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Anticonvulsant Effect of Celecoxib in Mice Induced by PTZ

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Abstract: The cyclooxygenases (COXs), the key enzymes that convert arachidonic acid to prostaglandins (PGs), have been implicated in physiological and pathophysiological functions in the CNS. NSAIDs (non-stesoidal anti-inflammatory drugs), COX inhibitors, are used largely to treat febrile condition, pain state and for prevention of and therapeutics of many diseases. However the role of PGs and NSAIDs in the seizure activity has been disputed. The aim of this study was to evaluate the effect of intraperitoneal injection of different doses of Celecoxib on PTZ-induced seizure threshold in mice. Mice were divided randomly into 9 groups: the first group received normal saline (i.p) (control group); the second group received carboxymethylcellulose (CMC) 0.5% (i.p) (vehicle group) and the next groups received respectively different doses of Celecoxib (1, 5, 10, 15, 20, 25 and 30 mg/kg b.wt. i.p) 45 minute before determination of seizure threshold induced by PTZ.Results showed that PTZ-induced seizure threshold in control mice was 34.75±1.54 mg/kg b.wt. Intraperitoneal injection of Celecoxib showed significant ($P<0.05$) increase of PTZ-induced seizure threshold in a dose dependently manner compared with control group. According to our results, Celecoxib has anticonvulsant effects on mice. Nevertheless, new studies must be carried out in order to determine the beneficial effects of NSAIDs in treatment of epilepsy.

Key words: Celecoxib · Seizure · PTZ · Threshold · Mice

INTRODUCTION

Epilepsy is one of the major neurological diseases in humans and about one percent of the population is involved. Neuroinflammation is an important mechanism in the defense response to pathogenic events, traumatic injury and environmental toxins, but it is also recognized as a major contributor to various neurological and neurodegenerative diseases such as seizure. An innate immune response is mediated by microglia that contributes to the progression of the diseases. Activated microglia produce several proinflammatory and neurotoxic mediators including complement, cytokines, chemokines, acid arashidonic and its metabolites and reactive oxygen and nitrogen species, several of which contribute directly to neuronal injury [1]. Alterations in the microenvironment such as microglial inflammation and the release of proinflammatory cytokines may affect normal cell proliferation and differentiation, which could cause ectopic neurogenesis, astrogliosis and ectopic synaptic reorganization [2]. Inflammatory processes have been implicated in both acute and chronic neurodegenerative conditions such as epilepsy [3].

The cyclooxygenases (COX) are the principle and obligatory enzymes in the synthesis of prostaglandins (PGs) and other prostanoids and also the key targets for anti-inflammatory drugs [3]. Although cyclooxygenases, the key enzymes that convert arachidonic acid to prostaglandins (including PGE_2, PGD_2, $PGF_2\alpha$, PGI_2 and thromboxane A2), have been implicated in physiological and pathophysiological functions in the CNS, the cellular mechanisms by which COX reaction products are involved have yet to be elucidated [4]. NSAIDs (non-stesoidal anti-inflammatory drugs), COX inhibitors, are used largely to treat febrile condition, pain state and for prevention of and therapeutics of many diseases. However the role of PGs and NSAIDs in the seizure activity has been disputed [5]. The enzyme exists as constitutive (COX-1) and inducible (COX-2) isoforms, being the latter a major player in inflammation [6]. In the brain, COX-2 expression has been associated with inflammatory and neurodegenerative processes of several human neurological diseases [6]. Reports indicated the up-regulation of cyclooxygenase enzyme following seizure activity [7]. In the CNS, COX-2 is mainly expressed in glutamatergic neurons particularly with in the

