Kainic acid (KA) induced epileptic seizures in mice is a commonly used experimental model of epilepsy. Previous studies have suggested the roles of various neurotransmitters and oxidative stress in KA-induced seizures. An important role of hypothyroidism has also been suggested in epilepsy. Thiamazole (TZ) is an anti-hyperthyroid drug with antioxidant property. This study reports the effect of TZ on KA-induced epileptic seizures in mice, produced by intraperitoneal (IP) injection of KA (18 mg/kg). Prior to KA injection, the animals were treated with TZ (12.5, 25 and 50 mg/kg IP). Our results showed that in KA alone group, about half of the animals developed seizures. Pre-treatment of mice with TZ significantly increased the frequency of seizures in dose-dependent manner. Administration of TZ significantly reduced the latency time and aggravated the severity of seizures. TZ also increased the mortality in KA-treated mice. Striatal dopamine and serotonin levels were markedly increased in KA alone treated mice, which were not significantly affected by TZ treatment. Among the indices of oxidative stress, we observed a significant reduction in cerebral vitamin E whereas the levels of cerebral malondialdehyde and conjugated dienes were significantly increased in animals with high severity of seizures. In conclusion, TZ potentiated the frequency and severity of experimental seizure in mice. There is a possibility of altered metabolism of KA in presence of TZ that might have potentiated the toxicity of KA. These findings suggest a caution while administering anti-hyperthyroid drugs in epileptic seizures.

1. Introduction

Epilepsy is a chronic neurological disorder, characterized by spontaneous and recurrent bursts of neuronal hyperactivity (seizures) generally arising in restricted regions of the brain. Seizures may either confined to their area of origin or spread to the whole cerebral hemispheres. Seizures have been traditionally characterized as an imbalance between excitatory and inhibitory neurotransmission. The outcomes of seizure mainly depend on the regions of brain that are affected by hyper activity (Bozzi and Borrelli 2013). Kainic acid (KA) is known to produce epileptic seizures in rodents as a result of selective degeneration of neurons that causes behavioral abnormalities (Ben-Ari, 1985, McKhann et al 2003, Tripathi et al 2009). As a potent agonist of glutamate receptors, KA produces excitotoxic damage of brain neurons (Chihara et al 2009, Wang et al 2005). The neurotransmitters including dopamine (DA), serotonin (5-HT) and acetylcholine have been implicated in seizure activity. Molla-Hosseini et al. (1985) suggested that KA-neurotoxicity is due in part to its effects on
GABA- and DA neurotransmissions. There are several other animal models of epilepsy and seizures with their own merits and demerits, as reviewed earlier (Loscher 2011).

Thiamazole (TZ) is an anti-hyperthyroid drug. Several studies have shown that hypothyroidism caused by TZ administration produces developmental abnormalities in cerebral regions of offspring animals (Berbel et al 2001, El-Bakry et al 2010). In brain cerebrum, the consumption of oxygen was found to be significantly reduced in hypothyroid state, possibly due to the decreased free mitochondria biogenesis (Martinez et al 2009). Exposure of KA to hypothyroid animals failed to decrease the population of CA3 hippocampal cells (Alva-Sánchez et al 2004). A decrease in hypothyroidism diminished the release of glutamate in hippocampus due to the reduced synthesis of glutamate (Sánchez-Huerta et al 2012). Thyroxin (T4) treatment sufficiently protected hippocampal nerve growth factor (NGF) expression and branching of dendrites to preserve normal behavior (O'Hare et al 2015).

In this investigation, we studied the effects of TZ on experimental epileptic seizures induced by KA in mice. We also analyzed the striatal levels of neurotransmitters, DA and 5-HT and determined different indices of oxidative stress in mice cerebrum.

2. Material and method

2.1. Animal and treatments

This study was performed in male Balb mice, weighing 30 ± 3 g. The mice were kept in a temperature- and humidity-controlled facility with 12-hour cycles of light and darkness. The animals had free access to chow food and clean water. The protocol of this study was approved by our Institutional Review Committee (No. HN201900233).

