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Original Article

Treatment of pilocarpine-induced epileptic seizures in adult male mice

Tratamento de crises epilépticas induzidas por pilocarpina em camundongos adultos machos

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Abstract

Epilepsy is one of the most common neurological disorders affecting most social, economic and biological aspects of human life. Most patients with epilepsy have uncontrolled seizures and drug side effects despite the medications. Patients with epilepsy often have problems with attention, memory, and information processing speed, which may be due to seizures, underlying causes, or anticonvulsants. Therefore, improving seizure control and reducing or changing the anti-epileptic drugs can solve these problems, but these problems will not be solved in most cases. In this work, we looked at the effects of pioglitazone, a Peroxisome Proliferator-Activated Receptor agonist used to treat type 2 diabetes, on pilocarpine-induced seizures in mice. The Racine scale was used to classify pilocarpine-induced convulsions. After that, all of the animals were beheaded, and the brain and hippocampus were dissected. Finally, biochemical techniques were used to determine the levels of Malondialdehyde and Catalase activity, as well as Superoxide Dismutase and Glutathione Reductase in the hippocampus. The results of this investigation suggest that pioglitazone's antioxidant action may play a key role in its neuroprotective properties against pilocarpine-induced seizure neuronal damage.

Keywords: seizure, pioglitazone, pilocarpine, oxidative stress, anticonvulsants.

Resumo

A epilepsia é um dos distúrbios neurológicos mais comuns que afetam a maioria dos aspectos sociais, econômicos e biológicos da vida humana. A maioria dos pacientes com epilepsia tem convulsões não controladas e apresenta efeitos colaterais de medicamentos. Pacientes com epilepsia, geralmente, têm problemas de atenção, memória e velocidade de processamento de informações, ocasionados por convulsões, causas subjacentes ou anticonvulsivantes. Portanto, melhorar o controle das crises e reduzir ou alterar as drogas antiepilépticas pode resolver esses problemas, mas, na maioria dos casos, eles não serão resolvidos. Neste trabalho, analisamos os efeitos da pioglitazona, um agonista do receptor ativado por proliferador de peroxissoma usado para tratar diabetes tipo 2, em convulsões induzidas por pilocarpina em camundongos. A escala de Racine foi usada para classificar as convulsões induzidas pela pilocarpina. Em seguida, todos os animais foram decapitados, e o cérebro e o hipocampo foram dissecados. Finalmente, técnicas bioquímicas foram utilizadas para determinar os níveis de atividade do malondialdeído e da catalase, bem como da superóxido dismutase e glutatona redutase no hipocampo. Os resultados desta investigação sugerem que a ação antioxidante da pioglitazona pode desempenhar um papel fundamental em suas propriedades neuroprotetoras contra o dano neuronal convulsivo induzido pela pilocarpina.

Palavras-chave: convulsão, pioglitazona, pilocarpina, estresse oxidativo, anticonvulsivantes.