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hippocampus and cerebral cortex, the areas that demonstrate prominent role in the onset of seizures [8]. It was found that COX-2 regulates cell membrane excitability and long term synaptic plasticity in the hippocampus [4], suggesting that COX-2 may play a critical role in convulsive states. However, results of previous studies about the role of COX-2 in the genesis and maintenance of convulsion are controversial; for instance both proconvulsant and anticonvulsant role for COX-2 has been reported in kainic acid-induced seizure [5]. Also, overexpression of COX-2 has been associated with neurotoxiticy in acute conditions, such as hypoxia/ischemia and seizures, as well as in chronic neurodegenerative diseases, including amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease [6]. Animal models of CNS injury have described a pivotal role for COX-2 in promoting neuropathology [9]. Furthermore, the induction of astrocytic COX-2 was observed in epilepsy patients with hippocampal sclerosis and the concentrations of PGs increased in the cerebrospinal fluid of these patients [10]. In one model of lithium chloride and tacrine induced status epilepticus seizures, there was an increased expression of COX-2 enzyme protein particularly, in dorsal hippocampus, further resulting in elevated brain PGE_2 levels [11]. In another study, COX-2 induction was found to be responsible for epileptic neuronal injury and that selective COX-2 inhibitors are neuroprotective [12]. During kainic acid-induced seizure, the $PGF_2\alpha$, PGE_2 and PGD2 was increased in the brain after a few minutes. Especially $PGF_2\alpha$ was the highest concentration in hippocampus following systemic kainic acid administration and the highest level of PGF2α reaches 30 min [13]. The drugs that inhibit COX-2 activity, such as indomethacin and selective COX-2 inhibitors, could reduce hippocampal cell death and seizure frequencies in several animal models of epilepsy [14-16]. Thus, drugs that reduce the production of PGs may have useful therapeutic effects in epilepsy. Most of the reports point to the anticonvulsant effects of NSAIDs focused on about orally administration of these drugs. With this background, the aim of this study was investigated the anticonvulsant effect of intraperitoneally administration of Celecoxib, a COX inhibitor, against PTZ-induced seizure threshold in mice.

MATERIALS AND METHODS

Animals: Experiments were performed on 22-25 g adult NMRI male mice in their 8-9 weeks (n=8 for each group), purchased from Razi Institute (Iran). Animals were housed 8 per cage in the Animal House of Veterinary Faculty of Tabriz Branch, Islamic Azad University in a temperature (20-22°C) and humidity (50±10%) controlled environment under a 12-hour light/dark cycle (lights on at 7 am). Food and water were available *ad libitum*. This study was performed in accordance with the Guide for the Care and Use of Laboratory Animals of Research affairs of Tabriz University of Medical Sciences, Tabriz, Iran. All efforts were made to minimize the number of animals which were used and their suffering degree. Animals were divided into 9 groups randomly: the first group received saline normal saline (i.p) (control group); the second group received carboxymethylcellulose (CMC) 0.5% (ip) (vehicle group) and the next groups received respectively different doses of Celecoxib (1, 5, 10, 15, 20, 25 and 30 mg/kg i.p) 45 minutes before PTZ-induced seizure threshold.

Chemicals: PTZ (Pentylenetetrazole) and Celecoxib were provided from Sigma-Aldrich. All other reagents were of analytical grade. Celecoxib was prepared by being suspended in 0.5% carboxymethylcellulose (CMC) and the vehicle group was given an equal volume of vehicle.

PTZ-Induced Clonic Seizure Threshold: Behavioral experiments were done in a quiet, temperature-controlled (20-22°C) room between 10 am and 4 pm. PTZ-induced clonic seizure threshold was determined by inserting a 30-gauge needle into the tail vein of mice and infusion of 0.5% PTZ solution at a constant rate of 1 ml/min to unrestrained freely moving animals. Minimal dose of PTZ (mg/kgb.wt.) needed to induce forelimb clonus followed by full clonus of the body was recorded as an index of clonic seizure threshold [17, 18].

Data Analysis: Group data are presented as mean±SEM and analyzed statistically using student test. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. The level for statistical significance was set at a $P<0.05$.

RESULTS

PTZ-induced seizure threshold in control mice was 34.75±1.54 mg/kg b.wt. In vehicle group, CMC have not shown significant change on PTZ-induced seizure threshold compared with control group (Fig. 1). Intraperitoneal injection of Celecoxib showed significant ($P<0.05$) increase of PTZ-induced seizure threshold in a dose dependently manner compared with control and vehicle groups (Fig. 1).

