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Research Report

Anticonvulsant potential of the peroxisome proliferator-activated receptor gamma agonist pioglitazone in pentylenetetrazole-induced acute seizures and kindling in mice

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ABSTRACT

Pioglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, is used in inflammatory brain diseases, and it was shown to protect against seizures in genetically epileptic mice. The present study, therefore, verified its potential antiepileptic effect in pentylenetetrazole (PTZ)-induced acute seizures and kindling in mice. Kindling was induced in male Swiss albino mice using a subconvulsive dose of PTZ (40 mg/kg, i.p., on alternate days) for 17 days, while acute epileptic animals received a single dose of PTZ (60 mg/kg, i.p.). Animals were pretreated with either pioglitazone (10 mg/kg, p.o.) or the standard antiepileptic drug valproate (50 mg/kg, p.o.). Kindled mice showed elevated cortical levels of TNF-α, IL-10, PGE_2, and caspase-3, while acute PTZ increased only the cytokines. However, inducible nitric oxide synthase (iNOS) was not expressed in the hippocampi of both acutely convulsed and kindled animals. In acute PTZ convulsion, as well as kindled mice, pioglitazone and valproate protected against PTZ-induced seizures and delayed seizure latency onset. Pioglitazone normalized all altered parameters except for PGE_2 in PTZ-kindled animals and, unpredictably, further elevated TNF-α in the acute model. Valproate showed also the same pattern but reinstated IL-10 partially in kindled mice. The present results revealed that both models increase pro- and anti-inflammatory cytokines, while only kindling elevates PGE_2 and caspase-3; nonetheless, neither model affects the expression of iNOS. The anticonvulsive effect of either pioglitazone or valproate is presumably associated with attenuating inflammation and preventing apoptosis.

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Abbreviations: HO, hemeoxygenase; IL, interleukin; NO, nitric oxide; iNOS, inducible nitric oxide synthase; nNOS, neuronal nitric oxide synthase; PIO, pioglitazone; PG, prostaglandin; PPAR, peroxisome proliferator-activated receptor; PTZ, pentylenetetrazole; PTZ-a, pentylenetetrazole acute; PTZ-k, pentylenetetrazole kindled; SOD, superoxide dismutase; TZD, thiazolidinedione; TNF, tumor necrosis factor; VPA, valproate

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1. Introduction

The therapeutic merit of the peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, thiazolidinediones (TZDs), reaches far beyond their insulin sensitizing action. Recently, these drugs were found to confer neuroprotection in several animal models, including acute cerebral ischemia, as well as Parkinson's and Alzheimer's diseases (Dehmer et al., 2004; Kiaei et al., 2005; Shimazu et al., 2005; Roses et al., 2007). Effects of TZDs extend to protect against epileptic disorders, where few attempts traced the anticonvulsant efficacy of PPAR-γ agonists (Okada et al., 2006; Maurois et al., 2008; Sun et al., 2008; Yu et al., 2008).

Increased inflammatory mediators are produced secondary to the epileptogenic insult and are important in the development and maintenance of seizure responses (Vezzani and Granata, 2005), possibly by modulating glutamate homeostasis (Vezzani et al., 2008). Elevated levels of proinflammatory cytokines, such as IL-1β and TNF-α, mRNA were documented in status epilepticus and electrical convulsive rats (Okada et al., 2002; Du et al., 2007). Moreover, prostaglandin E_2 (PGE_2) possesses a proconvulsive effect, which is attributed to increased glutamate release-mediated neuronal injury (Cole-Edwards and Bazan, 2005). Nitric oxide (NO) is known to play a role in epilepsy, where its anti- or proconvulsive effects have been revealed (Paul and Subramanian, 2002; El-Abhar and El Gawad, 2003; Itoh et al., 2004). Excessive NO production is linked to the activation of neuronal nitric oxide synthase (nNOS) in both acute (Bikjdaouene et al., 2003) and kindled (Itoh et al., 2004) PTZ models, while De Luca et al. (2006) showed that inducible nitric oxide synthase (iNOS) is associated with kindling responses.