The mice were grouped into 6 groups of 7 mice in each group. The animals in the control group were given saline only whereas drug alone group received TZ (50 mg/kg body weight). Experimental seizure was induced by IP injections of KA (18 mg/kg) in 4 experimental groups of mice; 3 of which were treated with three different doses of TZ (12.5, 25 and 50 mg/kg), 30 min before KA injections.

The incidence, latency and seventy of seizure was recorded. The seizure severity of was graded as 0 (no seizure), 1 (low), 2 (mild), 3 (moderate) and 4 (severe). The mice were sacrificed and brains were dissected out for analyses of neurotransmitters (dopamine and serotonin) in striatum and indices of oxidative stress such as vitamin E, malondialdehyde (MDA), glutathione (GSH) and conjugated dienes (CD) in cerebrum. Sera samples were analyzed for thyroid function test parameters including free thyroxin (FT4) and thyroid stimulating hormone.

2.2. Analysis of neurotransmitters in striatum

The levels of dopamine (DA) and 5-HT were analyzed in striatum of mice using chromatographic method (Tariq et al 1999, 2001). The striata were ground in 300 μl of perchloric acid (0.10 M) and EDTA (0.05%). After centrifugation (10000 rpm for 10 min) of homogenate and filtration (0.45 μm filter) of supernatant, the filtrates were injected (10 μl) to HPLC C-18 Bondapak column and the neurotransmitters were detected using an electrochemical detector. The mobile phase consists of a mixture of 0.1 M citric acid monohydrate, 0.1 M sodium acetate, 7% methanol, 100 mM EDTA and 0.01% sodium octane sulfonic acid. The flow rate of mobile phase was maintained at 1 ml/min.

2.3. Analysis of vitamin E in cerebrum

The levels of vitamin E in brain cerebrum were analyzed by high performance liquid chromatography (HPLC) according to method described earlier (Dexter et al 1992). Cerebral samples were homogenized with Tris buffer (50 mM, pH 7.6) containing 1.50% pyrogallol. The homogenate was incubated at 70 °C and 150 μl of 10 M potassium hydroxide were added followed by further incubation at 70 °C for 30 min. The contents were cooled to room temperature and extracted with hexane. After separation of organic layer by centrifugation, the aqueous fraction was further extracted with hexane. Both the extracts were added together and evaporated under nitrogen and then kept frozen until analyzed by HPLC using a Bondapak C-18 column and 95% methanol as a mobile phase. The flow rate of mobile phase was set at 1.5 ml/min and the absorbance was measured at 280 nm following 10 μl sample injection.

2.4. Analysis of glutathione in cerebrum

The analysis GSH in cerebrum was performed as reported previously (Owen 1980, Khan et al 2012). After homogenizing the tissue in 0.2 M perchloric acid containing 0.01% EDTA, the homogenate was centrifuged at 8000g for 5 min, and the supernatant was used for analysis. The reaction mixture consisted of 100 μl of supernatant + 800 μl of 0.3 M reduced nicotinamide adenine dinucleotide phosphate (NADPH) + 100 μl of 6.0 mM 5,5-dithiobis-2-nitrobenzoic acid (DTNB) + 10 μl of 50 units/ml glutathione reductase in a phosphate buffer (pH 7.50). The absorbance was recorded for a period of 2 min at 412 nm at 30 °C. The level of GSH was determined using the standard curve of GSH.

2.5. Analysis of malondialdehyde in cerebrum

The level of malondialdehyde (MDA) in cerebrum was analyzed spectrophotometrically (Ulley et al 1967, Khan et al 2012). After homogenizing the tissue (10% w/v) in 0.15 M potassium chloride, the tissue homogenates were incubated at 37 °C for 2 h and then 1.0 ml of trichloroacetic acid (10% w/v) was mixed. The contents were centrifuged (3000 rpm,10 min) and aliquots of the clear supernatant were mixed with 1 ml of thiobarbituric acid (0.67%) and placed in a water bath (95 °C) for 10 min, cooled to room temperature and diluted with distilled water. The absorbance was measured at 535 nm and tetraethoxypropane was used as external standard, for calculation of MDA concentration.