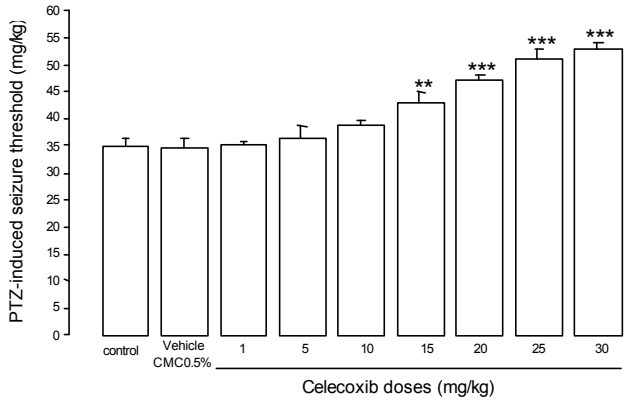

Fig. 1: PTZ-induced seizure threshold in mice (mg/kg). Effect of intraperitoneally injection of different doses of Celecoxib on seizure threshold. Each column represents mean±SEM of 8 mice. **P<0.01 and ***P<0.001 compared with control and vehicle groups.

DISCUSSION

Pentylenetetrazole (PTZ) has been used widely to produce the animal model of chemically induced seizure because this model is highly sensitive for comparing different chemical under standardized conditions [17, 18]. In this study PTZ-induced seizure threshold in control mice was 34.75±1.54 mg/kg and pretreatment with Celecoxib significantly increased the PTZ-induced seizure threshold in a dose dependently manner in mice. Previous studies have been demonstrated the protective effect of COX-inhibitors in various models of epilepsy in animals [11, 19-22], but effects of intraperitoneally injection of different doses of NSAIDs have not shown. The Effect of COX inhibitors on neuronal death also is disputed. It has been reported that the pretreatment of COX-2 inhibitors including celecoxib aggravated kainic acid-induced seizure activity in rodents and aggravated kainic acid-induced neuronal death in the hippocampus [23]. The broad COX inhibitor such as ibuprofen caused deficits in spatial learning in a water maze [24], whereas several reports showed the post-treatment of COX-2 inhibitors restored the memory deficit and learning behaviors and prevented seizure-induced neuronal death [15, 25, 26]. The effects of COX-2 inhibitors on the PTZ-induced seizures are also controversial; Dhir and coauthors reported the anticonvulsant effect of COX-2 inhibitors [11, 20], while Akasura and coauthors showed that COX-2 inhibitors have neither anticonvulsant nor proconvulsant effects on PTZ-induced seizures [27]. Treatment with indomethacin, a COX-inhibitor offered full recovery in the E1 mouse, a genetically prone mouse [28]. In one other report, nonselective COX-inhibitor such as indomethacin, aggravated kainic acid-induced seizure activity and the following hippocampal neuronal death [23]. Dhir *et al.* [11] also reported that COX inhibitors, viz. nimesulide and rofecoxib, administered 45 min prior to an epileptic challenge prolonged mean onset time of convulsions, decreased duration of clonus and decreased mortality rate against bicuculline-and picrotoxin-induced convulsions in mice [21, 22]. Different classes of NSAIDs like indomethacin, flurbiprofen and diclofenac were shown to decrease the LD_{50} and threshold for the PTZ-induced convulsion in mice. Based on these observations and the evidence that peripheral or intracerebral administration of PGs antagonized chemically-and electrically induced convulsions, it was suggested that endogenous PGs may exert anticonvulsant effect. In contrast, findings from other studies indicated that PGs may have proconvulsant effect as some NSAIDs, like paracetamol and diclofenac were found to increase the latency to onset of PTZ-induced seizures in mice as a result of blockade of PGs synthesis. Confirming this line of thinking, some studies have reported a potentiating effect of certain NSAIDs on concomitantly administered antiepileptic drugs in MES and PTZ seizure tests [29]. COX-2 inhibitors such NS-398, indomethacin, diclofenac and celecoxib aggravated significantly seizure activity in animal model, especially kainic acid-induced seizure model [23]. There were some evidences, in which Shafiq *et al*. [16] showed that there was an increase in percentage protection when celecoxib was combined with standard antiepileptic drug such as phenytoin against electroshock-induced convulsions [17]. Tu *et al.* [30] also demonstrated that the COX-2-selective inhibitor nimesulide attenuated kindling development [30]. In the other studies, effects of COX2 inhibitor on seizure activity are different according to seizure models,

