genes was increased in the dorsal hippocampus. For the *Tgfb1* gene, increase in expression was also observed in the temporal cortex ($F_{1,24} = 17.7$; $p < 0.001$). The planned contrasts analysis revealed that the increase in the *Bdnf* expression was statistically significant only in the Pilo group. In the dorsal hippocampus, PG administration significantly attenuated the pilocarpine-induced increase in the *Fgf2* expression (factor "Treatment": $F_{1,23} = 19.9$; $p < 0.001$; factor interaction: $F_{1,23} = 8.8$; $p = 0.007$), and *post hoc* comparisons revealed significant differences between the Pilo and Pilo+PG groups ($p < 0.001$). PG also influenced the *Tgfb1* gene expression in the dorsal hippocampus ($F_{1,22} = 4.7$; $p = 0.04$).

Thus, PG administration during the latent phase of epileptogenesis attenuated the model-characteristic increase in the *Fgf2* expression in the dorsal

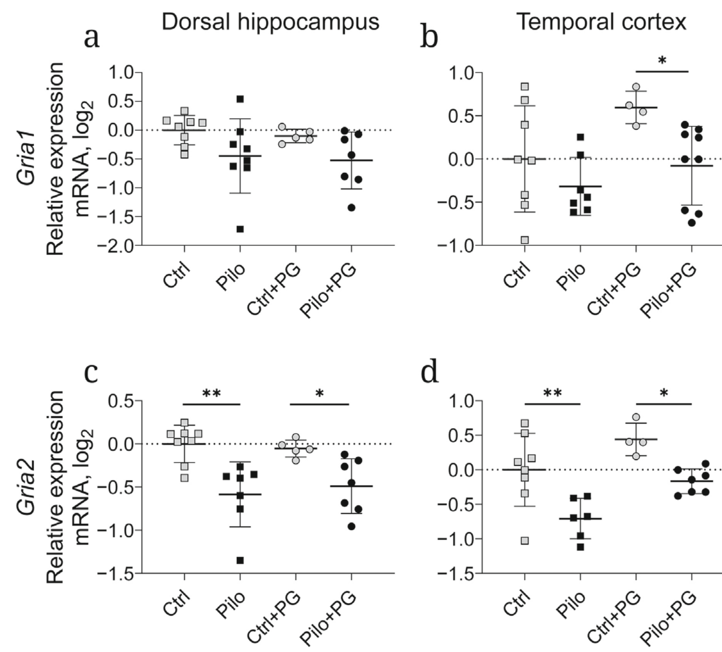

Fig. 7. a-d) Relative expression of glutamate AMPA receptor subunit genes in the dorsal hippocampus and temporal cortex of experimental (Pilo) and control (Ctrl) rats. PG – pioglitazone; * $p < 0.05$, ** $p < 0.01$, planned contrasts within the analysis of variance.