2.6. Analysis of conjugated dienes in cerebrum

The levels of conjugated dienes (CD) were measured spectrophotometrically (Handelman et al 1988, Tariq et al 1998). The cerebral tissue was homogenized with 1.0 ml of ethanol containing 1.2% pyrogallol. The homogenates were saponified by mixing with 150 μl of 10 M KOH and acidified to pH 3.0 using 1.0 M HCl. The contents were extracted with 3.0 ml of hexane. After evaporation under liquid nitrogen, the residue was reconstituted with 2.5 ml of cyclohexane. The concentration of CD was measured by recording the absorbance at 233 nm.

2.7. Thyroid function test

The thyroid function test parameters including FT4 and TSH were determined in sera samples using commercial ELISA kits (Boehringer Mannheim), according to manufacturer’s instructions.

2.8. Statistics

Data are expressed as means ± standard error of means. The frequencies of seizure incidence and mortality rates are given as percentage. For multi-group statistical comparisons, we used analysis of variance (ANOVA) and Dunnett’s post-hoc test was used for comparing means. The incidence and mortality rates were tested
by Fisher's exact test (Khan 2003). A P value < 0.05 rejected the null hypothesis.

3. Results

3.1. Effect of TZ on seizure incidence and severity

Injection of KA (in a single dose) produced seizures in 55% of animals. Pre-treatment with TZ significantly increased the frequency of seizures in a dose-dependent manner; higher dose of TZ (50 mg/kg) rendered all the KA-treated mice to be epileptic (Fig. 1). The onset of seizures in KA alone group was observed after 30.68 ± 0.45 min. The latency of seizures was significantly and dose-dependently reduced by pretreatment with TZ, while the onset of seizure was about 10 min earlier in mice treated with KA and high dose of TZ (ANOVA, F = 136.334, P < 0.001) (Fig. 2a). The KA dosage used in this study caused mild seizures with the severity index of 1.2 ± 0.2, which was significantly and dose-dependently aggravated by pretreatment with TZ (ANOVA, F = 18.798, P < 0.001) (Fig. 2b). The mice receiving higher dosage of TZ (50 mg/kg) plus KI exhibited a high severity index (3.66 ± 0.16) (Fig. 2b).

3.2. Effect of TZ on animal mortality

Only one animal died in KA alone treated group whereas combined treatment of KA and TZ appeared to be more lethal and the high dose of TZ resulted in 55.55% mortality in KA-treated mice (Fig. 1). There were no seizures and mortality in control and TZ alone treated mice (Fig. 1).

3.3. Effect of TZ on thyroid function test

Administration of TZ (50 mg/kg) reduced the levels of serum TSH as compared to TSH levels in control animals; this difference was statistically significant (ANOVA, F = 7.120, P < 0.001) (Fig. 3a). Despite the lower dose of TZ (12.5 mg/kg) failed to affect serum TSH levels, the medium (25.0 mg/kg) and higher (50.0 mg/kg) dosages of TZ caused significant reductions in serum TSH levels in KA-treated mice (Fig. 3a). We did not observe any significant change in the levels of serum FT4 in any of the treatment groups as compared to control TSH levels (ANOVA, F = 0.833, P = 0.535) (Fig. 3b).

