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Research report

Acute effects of aceclofenac, COX-2 inhibitor, on penicillin-induced epileptiform activity

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ABSTRACT

Purpose: The effects of COX-2 inhibitors on seizure activity are controversial. The aim of the current study was to determine the post-treatment effect of aceclofenac on penicillin-induced experimental epilepsy.
Methods: Male Wistar rats were used in all experiments (n = 18). The seizure activity was triggered by penicillin (i.c.). Aceclofenac was injected intraperitoneally at doses of 10 mg/kg and 20 mg/kg.
Results: Intraperitoneal administration of 10 and 20 mg/kg aceclofenac doses, exhibited proconvulsant properties on seizure activity on rats. The mean spike frequency and amplitude of aceclofenac 10 mg/kg were 41.89 ± 2.12 spike/min and 0.619 ± 0.094 mV, respectively. The mean spike frequency and amplitude of aceclofenac 20 mg/kg were 35.26 ± 2.72 spike/min and 0.843 ± 0.089 mV, respectively.
Conclusion: The results indicated that not all of the COX-2 inhibitors may have anticonvulsant or proconvulsant features on patients with epilepsy susceptibility and must be used with great care. It was also suggested that not only cyclooxygenase metabolic pathway but also lipoxygenase pathway should be considered together in further detailed studies.

1. Introduction

Epilepsy, the third common chronic neurological disorder after Alzheimer's/dementia and migraine (Fisher et al., 2005), is characterized by spontaneous and recurrent seizures (Shimada et al., 2014). However, the mechanism of epileptogenesis is still unclear (Vezzani et al., 2013). Injuries and seizures can stimulate inflammatory responses with microglia, monocytes and astrocytes in brain (Rojas et al., 2014). The inflammation leads to increase in neuronal stimulation and results in seizures (Curia et al., 2014).

Cyclooxygenases (COX-1 and COX-2) convert arachidonic acid into prostaglandins (PG), which was directly associated with several neurological diseases as epilepsy (Katori and Majima, 2000). COX-2 is localized in excitatory neuronal dendrites (Kaufmann et al., 1996), particularly in the hippocampus and cortex (Yamagata et al., 1993). It was reported that expression of COX-2 increased in several experimental epileptic models (Kawaguchi et al., 2005; Lee et al., 2007; Takemiya et al., 2006; Voutsinos-Porche et al., 2004). However, the effects of COX-2 inhibitors are controversial in severity and progression of epilepsy. Takemiya et al. (2006) reported that injection of COX-2 inhibitor NS-398 prevented neuronal cell loss in hippocampus in kainic-acid induced epilepsy (Takemiya et al., 2006). Kunz and Oliw (2001) reported that administration of nimesulide after kainic acid increased cell loss in hippocampus and also pretreatment with nimesulide triggered seizures and increased the mortality rate up to 69% (Kunz and Oliw, 2001). Katyal et al. revealed the anticonvulsant effect of etoricoxib injection at high-dose (10 mg/kg) and impairement of memory- cognitive function while having reverse effect at low-dose (1 mg/kg) (Katyal et al., 2015). In a similar study, Akula et al. found that rofecoxib exerted anticonvulsant effects through increasing the threshold in Pentylenetetrazol (PTZ) (2 and 4 mg/kg) induced epilepsy. However, at 1 mg/kg dose, rofecoxib failed to increase the threshold (Akula et al., 2008). Kim et al. stated that pre and post treatment of indomethacin, nimesulide and ketoprofen drugs increased the seizure activity in kainic acid-induced epilepsy (Kim et al., 2008).

Aceclofenac is used for relieving pain, rheumatoid arthritis and osteoarthritis in the clinic. A COX-2 inhibitor aceclofenac is a common and well-established non-steroidal anti-inflammatory drug. Aceclofenac and 4-hydroxy aceclofenac are the conversion products of aceclofenac and major metabolites in human. However, for rats diclofenac is the major metabolite. During inflammation process, aceclofenac and 4-hydroxy aceclofenac are hydrolyzed into active metabolites diclofenac and 4-hydroxy diclofenac and as a

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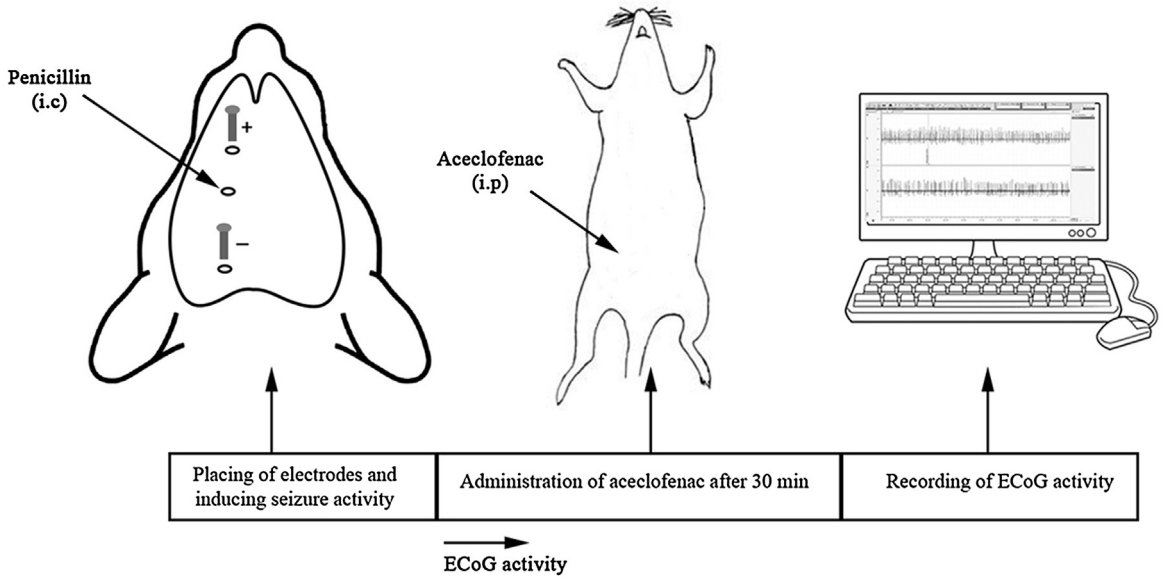