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1. Introduction

Epilepsy is a central nervous system (CNS) illness that causes abnormal brain activity, resulting in seizures, odd behavior, and occasionally loss of consciousness. The brain's electrical activity is periodically disturbed, resulting in some degree of temporary brain dysfunction (Camporeze et al., 2018; Liu et al., 2018, 2019; Malik and Willnow, 2019). People of various ages, genders, and ethnicities can be affected by epilepsy. The terms "seizures" and "epilepsy" are not interchangeable (Dhrivastava et al., 2019). Seizures are one of the epilepsy symptoms, although not everyone who has one has epilepsy (Beghi, 2020). Seizures are a single occurrence, but epilepsy is a neurological condition marked by two or more seizures. Seizures include a wide range of symptoms. Uncontrollable bodily movements are not always associated with seizures. During a seizure, some persons with epilepsy stare at a single location for a few seconds, while others move their arms or legs abnormally (Mahamud et al., 2018; Zelano et al., 2020; Karoly et al., 2021). Seizures are classified according to how they begin and which portion of the brain they affect (Pack, 2019). The majority of seizures last between 30 and two minutes. A medical emergency is a seizure that lasts more than five minutes (DeLorenzo et al., 1999; Shinnar et al., 2001). In industrialized countries, epilepsy affects 40-70 people per 100,000, but in poor countries, it affects 100-190 people per 100,000 (Keykhosravi et al., 2019). When Alfred Hartmann developed phenobarbital in 1912, pharmacologic epilepsy therapy became widespread around the turn of the century (Villalba, 2017; Rostamian et al., 2021). Phenytoin, valproate, and carbamazepine were among the antiepileptic medications found during the next few decades (Wat et al., 2019). Anticonvulsant drugs are required by more than 60% of persons with epilepsy (Thijs et al., 2019). Cognitive problems, ataxia, and drowsiness are all adverse effects of these medicines. Even after the use of existing treatments, seizures are still occurring in 30% of individuals (Brunbech and Sabers, 2002; Zaccara et al., 2008). As a result, new anticonvulsant drugs with reduced side effects and excellent effectiveness are urgently needed. Antioxidants, such as melatonin, added to antiepileptic medicines have been demonstrated in clinical studies to lessen epilepsy-related neurological problems (Naziroğlu, 2015; Rocha et al., 2018; Dinka, 2020; Wałowski, 2021). Due to a change in sources of energy, like the use of fat-derived ketone bodies, ketogenic diets lower mitochondrial reactive oxygen/nitrogen species (ROS/RNS) (Zhou et al., 2021).

Seizures, Alzheimer's disease, stroke, and migraine are the most common neurological ailments related to epilepsy (Farrell et al., 2017; Azimi and Asgarpanah, 2021; Alharbi, 2021). According to research, seizures have been demonstrated to attack neurons by causing oxidative stress and generating free radicals (Patel, 2002, 2004; Lin et al., 2020). Status epilepticus can lead to energy loss due to mitochondrial respiratory chain malfunction (Young and Dragunow, 1994). The results may exacerbate oxidative stress and lead to hippocampal neuronal death (Freitas et al., 2005; Liu et al., 2010). As a result, taking antioxidants may lower the chance of seizures causing brain damage. Oxidative stress produced by employing

pilocarpine in large dosages harms the hippocampus's GABAergic (gamma-aminobutyric acidergic) neurons, which finally leads to status epilepticus is one way to induce seizure in rodents (Freitas et al., 2004; Alharbi, 2021). Pioglitazone, an agonist of the Peroxisome Proliferator-Activated Receptor γ nuclear receptor, improves insulin receptor sensitivity and is used to treat type 2 diabetes (Yap et al., 2020). According to research, Pioglitazone possesses antioxidant properties and shields neurons from oxidative stress-related damage (Nicolakakis et al., 2008; Khasabova et al., 2019). Pioglitazone strengthens the antioxidant defense system by scavenging free radicals (Mahamud et al., 2018). Thus, the pilocarpine-induced seizures in mice under the pioglitazone's anticonvulsant and antioxidant effects were investigated in the current study.

2. Materials and Methods

Epilepsy is a persistent brain condition that impacts roughly 1% of the global population. It can have a detrimental influence on a patient's safety, relationships, employment, and life quality. In roughly 70% of instances, seizures may be controlled with anti-epileptic medicines, whereas 30% of patients remain resistant. It is consequently necessary to find new anti-epileptic targets. In this study, 28 adult male mice (about six weeks old) weighing 20 ± 2 grams were obtained. Throughout the research, the mice had unrestricted access to water and food. They were housed in separate cages at 22-24°C room temperature with a 12-hour light/dark cycle. This research was carried out in conformity with institutional, national, and international regulations and standards for animal testing (OPRR, 1986; OLAW, 2002; Couto and Cates, 2019). The following chemicals were bought from Sigma Aldrich: pilocarpine hydrochloride (P6503), xylazine hydrochloride (X1251), ketamine hydrochloride (K113), and pioglitazone hydrochloride (E6910). In this investigation 80 mg/kg of pioglitazone was dissolved in 0.1% carboxymethyl cellulose (w/v) and given to the mice orally (Rajaba et al., 2014). To induce seizure, 400 mg/kg of pilocarpine (a single dose) was administered intraperitoneally (IP) (Figure 1) (Alharbi, 2021).