types of NSAIDs and methods of administration [19, 31]. In electroshock convulsion, celecoxib showed anticonvulsant action [16] and also posttreatment of celecoxib improved learning and memory deficit [25]. Nimesulide and rofecoxib were reported to aggravate kainic acid-induced seizures and reduce the cell loss. However those authors reported rofecoxib did not reduce memory deficit and delayed neuronal death [32]. In associated with febrile seizure, the potent COX inhibitor has more disadvantage of seizure activity than weak COX inhibitor [33]. However the preventive use of ibuprofen as a safe NSAID used largely worldwide for recurrent febrile seizure was not recommended. Ibuprofen also induced the learning and memory deficit. These cumulated data shows that NSAID including COX-2 inhibitors might be harmful especially in seizure conditions [5].

The molecular mechanisms of the anticonvulsant and neuroprotective effects of NSAIDs (COX-inhibitors) have not been fully clarified, but evidences tend to suggest the possible involvement of ã-amino butyric acid (GABA) because rofecoxib and nimesulide (both COX-2 inhibitors) potentiated the anticonvulsant effects of subprotective dose of diazepam and muscimol, both GABAergic modulators [3]. Similarly the effect of tiagabine, a GABA reuptake inhibitor and a newer antiepileptic was also potentiated by rofecoxib [11]. Such similar studies have been reported by Tandon *et al.* [34] against electro-and chemoconvulsions, respectively [34]. In other study, the combined effect of rofecoxib and topiramate had a synergistic action in protecting against PTZ-induced convulsions, has been reported. Topiramate is a antiepileptic agent and is reported to enhance GABA-evoked whole cell Cl^- currents in mouse cerebral cortical neurons in culture. Besides enhancement of GABA-mediated Cl^- fluxes into neurons, topiramate is also considered to produce its antiepileptic effect through several other distinct mechanisms, including modification of Na^+ and/or Ca^{2+} dependent action potentials and inhibition of kainate-mediated conductance at glutamate receptors of the AMPA/kainate type. Therefore, rofecoxib when administered concurrently with topiramate displayed synergistic effect, indicating that both the drugs acted through the same mechanism [3]. In study of Zhang *et al*. [2] NS398, a selective cox-2 inhibitor, increased the frequency of mIPSCs and the decay-time constant. Bicuculline completely blocked mIPSCs, indicating that these synaptic events were mediated by GABAA receptors. These results indicate that NS398 clearly enhances GABAergic transmission in the hippocampus. Also the Western blotting analysis results showed that celecoxib upregulated the expression of GABAA receptors protein. COX inhibitors might be acting through GABAergic neurons, thus increasing the inhibitory neurotransmitter and the expression of GABAA receptor protein [2]. Furthermore, arachidonic acid which is metabolized to prostaglandins by cyclooxygenases and has been proposed to be a diffusible second messenger in the CNS with a pathophysiological role in epilepsy. This is possibly due to the ability of arachidonic acid to enhance extra-neuronal glutamate concentration. Cyclooxygenase induction lead to the increase in prostaglandins levels particularly PGE2, which may facilitates glutamate release from the nerve terminal and astrocytes. Glutamate is an excitatory neurotransmitter that can leads to decrease in GABA input, results in convulsions. Therefore, it may be conceived that COX inhibitors is acting through glutamate and GABAergic modulation [11]. Other mechanisms by which PGE2 could indirectly contribute to synaptic plasticity include modulation of adrenergic, noradrenegic and glutamatergic neurotransmission and regulation of membrane excitability [6]. The possibility is that activation of cyclooxygenases causes increases in free-radical production, leading to oxidative stress and apoptosis of GABAergic neurons, thus increasing glutamate and causing epileptic discharges. Also COX-2 may play a role in excitatory synapses, as excitatory amino acid agonists such as NMDA induce strong COX-2 immunostaining in many regions of the limbic cortex and isocortex, hippocampus and amygdale [2]. Furthermore, NMDA-receptor-induced c-fos expression is prostaglandin-dependent and the calcium-dependent activation of cyclooxygenases results in superoxide production [35].

