Bupropion attenuates kainic acid-induced seizures and neuronal cell death in rat hippocampus

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A R T I C L E  I N F O

Article history:
Received 23 January 2013
Received in revised form 30 May 2013
Accepted 30 May 2013
Available online 11 June 2013

Keywords:
Bupropion
Excitotoxicity
Hippocampus
Kainic acid
Neuroprotection
Seizure

A B S T R A C T

Excessive release of glutamate is believed to be a major component of cell damage following excitotoxicity associated with epilepsy. Bupropion, an atypical antidepressant, has been shown to inhibit glutamate release from rat cerebrocortical nerve terminals. The present study was undertaken to investigate whether bupropion has anti-seizure and anti-excitotoxic effects by using a kainic acid (KA) rat seizure model, an animal model for temporal lobe epilepsy and excitotoxic neurodegeneration. Our results show that bupropion (10 or 50 mg/kg), administrated intraperitoneally to the rats 30 min before the KA (15 mg/kg) intraperitoneal injection, increased the seizure latency and decreased the seizure score. Bupropion pretreatment attenuated KA-induced neuronal cell death and microglia activation in the CA3 region of the hippocampus. Furthermore, KA-induced c-Fos expression and extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in the hippocampus were also reduced by bupropion pretreatment. These results suggest that bupropion has therapeutic potential in the treatment of seizure and other neurological diseases associated with excitotoxicity.

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1. Introduction

Epilepsy, which affects approximately 2% of people worldwide, is one of the most common brain disorders. Although the exact cause of sei

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http://dx.doi.org/10.1016/j.pnpbp.2013.05.016

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http://dx.doi.org/10.1016/j.pnpbp.2013.05.016

Abbreviations: KA, kainic acid; i.p., intraperitoneal; MAPKs, mitogen-activated protein kinases; ERK1/2, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; PBS, phosphate-buffered saline; TBS, Tris-buffered saline.
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We previously showed that bupropion depresses glutamate release from nerve endings (Lin et al., 2011), and suggested that bupropion may have a potential role in preventing excitotoxicity-induced seizure genesis. To further our understanding, in this study we used a KA-injected rat seizure model to assess whether bupropion has an anticonvulsant effect and a neuroprotective role.
2. Methods

2.1. Chemicals and reagents

Bupropion was obtained from Tocris Cookson (Bristol, UK). Rabbit monoclonal antibodies directed against phospho-extracellular signal-regulated protein kinase 1/2 (p-ERK1/2), rabbit polyclonal antibodies against phospho-p38 (p-p38) and phospho-c-Jun N-terminal kinase (p-JNK) were bought from Cell Signaling Technology (Beverly, MA, USA). Rabbit polyclonal anti-c-Fos and mouse monoclonal anti-OX-42 were purchased from Santa Cruz Biotechnology Inc. (Dallas, TX, USA) and AbD Serotec (Oxford, UK), respectively. Kainic acid (KA), and all other reagents were obtained from Sigma-Aldrich Co. (St. Louis, MO).

2.2. Animals and seizure induction

Adult male Sprague-Dawley rats (150–200 g) were used in this study and were randomly divided into four experimental groups: (1) “saline + saline” (control) group; (2) “KA + saline” group; (3) “KA + bupropion 10 mg/kg” group; and (4) “KA + bupropion 50 mg/kg” group. All animal procedures were carried out in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals, and were approved by the Fu Jen Institutional Animal Care and Utilization Committee. All efforts were made to minimize animal suffering and to reduce the number of animals used.

The experimental design is shown in Fig. 1. Seizures were induced by intraperitoneal (i.p.) administration of rats with KA (15 mg/kg) in phosphate-buffered saline (PBS). After KA administration, animals were continuously monitored for seizure activity for 4 h. Behavioral seizures were graded according to the Racine scale (Racine, 1972): stage 1, facial clonus; stage 2, head nodding; stage 3, forelimb clonus; stage 4, forelimb clonus with rearing; stage 5, rearing, jumping, and falling. Bupropion (10 and 50 mg/kg) was injected i.p. 30 min before KA injection. Time of seizure initiation and seizure scores were analyzed.