Figure 1. The medication was injected intraperitoneally into the mice.

The animals were also given Xylazine or Ketamine IP to induce anesthesia. The mice were separated into the following classes:

1. 240 minutes after the oral dose of carboxymethyl cellulose 0.1%, normal saline was injected (*Control group*);
2. 240 minutes following the 80 mg/kg oral dose of pioglitazone, normal saline was injected (*Pioglitazone group*);
3. 240 minutes after an oral dose of carboxymethyl cellulose 0.1%, pilocarpine was administered at 390 mg/kg (*Pioglitazone group*);
4. 240 minutes after 80 mg/kg of pioglitazone was given orally, pilocarpine was administered at 390 mg/kg (*Treatment group*).

For 60 minutes following the pilocarpine injection, the animals' convulsive behavior was recorded on camera. Based on a modified Racine's scale (Cela et al., 2019), the strength of the convulsions was recorded as no response (Phase 0); vibrissae twitching, restlessness, and hyperactivity (Phase 1); myoclonic jerks, clonus, and head nodding (Phase 2); bilateral or unilateral limb clonus (Phase 3); clonic seizures of forelimbs (Phase 4); and generalized tonic-clonic seizures and falling (Phase 5).

After determining the intensity of seizures, animals were killed by guillotine under deep levels of ketamine-induced anaesthesia. The hippocampus was detached from the brain, homogenized in 1.5% KCl solution weighed, and blotted dry as soon as the brain was removed from the cranium. The homogenates subsequently centrifuged to yield hippocampal PMF (Post-Mitochondrial Fluid), which was used in the biochemical experiment. The quantity of proteins in the hippocampus was measured using bovine serum albumin as a reference (Sultan, 2013).

Employing the Thiobarbituric Acid technique, the Malondialdehyde level in the mice's hippocampus was evaluated to assess lipid peroxidation.

One ml Thiobarbituric Acid and three ml phosphoric acid (3%) were added to a centrifuge tube containing 0.5 ml hippocampal sample. In a boiling water bath, the solution was boiled for 45 minutes. Then, a spectrophotometer was used to measure the absorbance of the n-butanol (organic layer) at 539 nm. With 1, 1, 3, 3-tetramethoxypropane as the standard, a standard curve was produced. Malondialdehyde nanomoles contained in one gram of hippocampus were used to represent the results (Naderi et al., 2017, 2020). The Catalase activity was measured using the Claiborne technique. The reaction solution for this technique was made up of 1.89 mL phosphate buffer (pH=7.3, 0.12 M), 1.1 mL H₂O₂ (0.02 M), and 0.049 mL PMF. Afterwards, at 240 nm the absorbance was measured, and the findings were represented (Rashid et al., 2014; Kandemir et al., 2017).

The capacity of such an enzyme to block the degradation of NBT (Nitroblue-tetrazolium) was used to measure Superoxide Dismutase activity. The sample (0.1 mL) was mixed in with the reagent solution made up of 1.5 mM NBT, 0.3 mM NaCN, 0.1M EDTA, and 0.067 M KHPO₄ (pH 7.8). For 10 minutes the reaction mixture was incubated after adding 0.12 mM riboflavin to the samples. At 560 nm the absorbance was measured using a spectrophotometer. The enzyme unit/mg protein was used to quantify the data. The quantity of enzyme necessary to achieve a 50%

inhibition was one unit (Zhang et al., 2016). The activity of glutathione reductase was measured using the method of Carlberg and Manevick (Shakeel et al., 2017). The reagent mixture consisted of 0.1 mL 10% PMS, 0.1 mL NADPH (0.1 mM), 0.05 mL GSH (1 mM), 0.1 mL EDTA (0.5 mM), and 1.65 mL phosphate buffer (pH=7.3, 0.12 M). NADPH consumption was used as a metric for determining enzyme activity. Nmol NADPH oxidized/min/mg/protein was used to represent the data (Sandhir and Gill, 1995), and at 340 nm, the absorbance was measured.