The results of the Zandieh *et al*. [36] study indicated that the selective COX-2 inhibitor, celecoxib attenuates seizure induced by PTZ. Co-administration of sub-effective doses of L-NAME and celecoxib protected the animals against PTZ. In addition, L-NAME improved the anticonvulsant activity of celecoxib significantly. L-arginine at the dose which was not able to influence PTZ-induced convulsion, blunted the anticonvulsant effect of celecoxib. In the CNS, NO behaves as a multifunctional messenger and neurotransmitter, influences various physiological and pathological functions. The main intracellular action of NO is activation of the soluble guanylate cyclase which leads to the formation of cycline guanine monophosphate (cGMP) in the CNS. An increase in cGMP follows stimulation of L-glutamate receptors mainly of the NMDA type. It has been shown that NO as a retrograde messenger that is synthesized postsynaptically and acts on presynaptic

terminals, plays an important role in hippocampal LTP. Further, there is direct evidence from hippocampal cultures that NO can potentiate synaptic transmission. In addition, It has been reported that PTZ kindling in mice is associated with an increase in the amount of neuronal NOS. In concordance with aforementioned findings, NO is considered to be involved in the pathophysiology of epilepsy, although the results of experiments carried out by several authors are often conflicting. Different findings may arise as a consequence of discrepancies in the kinds of drugs, the model of seizures and the species of animals used in experiments. In study of Zandieh *et al*. [36] showed that L-NAME, a drug that inhibits all subtypes of NOS non-specifically, attenuates PTZ-induced convulsion dose-dependently which is consistent with previous studies. There are evidences implying the possible interaction between NO and COX pathways in some pathophysiological states including osteoarthritis, angiogenesis, renal perfusion and endotoxin-induced cardiomyopathy [36].

Salvemini *et al*. [37] reported that COX activity is regulated by NO. They found that NO directly increases COX-1 activity which leads to increase in prostaglandin E2 production. Similarly, it has been reported that inhibition of NOS inhibits not only NO but also prostaglandin production, suggesting that COX enzymes are targets for pathophysiological roles of NO [37].

Rimoli *et al*. [38] have been shown that two imidazo[1,2-b]pyridazine derivatives, namely DM1 and DM2 are completely devoid of COX-1 and COX-2 inhibitory activity, but are effective in suppressing spike and wave discharges (SWDs) in WAG/Rij rats, a genetic rodent model of absence epilepsy, similar to what was described for their structural congener indomethacin (IDM), which significantly decreased SWDs in these rats. As T-type channel blockade has been considered as an electrophysiological feature common to antiabsence drugs, they also investigated whether DM1 and DM2 COX-independent antiseizure effect could depend on T-type channel blockade and they found that these compounds are indeed powerful T-type channel blockers and that this property is displayed by IDM as well. The Rimoli *et al*. [38] paper showed that IDM suppresses SWDs *in vivo* in a rat model of absence epilepsy and blocks CaV3.1 channels *in vitro* [38].

Ion channel blockade is probably one of the best examples of such a COX-independent action of NSAIDs. Several published studies already demonstrated that other members of the NSAID superfamily do affect the activity of ion channels by a direct interaction with channel subunits as it has been shown, for instance, for acid sensitive channels [39] are directly blocked by aspirin, diclofenac and flurbiprofen; high voltage activated $Ca2^{+}$ channels [40], voltage gated Na^{+} channels [41] activity is increased by celecoxib; chloride channels [42], KCNQ channels [43] and hERG channels [44] are activated by fenamates. Therefore, COX inhibitors may have useful therapeutic effects in seizure. Nevertheless, new and completely studies must be carried out in order to determine in more detail the beneficial actions of NSAIDs regarding the reduction of epilepsy.

CONCLUSION

According to our results, Celecoxib has anticonvulsant effects on mice. Probably any tendency to inhibit the COX-2 enzyme by NSAIDs to be more, neuroprotective and anticonvulsant effect of drugs will be higher. Nevertheless, new studies must be carried out in order to determine the beneficial effects of NSAIDs in treatment of epilepsy.

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