After behavioral assessment, rats were either sacrificed immediately 4 h or 3 days after KA injection with an overdose of anesthetics (chloral hydrate, 650 mg/kg, i.p.). The rats sacrificed at 4 h were used for detecting protein expression of c-Fos, whereas those for experiments of pathological and inflammatory changes (neuronal death and microglia activation) were euthanized 3 days after induction of seizure (Fig. 1A). Then, animals were perfused transcardially with saline (room temperature) followed by cold 4% paraformaldehyde in 0.1 M PBS. The brains were removed immediately and post-fixed in the same fixative overnight at 4 °C, and then cryoprotected in 30% sucrose for 24–48 h. In addition, to investigate effects of bupropion on protein expression of p-ERK1/2, p-p38, and p-JNK, another group of rats were sacrificed and perfused at different time points (0.5, 1, 2, and 4 h) after KA administration (Fig. 1B).

2.3. Neutral red and Fluoro-Jade B staining

For neutral red staining, the brains were sectioned coronally at a thickness of 30 μm in a cryostat and the sections were mounted on gelatin-coated slides, air dried and then stained with neutral red solution. Staining for Fluoro-Jade B (Chemicon, Millipore Ltd, Billerica,
MA) was performed as described previously (Schmued and Hopkins, 2000). In brief, the sections (20 μm) were mounted on gelatin-coated slides and dried at room temperature followed by a solution containing 1% sodium hydroxide in 80% ethanol for 5 min. After the slides were immersed in 70% ethanol for 2 min and in distilled water for 2 min, the sections were oxidized in 0.06% potassium permanganate for

![Image](image_url)

**Fig. 2.** Bupropion reduces KA-induced seizure behavior in rats. The rats were pretreated either with saline, or bupropion (10 or 50 mg/kg, i.p.) 30 min before KA (15 mg/kg, i.p.) injection. The seizure behavior test (seizure latency (A) and seizure score (B)) were performed during 1–4 h after KA administration, according to the methods. Data are expressed as mean ± SEM. ***P < 0.001, **P < 0.01, as compared with the KA-treated group.

![Image](image_url)

**Fig. 3.** Bupropion attenuates KA-induced neuronal death in the hippocampal CA3 region. Bupropion (10 or 50 mg/kg) was administrated intraperitoneally 30 min before KA injection, and extents of neuronal losses in the hippocampus were evaluated 3 days after KA injection by staining with neutral red (A–D) and Fluoro-Jade B (E–H). Representative photomicrographs illustrating neuronal cell death in the hippocampal CA3 region of control (A and E), KA (B and F), KA + bupropion 10 mg/kg (C and G), and KA + bupropion 50 mg/kg (D and H). (I) Quantification of Fluoro-Jade B-positive neurons in the CA3 region of the hippocampus. Data are expressed as mean ± SEM. **P < 0.01, as compared with the KA-treated group. Scale bar = 100 μm for A–H.
15 min, washed with water, and then immersed in 0.001% Fluoro-Jade B solution for 30 min in the dark. Thereafter, slides were washed in distilled water, air-dried, cleared, and coverslipped.

2.4. Immunohistochemistry

Brains were cut into 40 μm thick coronal sections in a cryostat and then free-floating staining with immunohistochemical ABC method. In brief, after being rinsed three times with PBS the sections were blocked with 2% normal goat serum containing 0.3% Triton X-100 for 1 h at room temperature. Then, the sections were incubated overnight at 4 °C with appropriate primary antibodies (rabbit polyclonal anti-c-Fos, 1:500; mouse monoclonal anti-OX-42, 1:500; rabbit monoclonal anti-phospho-ERK1/2, 1:200; rabbit polyclonal anti-phospho-p38, 1:500; rabbit polyclonal anti-phospho-JNK, 1:200). Then, sections were incubated with either goat biotinylated anti-rabbit or goat biotinylated anti-mouse secondary antibody (1:200; Vector Laboratories, Burlingame, CA) for 2 h and subsequently with ExtraAvidin peroxidase (1:1000, Sigma-Aldrich) for 1 h at room temperature. After rinsing in 0.1 M PBS for 20 min, sections were reacted with 0.025% 3,3′-diaminobenzidine tetrahydrochloride (DAB) solution in PBS containing 0.0025% hydrogen peroxide for 6 min. Finally, sections were mounted onto gelatin-coated glass slides, air-dried, dehydrated, cleared with xylene, and coverslipped with Entellan mounting medium (Merck, Darmstadt, Germany).