For the data analysis, we utilized GraphPad prism 8. In groups of seven items, all data was presented as Means±SEM. We further employed a one-way analysis of variance (ANOVA) to analyze the mean differences. Statistical significance was defined as a P<0.05.

3. Results and Discussion

Plasma glucose levels were evaluated at baseline and after 14 days of daily therapy with either dimethyl sulfoxide (DMSO) or pioglitazone + DMSO, but before pilocarpine injection, to see if pioglitazone altered plasma glucose levels and neuronal excitability in experimental mice. Pioglitazone and DMSO had no effect on blood glucose levels (Figure 2).

Mice were given daily doses of pioglitazone or DMSO to see if activating Peroxisome Proliferator-Activated Receptor- γ might reduce the severity of seizures. The mice were given pilocarpine after 14 days to produce seizures and excitotoxicity. Pioglitazone had no effect on the latency period of acute seizures in any of the groups (Figure 3).

The study found that neither 80 mg/kg pioglitazone nor the control group caused the mice to have seizures. After injection, 400 mg/kg pilocarpine caused to phase 1-5 seizures. The injection of pioglitazone 4 hours prior to administering pilocarpine substantially exacerbated the beginning of phases 1 to 4 of seizure, according to observations seen between pilocarpine and pioglitazone groups (P<0.01-0.001). Furthermore, pioglitazone stopped pilocarpine-induced seizures from progressing to phase 5 (Table 1).

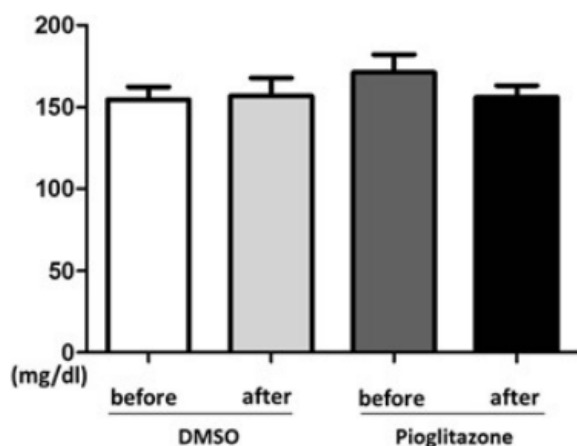


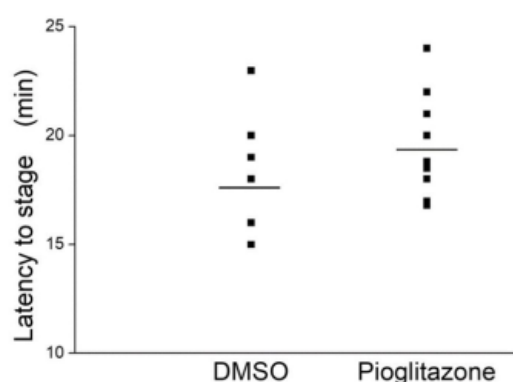
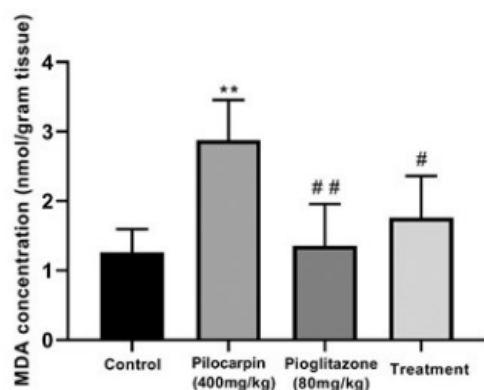
Figure 2. Pioglitazone treatment for two weeks had no effect on mice's blood glucose levels.