Beside the well-recognized anti-inflammatory effect of TZDs (Dehmer et al., 2004; Kim et al., 2005; Michalik et al., 2006; Krag et al., 2009), their antioxidant properties may add to their antiepileptic efficacy (Okada et al., 2006; Sun et al., 2008; Yu et al., 2008). PPAR-γ agonists enhance the antioxidant enzymes superoxide dismutase-1 and -2 (SOD-1 and -2), as well as catalase gene expression (Girnun et al., 2002; Hwang et al., 2005; Ding et al., 2007). Although Maurois et al. (2008) documented that rosiglitazone was ineffective against audiogenic and ibotenate-induced epilepsy, Yu et al. (2008) conveyed that the anticonvulsive effect endowed by this PPAR-γ agonist was linked to its antioxidant properties in lithium–pilocarpine-induced status epilepticus model. These authors concluded that the suppression of hemeoxygenase-1 (HO-1) expression, a stress-related protein, and superoxide anion generation are important entities in its antiepileptic action.

Since the available data on PPAR-γ agonists in experimental seizure models are contentious, ranging from inhibition to ineffectiveness (Maurois et al., 2008; Yu et al., 2008), and the study of Okada et al. (2006) is the first to document pioglitazone's antiepileptic efficacy, the current investigation aimed to evaluate further its effect in PTZ-induced acute seizures and kindling mice models. In this context, the influence of pioglitazone, in comparison with the antiepileptic drug, valproate, on inflammation, apoptosis, and iNOS was assessed.

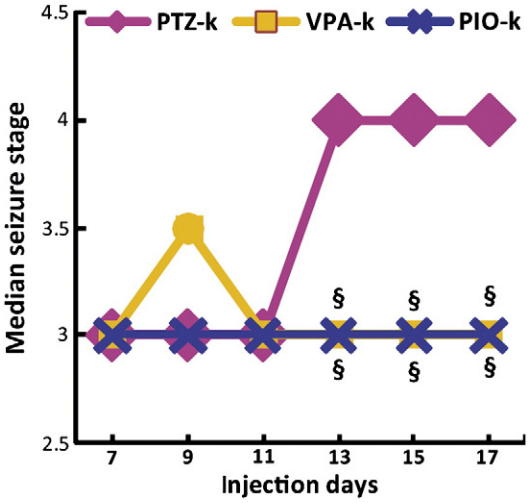

Fig. 1 – Effect of pioglitazone (PIO-k, 10 mg/kg, p.o.) and valproate (VPA-k, 50 mg/kg, p.o.) on seizure stage in PTZ kindled (PTZ-k; 40 mg/kg, i.p., nine injections on alternate days) mice. Values are median of 11–13 mice; as compared to PTZ-k group (§); Kruskal–Wallis test (nonparametric ANOVA) followed by Dunn's multiple comparisons test.

Table 1 – Effect of pioglitazone (PIO; 10 mg/kg, p.o.) and valproate (VPA; 50 mg/kg, p.o.) on PTZ-induced acute seizures (PTZ-a; 60 mg/kg, i.p.) and kindling (PTZ-k; 40 mg/kg, nine injections on alternate days) in mice.

Groups	Median seizure stage	Stage 4/5 seizure latency (min)	Stage 4/5 seizure incidence (%)
PTZ-a	4	9:3 ± 0.02[a]	100
PTZ-k	4	4:2 ± 1.03[b]	100
VPA –a	0	16:6 ± 3.40[b]	20[b]
VPA-k	3	16:1 ± 1.91[a]	9[a]
PIO-a	3	18:3 ± 1.70[b]	20[b]
PIO-k	3	19:1 ± 1.33[a]	31[a]

In the seizure stage, values are median of 11–13 mice; statistical comparisons were carried out using Kruskal–Wallis test (nonparametric ANOVA) followed by Dunn's multiple comparisons test. In the parametric analysis (stage 4/5 seizure latency), values are means of 11–13 animals ± SEM; statistical comparisons were carried out using one-way ANOVA followed by Student–Newman–Keuls multiple comparisons test. Stage 4/5 seizure incidence (11–13 animals) was compared using Fisher's exact probability test. As compared with PTZ-k ([a]) and PTZ-a ([b]) groups, $P<0.05$. VPA-a, valproate-acute; VPA-k, valproate-kindled; PIO-a, pioglitazone-acute; PIO-k, pioglitazone-kindled.