2.5. Western blotting

Rats were killed by decapitation and hippocampi rapidly dissected. The hippocampi were homogenized in a lysis buffer (10 mM HEPES buffer, pH 7.4), 1% Triton X-100, and protease inhibitor mixture. Lysates were clarified by centrifugation, and protein concentration was determined using a protein assay kit (Bio-Rad Laboratories, Hercules, CA, USA). Equal amounts of proteins were separated by SDS-PAGE and transferred to nitrocellulose membrane. The membranes were blocked with Tris-buffered saline (TBS) that contained 5% low-fat milk and incubated with appropriate primary antibodies (rabbit polyclonal anti-c-Fos, 1:1000; rabbit polyclonal anti-phospho-p38, 1:2000; rabbit monoclonal anti-phospho-ERK1/2, 1:2000; rabbit polyclonal anti-phospho-JNK, 1:2000) overnight at 4 °C. After three washes in TBS, the membrane was then treated with the secondary horseradish peroxidase-conjugated antibody (1:3000) for 1 h at room temperature. The membranes were then washed at least three times with TBS and visualized using the enhanced chemiluminescence system (Amersham, Buckinghamshire, UK). The level of expression or phosphorylation was assessed by band density, which was quantified by densitometry. Densitometric quantification of bands was analyzed using Syngene software (Synoptics, Cambridge, UK).

2.6. Quantification and statistical analysis

According to previous studies (Friedman et al., 1994; Park et al., 2008), the hippocampus CA3 is the most vulnerable area to excitotoxic lesions caused by kainic acid. Thus, the CA3 region was visualized under 100× magnification using an upright fluorescence microscope (Zeiss Axioskop 40, Goettingen, Germany) and digitized photomicrographs for analysis were captured with a digital camera (Nikon D80, Tokyo, Japan) between bregma −2.30 mm and −3.60 mm according to the rat brain atlas of Paxino and Watson (1998). For comparison of neuronal death between the experimental groups, the number of Fluoro-Jade B-positive cells was measured in an area of 255 × 255 μm of the hippocampal CA3 in 6 to 8 randomly chosen sections from each animal and averaged for each animals using a computer-assisted image analysis system (Image J; NIH Image, National Institutes of Health, Bethesda, MD, USA) by an examiner blind to experimental conditions. Results were expressed as mean ± SEM of labeled cells per 0.1 mm². For Western blots, the intensities of the bands were quantified by densitometry. Statistical comparisons for significance among the different groups of animals were performed by one-way ANOVA with LSD comparisons.
post hoc tests for multiple comparisons. Data are expressed as mean ± SEM. A value of p < 0.05 was considered significant.

3. Results

3.1. Bupropion pretreatment attenuates KA-induced seizures

Kainic acid (i.p.) induced epileptic seizures in 85% of injected rats, with 6% mortality. The latency and score of seizures was 61.8 ± 4.2 min and 4.6 ± 0.2, respectively (Fig. 2A and B). Administration of bupropion (10 or 50 mg/kg, i.p.) 30 min before KA administration increased the seizure latency [F (2, 47) = 28.34, P < 0.001; Fig. 2A] and decreased the seizure score [F (2, 47) = 12.653, P < 0.001]. Three of the 15 animals pretreated with 10 mg/kg of bupropion had no seizures, 7 had mild seizures (stage 2), 2 had moderate seizures (stage 3), and the remaining 3 had severe seizures (stage 5) (mean seizure score 2.3 ± 0.4; Fig. 2B). The mean latency of seizures in this group was 122.3 ± 6.7 min, which was statistically different from the seizure control group (P < 0.001; Fig. 2A). Two of the 17 rats pretreated with 50 mg/kg of bupropion had no seizures, 6 had mild seizures, 6 had moderate seizures, and 3 had severe seizures. In this group, the seizure latency (108.1 ± 5.3) and seizure score (2.6 ± 0.3) were significantly different from the seizure control group (P < 0.01; Fig. 2A and B).

3.2. Bupropion pretreatment reduces KA-induced neuronal cell death in the CA3 region of the hippocampus

The seizure-induced neuronal death after KA administration (72 h) was indicated by neutral red and Fluoro-Jade B staining. As shown in Fig. 3A and B, neutral red staining showed considerable neuronal loss in the hippocampal CA3 area in the KA-injected rats. Bupropion pretreatment (10 or 50 mg/kg) significantly attenuated the neuronal loss induced by KA (Fig. 3C and D). A similar protective effect of bupropion against neuronal death was observed with Fluoro-Jade B staining. In Fig. 3E, no staining was observed in the saline-injected rats (control). Fluoro-Jade B-positive neurons were found in the hippocampal CA3 region of KA-treated rats (P < 0.001; Fig. 3F). In rats pretreated with bupropion (10 or 50 mg/kg), the number of Fluoro-Jade B-positive neurons in CA3 was significantly decreased in comparison to KA-treated rats [F (2, 31) = 9.591, P < 0.01; Fig. 3G–I].