Table 1. Pioglitazone's effect on convulsion latency in seizures induced by pilocarpine in mice.

Groups	Means±SEM				
	Phase 5	Phase 4	Phase 3	Phase 2	Phase 1
Treatment (Pioglitazone + Pilocarpine)	-	392.6±12.612	216±22.971	113.4±7.733	92.8±15.19
Pioglitazone	-	-	-	-	-
Pilocarpine	254±13.95	218.6±19.241	95.6±3.744	88.1±8.785	41.6±9.17
Control	-	-	-	-	-

Table 2. After a seizure induced by pilocarpine in mice, the pioglitazone effects on the Catalase, Superoxide Dismutase, and Glutathione Reductase in the hippocampus are presented.

Groups	Means±SEM		
	Catalase activity	Superoxide Dismutase activity	Glutathione Reductase activity
Treatment (Pioglitazone + Pilocarpine)	12.6±0.86	58.12±8.73	45.32±5.73
Pioglitazone	13.73±2.31	60.13±18.23	54.84±6.32
Pilocarpine	6.23±0.83	27.23,6±7.53	25.63±7.32
Control	13.76±1.86	60.06±17.32	51.13±8.12

**Figure 3.** Seizures caused by DMSO and pioglitazone in the pioglitazone group (There is no discernible change in latency).**Figure 4.** After a seizure induced by pilocarpine, the pioglitazone effect on Malondialdehyde (MDA) levels in the hippocampus of mice. ** $P < 0.01$ compared to the control group. # $P < 0.05$ compared to the pilocarpine group. ## $P < 0.01$ compared to the pilocarpine group.

The levels of lipid peroxidation in the hippocampus of mice were considerably increased by pilocarpine-induced seizures, resulting in a much-elevated level of Malondialdehyde than the control group ($P < 0.01$; Figure 4). However, the level of Malondialdehyde in pioglitazone-treated mice was considerably lower than in pilocarpine-treated mice. As a result, after pilocarpine-induced seizures in mice, pioglitazone injection dramatically reduced the degree of lipid peroxidation (Figure 4).

When compared to the control group, the pilocarpine-induced seizure reduced Glutathione Reductase ($P < 0.001$), Superoxide Dismutase ($P < 0.05$), and Catalase activity ($P < 0.01$) in the hippocampus of mice (Table 2). Furthermore, as compared to the pilocarpine group, 80 mg/kg pioglitazone given 4 hours preceding 400 mg/kg pilocarpine injection substantially elevated Glutathione Reductase ($P < 0.001$), Superoxide Dismutase ($P < 0.05$), and Catalase activity ($P < 0.05$) (Table 2). Finally, as compared with the control group, the injection of pioglitazone had no influence on the function of these enzymes in the hippocampus of mice ($P > 0.05$) (Table 2).

4. Conclusion

In the current study, seizure severity was assessed based on the Racine scale. According to our results, the injection of pioglitazone 4 hours preceding injecting pilocarpine accelerated the beginning of phases 1 to 4 of pilocarpine-induced seizures. According to previous research, the excessive formation of free oxygen radicals has been linked to neuronal injury in mice suffering from pilocarpine-induced seizures. Increased generation of free oxygen radicals after a pilocarpine-induced seizure causes lipid peroxidation and the formation of

Malondialdehyde in the hippocampus of mice. Pilocarpine administration also elevated Malondialdehyde levels in the hippocampus of mice while decreasing the Glutathione Reductase, Superoxide Dismutase, and Catalase enzymes' antioxidant activity. Throughout this investigation, the latency of the commencement of seizure caused by pilocarpine was dramatically delayed after pre-treatment with pioglitazone. Furthermore, it prevented pilocarpine-induced status epilepticus. In the hippocampus, pioglitazone simultaneously enhanced antioxidant defenses and reduced oxidative stress. Because pioglitazone decreased oxidative threat posed by pilocarpine toxicity, the results of this paper imply that it has anticonvulsant properties.

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