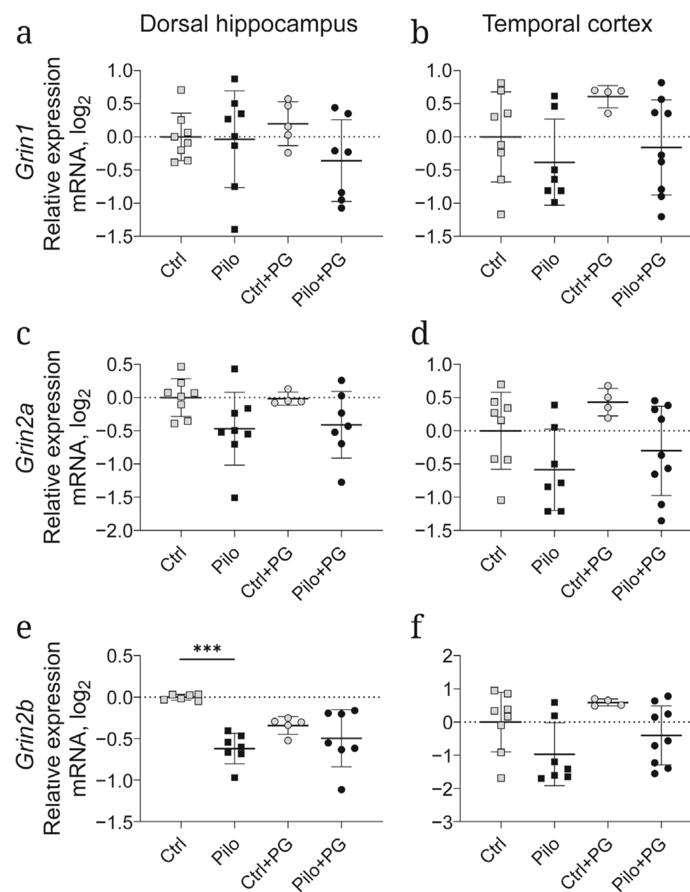

Fig. 8. a-f) Relative expression of the glutamate NMDA receptor subunit genes in the dorsal hippocampus and temporal cortex of the experimental (Pilo) and control (Ctrl) rats. PG – pioglitazone; *** $p < 0.001$, planned contrasts within the analysis of variance.

hippocampus. A trend toward normalization was also observed for the *Bdnf* gene.

Expression of glutamate AMPA and NMDA receptor genes. Epileptogenesis was accompanied by the decrease in expression of the AMPA receptor subunit genes (Fig. 7) both in the dorsal hippocampus (Model: *Gria1* – $F_{1,24} = 6.3$; $p = 0.02$; *Gria2:* $F_{1,22} = 19.2$, $p < 0.01$), and in the temporal cortex (Model: *Gria1* – $F_{1,24} = 7.4$; $p = 0.01$; *Gria2*: $F_{1,21} = 19.3$; $p < 0.001$). PG administration influenced the level of expression of the AMPA receptor genes in the temporal cortex (factor “Treatment”: *Gria1* – $F_{1,24} = 5.2$; $p = 0.03$; *Gria2*: $F_{1,21} = 10.8$; $p < 0.01$).

Analysis of the NMDA receptor subunit expression (Fig. 8) revealed no substantial changes in the *Grin1* mRNA levels in either of the brain structures examined. At the same time, the *Grin2a* gene expression was altered in the dorsal hippocampus (Model: $F_{1,23} = 6.3$; $p = 0.02$) and in the temporal cortex ($F_{1,24} = 8$; $p < 0.01$). The *Grin2b* gene expression was altered in the dorsal hippocampus of the rats with temporal lobe epilepsy (Model: $F_{1,22} = 12{,}5$; $p < 0.01$). Analysis of planned contrasts in the dorsal hippocampus revealed decrease in the *Grin2b* mRNA levels only in the untreated model animals compared to the control.

DISCUSSION

In the present study, we investigated the effect of PG on behavioral and molecular alterations during the latent phase of epileptogenesis. Animals with the lithium-pilocarpine model of epilepsy exhibited characteristic behavioral disturbances: increased locomotor activity in the Open Field Test and impaired social interaction in the Social Interaction Test, which is consistent with the published data on the early development of behavioral disorders during epileptogenesis [26, 27]. PG administration attenuated the pilocarpine-induced deficits in social behavior. A similar effect of PG was previously demonstrated in the febrile seizure model [28].

We also identified significant changes in the expression of the genes associated with neuroinflammation. We observed marked activation of the glial cells, as evidenced by the increased mRNA levels of the astroglial marker *Gfap* and the microglial marker *Aif1* in the temporal cortex. These changes were more pronounced in the cortex than in the hippocampus, which may reflect distinct dynamics of the neuroinflammatory response during epileptogenesis. GFAP is an established marker of reactive astrogliosis [29], and AIF1 reflects microglial activation [30]. Our data are consistent with numerous clinical and experimental observations demonstrating persistent glial activation in the temporal lobe epilepsy [4, 19]. Importantly, glial activation is not merely a secondary consequence of epileptic activity but also one of the factors that sustain the pathological process and promote disease progression through the persistence of neuroinflammation [31]. PG administration did not significantly attenuate these changes.

Glial activation in our experiment was accompanied by the increased expression of both pro-inflammatory (*Il1b*) and anti-inflammatory (*Il1rn*) cytokine genes, which is consistent with the published data [32, 33]. PG administration had a limited effect on the expression of pro- and anti-inflammatory cytokine genes, and no statistically significant intergroup differences were detected). Previous studies using the lithium-pilocarpine model and the pentylenetetrazole-induced acute seizure model have shown that the PPARγ agonists suppress expression of the pro-inflammatory cytokine genes in the hippocampus [34, 35]. The less pronounced effect of PG on the expression of these genes in the present study may be attributable to the relatively low dose of the drug used.