Fig. 1. Study methodology. Seizure activity was induced by penicillin G potassium (500 units, i.c.). Injection of aceclofenac doses were performed 30 min after penicillin. ECoG activity was recorded with PowerLab recording device.

result, production of PGE2 is prevented at the site of inflammation (Sanchez et al., 2002; Yamazaki et al., 2000).

In literature, there is no study about the effects of aceclofenac in penicillin-induced experimental epilepsy. Our results provide important contributions to the literature about the proconvulsant effects of aceclofenac drug.

2. Material and methods

2.1. Animals

Male Wistar rats were used in all experiments. Animals were purchased from Animal Research Center of Erciyes University. at a body weight of ~300 g (12 weeks old, n = 18). Animals were kept under controlled conditions (22 ± 2 °C; 12/12 h reversed light/dark cycle).The experimental protocols and procedures used in trials were approved by Local Ethics Committee for Animal Experiments (ERU-HADYEK) (decision no: 16/082), Erciyes University, Turkey. The rats were treated in three groups as follows;

1) 500 units penicillin (Control group) (2.5 μl, i.c.) (n = 6)
2) 500 units penicillin (2.5 μl, i.c.) + aceclofenac (10 mg/kg, i.p) (n = 6)
3) 500 units penicillin (2.5 μl, i.c.) + aceclofenac (20 mg/kg, i.p) (n = 6)

2.2. Experimental protocol

Animals were anesthetized via intraperitoneal injection of 1.25 mg/kg of urethane. Then animals were placed into a stereotaxic apparatus. Following the incision of the scalp from the midline, two holes were opened to place the stainless steel screw electrodes over the left fronto parietal cortex. For injection of penicillin, another hole in left cortex (3.0 mm lateral to the midline, 2.0 mm posterior to Bregma and 3.2 mm below the surface of the skull) was opened. The electrodes were attached to Bio-amplifier (Animal Bio Amp, ML136, ADInstruments) and the recording device (PowerLab 16/SP, ADInstruments, Australia). Filter settings were set as follows; 0.3–100 Hz Low and High Pass Filter, 50 Hz notch filter.

Penicillin G potassium (I.E Ulagay) was dissolved in distilled water (0.0670g in 0,5 ml distilled water). The seizure activity was triggered by penicillin G potassium (500 units, i.c). Biofenac (Almirall) tablets, obtained from a retail pharmacy, was dissolved in artificial cerebrospinal fluid (aCSF) (7.305 g NaCl, 0.373 g KCl, 0.170 g KH_2PO_4, 0.367 g $CaCl_2.2H_2O$, 0.308 g $MgSO_4.7H_2O$, 2.160 g $NaHCO_3$, 1.8 g D(+) glucose for 1000 ml solution). After stabilization of ECoG activity in 30 min, aceclofenac was injected intraperitoneally at doses of 10 mg/kg and 20 mg/kg. ECoG activity was recorded for 3–4 h (Fig. 1).

2.3. Statistical analysis

Statistical analysis were performed by SPSS software version 22.0. Electrophysiological data were analyzed using Chart program (Version 7.3.7). After the injections of drugs, data were calculated in 10 min periods during three hours. Values are expressed as means ± S.E.M. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. Results were considered significant at confidence limits of $p < 0.05$.

3. Results

Penicillin (500 units) was used to induce the epileptiform activity. Approximately 30 min after administration of penicillin doses, the activity reached a constant level. Epileptiform activity last about for 4–5 h. The mean of spike and amplitude of the epileptiform activity were 36.71 ± 1.54 spike/min and 0.853 ± 0.22 mV, respectively.

We investigated the effects of aceclofenac 10 mg/kg and aceclofenac 20 mg/kg on penicillin-induced experimental epilepsy in rats. About 30 min after penicillin administration, aceclofenac doses were separately injected. The mean spike frequency and amplitude of aceclofenac 10 mg/kg were 41.89 ± 2.12 spike/min and 0.619 ± 0.094 mV, respectively. In the presence of aceclofenac 10 mg/kg, the mean of spike frequency increased in the 40 min, but it became statistically significant after 60 min. On the other hand, mean of amplitude decreased during 40 min and exhibited significance in the range of 10–160 min (Figs. 2 and 3). The mean spike frequency and amplitude of aceclofenac 20 mg/kg were 35.26 ± 2.72 spike/min and 0.843 ± 0.089 mV, respectively. Administration of aceclofenac 20 mg/kg did not cause any change in the mean spike frequency of epileptiform activity. Effects of ace-