3.4. Effect of TZ on neurotransmitters levels

The levels of DA in striatum of control mice were 17.66 ± 0.73 μg/g, which were significantly increased post-dosing of KA (24.12 ± 1.92 μg/g) or TZ alone (23.72 ± 1.36 μg/g) (ANOVA, F = 3.690, P = 0.008). The animals receiving combined treatment of both KA and TZ showed significantly high levels of striatal DA as compared to control levels (Fig. 4a). Administration of KA alone insignificantly increased the striatal serotonin (5-HT), but the higher dosage of TZ alone significantly increased the striatal 5-HT levels (ANOVA, F = 2.904, P = 0.027). Pre-treatment with the medium and higher dosages of TZ caused significant increase 5-HT levels in mice striatum as compared to control levels (Fig. 4b).
3.5. Effect of TZ on markers of oxidative stress

Treatment of mice with TZ alone did not affect vitamin E levels in mouse cerebrum however KA alone significantly decreased vitamin E levels (ANOVA, F = 10.280, P < 0.001). The groups of mice receiving combined treatment with KA and TZ also showed significantly low cerebral vitamin E levels in comparison with control (Fig. 5a). The levels of cerebral GSH remained unaffected by any of the treatment regimens (ANOVA, F = 0.983, P = 0.442) (Fig. 5b). Although, both KA and TZ individually failed to cause any significant alteration in cerebral MDA levels, combined exposure of KA with medium and higher doses of TZ significantly increased cerebral MDA levels than the control group (ANOVA, F = 7.001, P < 0.001) (Fig. 5c). Cerebral CD levels were also not affected by the injection of KA or TZ alone, whereas, combined treatment of KA with higher dosage of TZ significantly increased cerebral CD levels (ANOVA, F = 2.860, P = 0.028) (Fig. 5d).

4. Discussion

The findings of this study revealed that TZ significantly increased the frequency (Fig. 1) and aggravated the severity of experimental seizures in mice, in a dose-dependent manner (Fig. 2). Injection of KA also increased the striatal levels of neurotransmitters dopamine and serotonin, which were potentiated by pretreatment with TZ (Fig. 4). In a previous study, TZ treatment decreased the activity of Na/K ATPase in the selective regions of brain which were related to seizure onset in rats; however, this effect was avoided by coadministration of thyroid hormone (Pacheco-Rosado et al 2005). TZ-induced hypothyroidism increased hypersensitivity to noxious stimuli, whereas the supplementation of T4 rescued the imbalance between excitatory and inhibitory transmissions in brain cortex (Yi et al 2014).

Starr (1996) has reported varying level of both dopamine and its metabolites, according to the seizure type and experimental
model. In experimental temporal lobe epilepsy, elevated level of DA (Meurs et al 2008) and high firing of dopaminergic neurons (Cifelli and Grace 2012) have been observed. The spread and onset of limbic seizures have been associated with the activation of various subtypes of DA receptors (Starr 1996). In fact, different receptor subtypes of the same neurotransmitter could have a pro- or anti-convulsant effect (Wada et al 1997). Therefore, the stimulation of various subtypes of dopaminergic and serotonergic receptors govern the origin and spread of seizures (Tripathi and Bozzi 2015).

Biassoni and Vaccari (1985) have reported that antithyroid drugs interfere with the binding of neurotransmitters to their membrane receptors in rat brain. Kainic acid produces significant increase in 5-HT metabolite (5-HIAA) levels different regions of brain including hippocampus, striatum, and frontal cortex of rats after 2 and 24 h following IP injection of KA (Osorio-Rico et al 2003). In another study, increased levels of 5-HIAA in striatum persisted for ten days following KA injection, but returned to control value, ten weeks after KA exposure (Sperk et al 1981). Naudon et al. (2001) also reported significant increases in striatal levels of homovanillic acid (HVA, a metabolite of DA) and 5-HIAA in the KI-lesioned striatum. Nicotine, a DA agonist, significantly exacerbated the pro-convulsive effect of kainic acid and decreased its CD50 (convulsive dose in 50% of animals) from 2.6 mg/kg to 1.4 mg/kg, intraperitoneally in mice (Sood et al 2011). Another study represented that an increase in receptor concentration is responsible for increased sensitivity of DA receptor in hypothyroidism (Crocker et al 1986). Nakazato and Akiyama (1997) suggested that changes in DA and 5-HT releases could have resulted due to degenerative cascade at presynaptic terminal or by some functional modifications. Moreover, TZ-induced hypothyroidism also impaired the response of vasodepressor to serotonin that could have some role in hypertension caused by hypothyroidism (Cobos-Puc et al 2020).