In interpreting the increased expression of the *Gfap* and *Aif1* genes, we considered these changes in the context of glial polarization. Despite the growing understanding of the spectrum of glial states [7, 36], the markers we examined remain reference points for identifying pro-inflammatory (M1/A1) and anti-inflammatory (M2/A2) phenotypes [7, 17]. Since previous studies have demonstrated the effect of PPARγ agonists on polarization of the microglial [37] and astroglial [38, 39] cells in various models of neuropathology, we assessed the effect of PG on the expression of the genes associated with reactive glial and macrophage phenotypes (*Lcn2*, *S100a10*, *Nos2*, *Nlrp3*, *Arg1*). A small number of macrophages may have been present in the samples, as our analysis was performed on tissue homogenates.

The lithium-pilocarpine model of epilepsy was associated with bidirectional changes in the M1/M2 phenotype markers, and magnitude and direction of these changes differed depending on the brain structure. In the temporal cortex, expression of the *Nlrp3* gene was increased, which is consistent with the published data obtained in several models of epilepsy [17, 40]. No significant changes in the *Nlrp3* gene expression were detected in the dorsal hippocampus, which may be attributable to the differences in the time points of testing. Expression of the *Arg1* gene was reduced in both structures; however, this reduction was more pronounced in the hippocampus ($F_{1,20} = 27.2$; $p < 0.0001$) than in the cortex ($F_{1,23} = 9.4$; $p = 0.006$), which may reflect a more profound suppression of the anti-inflammatory M2 mechanisms in the hippocampus. Similar changes were identified in our previous studies in the latent [32] and chronic [41]

phases of the model, as well as by Peng et al. [42]. In contrast to expression of the *Nlrp3* and *Arg1* genes, expression of the *Nos2* gene was reduced in the cortex, whereas no significant changes were observed in the hippocampus. This is inconsistent with the previously described increase in iNOS during the acute period of epileptogenesis [32]; this discrepancy may be due to the differences in the time points of testing and region-specific nature of the response. PG administration did not affect expression of the *Nlrp3* or *Arg1* genes in either structure, which differs from the findings of Peng et al. [42], who demonstrated efficacy of another PPARγ agonist, rosiglitazone. This discrepancy may be explained by the differences in the drugs used.

We also analyzed expression of the *Lcn2* gene (a marker of the neurotoxic response in astrocytes and microglia/infiltrating cells), and of the *S100a10* gene (marker of the protective A2 astrocyte state). Notably, both genes were simultaneously upregulated, indicating concurrent activation of both detrimental and protective pathways, a phenomenon previously described in the kainate model of epilepsy [43]. However, regional specificity was also evident here: the *Lcn2* gene was upregulated only in the dorsal hippocampus (and remained unchanged in the cortex), and PG prevented this increase. The *S100a10* gene was upregulated in both structures, but with different dynamics: in the hippocampus – in both model groups (Pilo and Pilo+PG), whereas in the cortex – only in the PG-treated group.

Thus, analysis of the expression of the astroglial and microglial/macrophage markers revealed region-specific changes during the latent phase of the lithium-pilocarpine model. The temporal cortex exhibited a broader and more pronounced inflammatory response than the dorsal hippocampus, including activation of astrocytes (*Gfap*) and microglia (*Aif1*), increase in the *Nlrp3* expression, and decrease in the *Nos2* expression. A more profound decrease in expression of the anti-inflammatory marker *Arg1* was observed in the hippocampus accompanied by the increase in expression of the neurotoxic marker *Lcn2*.

PG did not block the main pathological changes (glial activation, increased *Il1b*, decreased *Arg1*) but exerted selective effects: it prevented the increase in *Lcn2* expression in the hippocampus, counteracted the decrease in *Nos2* expression, and induced increase in the *S100a10* expression in the cortex. This indicates a region-dependent modulation of specific glial pathways rather than systemic anti-inflammatory effect of the drug during the latent phase.

Since epileptogenesis involves not only inflammatory but also regulatory systems, including neurotrophic factors that are under metabolic control [44], we investigated expression of three growth factor genes – *Fgf2*, *Bdnf*, and *Tgfb1*. In the rats with the lithium-pilocarpine model, we observed increased expression of the *Bdnf* and *Fgf2* genes in the dorsal hippocampus, and of *Tgfb1* in both the hippocampus and the temporal cortex. It is known that the *Bdnf* gene activity is increased in the temporal cortex of the patients with epilepsy [45], and that the levels of expression of the *Bdnf* and *Fgf2* genes are upregulated in the hippocampus of the animals in the pilocarpine model [46, 47]. However, the increased expression of the growth factors studied may exert a dual effect on epileptogenesis. For example, BDNF exerts neuroprotective and cognition-enhancing effects via the CREB activation [48] but also promotes mossy fiber sprouting, a key mechanism in the development of temporal lobe epilepsy [49]. FGF2 could prevent neuronal death [50] but, at the same time, it could induce ictal activity [51]. TGF-β1 plays a similarly dual role, possessing anti-inflammatory properties [52] while also contributing to seizure induction and astrogliosis [53].

In our study, PG influenced expression of the neurotrophic factor genes only in the hippocampus: it partially prevented the pilocarpine-induced increase in the *Fgf2* expression. At the same time, its effect on the *Tgfb1* and *Bdnf* expression was less pronounced and did not reach statistical significance in the intergroup comparisons. Previously, effect of rosiglitazone on the *Bdnf* gene expression was demonstrated in a similar model [54]. Greater sensitivity of the dorsal hippocampus to PG may be explained by the higher density of PPARγ in this brain region [55]. Significance of the selective suppression of the *Fgf2* gene in the hippocampus for epileptogenesis requires further investigation.

Given the key role of glutamate receptors in the pathogenesis of epilepsy, we analyzed expression of the genes encoding their major subunits in the lithium-pilocarpine model and the effect of PG on their expression. We found that expression of the *Grin2a* and *Grin2b* genes, which encode the GluN2A and GluN2B subunits of the NMDA receptors, was reduced in the dorsal hippocampus of the experimental rats. Data on the expression of the NMDA receptor subunit genes in epilepsy models are contradictory, which is likely explained by the differences in experimental protocols and examination time points. For example, the increased *Grin2b* expression was observed in the chronic phase of the pilocarpine model without lithium [56], whereas we previously observed decrease in its expression during the latent phase of the lithium-pilocarpine model [57]. We also found decrease in the expression of the *Gria2* gene (encoding the GluA2 subunit of AMPA receptors) in both brain regions examined, which is consistent with our previous data [58] and observations in other models of epilepsy [59]. In the hippocampus, PG prevented the

epilepsy-associated downregulation in the *Grin2b* expression, restoring its level to values indistinguishable from the control. This result may reflect the neuroprotective effect of PG demonstrated by other authors in the lithium-pilocarpine model [60] and in the pentylenetetrazole-induced seizure model [61]. This finding suggests that activation of PPARγ as a metabolic sensor may stabilize transcriptional programs important for synaptic homeostasis. However, precise molecular mechanisms underlying this effect require further investigation.

Thus, this study demonstrated that the PPARγ agonist PG attenuates behavioral disturbances and selectively restores expression of the glutamate receptor subunit genes (*Grin2b*) and the neurotrophic factor *Fgf2* in the dorsal hippocampus during epileptogenesis, while exerting only weak effect on the glial markers and neuroinflammation. Since glutamate receptors are expressed predominantly in neurons, it is reasonable to assume that the neuroprotective potential of PG during epileptogenesis may be primarily associated with modulation of neuronal rather than glial processes. This highlights the promise of further investigation of PG within the framework of strategies aimed at correcting disturbances related to neuronal metabolism and excitability in epilepsy.

Abbreviations

Ctrl	control group
PG	pioglitazone
Pilo	lithium-pilocarpine model of temporal lobe epilepsy
PPAR	peroxisome proliferator-activated receptors
RT-qPCR	real-time reverse transcription polymerase chain reaction
SE	status epilepticus

Supplementary information
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Contributions
A.R.K. performed experiments, processed data, prepared illustrations, and wrote and edited the manuscript; O.E.Z. conceptualized the study, processed data, and wrote and edited the manuscript; D.S.S. performed experiments, conducted statistical analysis, and prepared illustrations; A.A.K. performed experiments and edited the manuscript; A.V.Z. conceptualized and supervised the study and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

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Ethics approval and consent to participate
The study was conducted in accordance with the EU Directive 2010/63/EU on the protection of animals used for scientific purposes and was approved by the Ethics Committee of the I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences (Ethical Approval no. 1-16, January 26, 2023).

Conflict of interest
The authors of this work declare that they have no conflicts of interest.

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