The results showed a high level of oxidative stress in cerebral tissues of mice receiving combined treatment with KA and TZ (Fig. 5). Excessive generation of potentially toxic free radicals together with poor antioxidant defense leads to oxidative stress that has been linked to neuronal degeneration. Lipid peroxidation due to oxidative stress has been associated with triggering inflammatory mediators and cellular damage following KA exposure (Ueda et al 2002). Several intermediates or end products of lipid peroxidation such as isofurans and isoprostanes resulted after induction by seizures could serve as sensitive markers of oxidative stress.

**Fig. 5.** Effects of TZ on KA-induced changes in cerebral vitamin E, GSH, MDA and conjugated dienes (CD). *P < .05, **P < .01 and ***P < .001 vs control, using Dunnett’s test.
stress (Patel et al. 2008). Oxidative reactions involving polyunsaturated fatty acids yield excessive amount of peroxidation product including conjugated dienes. Breakdown of these molecules produces several aldehyde types (like MDA), that can be used as indirect markers of oxidative damage.

The level of lipid hydroperoxides, tested by measuring thiobarbituric acid-reactive substances (TBARS), has been found to be reduced in hyperthyroidism but not in hypothyroid animals as compared to controls (Mano et al., 1995). There were significant reductions in the levels of antioxidant enzymes, catalase (CAT) and superoxide dismutase (SOD) in TZ-induced hypothyroid rats (Oktay et al. 2017). Ben Amara et al. (2009) also reported that TZ treatment significantly decreased the activity of glutathione peroxidase (GSH-Px), CAT and SOD, whereas the concentrations of MDA were significantly elevated in cerebrum and cerebellum. Administration of KA reduced the GSH level and increased the generation of reactive oxygen species (ROS) whereas pre-treatment with asatitic acid or maslinic acid reversed these alterations and alleviated seizure intensity in mice (Wang et al. 2018). Another drug, decursin, strongly inhibited KA-induced neurodegeneration, gliosis, and generation of oxygen-derived free radicals and attenuated kainate-induced seizure in mouse (Lee et al. 2014). Exposure of KA caused a significant depletion of GSH and reduction of GPx activity, whereas it elevated TBARS levels in brain tissues; concomitant treatment with Petasites japonicus (butternut) attenuated these effects and ameliorated the behavioral signs in KA-treated mice (Sok et al. 2006).

Pre-treatment with carophyllene, a phytochemical, not only significantly decreased seizure activity but also reduced the mortality rate in KA treated mice, by preserving antioxidant enzymes and reducing inflammatory mediators (Liu et al. 2015). Lycopene, a carotenoid, increased the activity of SOD activity and reduced MDA levels in experimental seizure induced by KA exposure (Li et al. 2019). The flavonoid rutin also showed both antioxidant and anti-convulsant properties against oxidative damage and neurotoxicity in a mouse model of experimental seizures (Nassiri-Asl et al. 2013). Kim et al. (2014) suggested that physical activity along with lipoic acid treatment is a highly effective modality for inhibiting seizures as well as oxidative injury in KA-induced seizure in mice. The anti-convulsivin pharmacological potential of sinapic acid was attributed to activation of GABA receptor and scavenging of free radicals (Kim et al., 2010).

Thiamazole inhibits iodine and peroxidase from their normal interactions with thyroglobulin (Nakamura et al. 2007) and it causes cellular protection or cellular damage (Tutuncuc et al. 2007, Bruck et al. 2007). Moreover, there are some extra-thyroidal effects of anti-thyroid drugs (Bandyopadhyay et al. 2002). TZ causes cellular damage in the liver, kidney, spleen and heart and these effects are not caused by hypothyroidism itself (Cano-Europa et al. 2011). TZ in both acute and chronic application potentiate some of the effects and ameliorate the behavioral signs in KA-treated mice (Sok et al. 2006).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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