3.3. Bupropion pretreatment suppresses KA-induced microglial activation in the CA3 region of the hippocampus

To examine whether bupropion affected inflammatory processes in KA-injected brains, the activation of microglia was analyzed by detection of the expression of OX42, a surface marker for microglia. In saline-treated rats (control), microglial cells in the CA3 region showed a resting morphology with small cell bodies and thin processes (Fig. 4A). In contrast, in KA-injected rats, the number of microglial cells increased remarkably in the CA3 region. These cells displayed enlarged cell bodies with considerably shorter and thicker processes (indicating the activation state; Fig. 4B). KA-induced microglial activation was significantly suppressed in the animals pretreated with bupropion (10 or 50 mg/kg); most microglial cells were in a ramified or resting state (Fig. 4C and D).

3.4. Bupropion pretreatment reduces KA-induced c-Fos expression and ERK1/2 phosphorylation in the hippocampus

In Fig. 5A, very low c-Fos immunoreactivity was observed in the hippocampal region in control rats, whereas increased c-Fos immunoreactivity in the CA3 region of the hippocampus was observed 4 h after KA administration (i.p.; Fig. 5B). This KA-induced increased immunoreactivity of c-Fos protein was decreased in animals treated with bupropion (10 or 50 mg/kg, i.p.) 30 min before KA administration (Fig. 5C and D). Western blot analysis of c-Fos showed results consistent with those observed by immunohistochemistry. KA increased c-Fos expression in the hippocampus (P < 0.001); this phenomenon was decreased by pretreatment with bupropion [F (2, 7) = 46.17, P < 0.05; Fig. 5E and F].

Next, this study evaluated the effect of bupropion treatment on activation (phosphorylation) of mitogen-activated protein kinases (MAPKs) (i.e., ERK1/2, p38, and JNK) by immunohistochemistry and Western blot. In Table 1, results obtained by Western blot showed an...
increase of ERK1/2 phosphorylation in hippocampus at 0.5 h after KA administration and it was maintained for up to 4 h (P < 0.001). Increase of phosphorylation of JNK in hippocampus was seen at 0.5, 1, and 2 h after KA injection (P < 0.01), and absent at 4 h after KA injection. However, the phosphorylation of p38 in hippocampus was only increased at 0.5 h and 1 h after KA administration (P < 0.001). Bupropion administration (10 or 50 mg/kg, i.p.) 30 min before KA treatment only attenuated the phosphorylation of ERK1/2 [0.5 h: F(2, 9) = 8.739, P < 0.05; 1 h: F(2, 9) = 16.921, P < 0.05; 2 h: F(2, 9) = 44.335, P < 0.05], but it did not affect the phosphorylation of JNK [0.5 h: F(2, 9) = 0.28, P = 0.948; 1 h: F(2,9) = 0.039, P = 0.786; 2 h: F(2, 9) = 0.203, P = 0.76], and p38 [0.5 h: F(2, 9) = 0.157, P = 0.755; 1 h: F(2, 9) = 1.091, P = 0.525] (Table 1). Fig. 6A–B and E–F show that a significant increase of ERK1/2 phosphorylation in hippocampus was observed at 4 h after KA administration (i.p.) (P < 0.001), and bupropion pretreatment (10 or 50 mg/kg, i.p.) blocked the response [F (2, 12) = 24.27, P < 0.05; Fig. 6C–F].

4. Discussion

Excessive release of glutamate is known to be a critical factor in the neuropathology of epilepsy (Carlson et al., 1992; Chapman et al., 1996; Meldrum, 1994), regulating its release may be an important mechanism of antiepileptic drugs. Bupropion is used clinically as an atypical antidepressant with a mixed neuropharmacological profile (Ascher et al., 1995; Dwoskin et al., 2006; Wilkes, 2006). Since we previously found that bupropion depresses glutamate release from nerve terminals (Lin et al., 2011), we hypothesized that bupropion would have an anticonvulsant effect. This study further confirms this hypothesis by using the KA seizure model in adult rats. We chose this model because KA-induced seizure activity and brain damage are similar to human temporal lobe epilepsy (Ben-Ari and Cossart, 2000; Friedman et al., 1994; Park et al., 2008; Pollard et al., 1993). Furthermore, these KA-induced alterations are associated with the excessive release of glutamate (Chittajallu et al., 1996; Ferkany et al., 1982; Sperk, 1994).

In the present study, KA administration (15 mg/kg, i.p.) induced epileptic seizures. This is consistent with the results obtained when other groups applied the same-status epilepticus induction procedure (Friedman et al., 1994; Spigolon et al., 2010). Bupropion administered (10 or 50 mg/kg, i.p.) before KA injection resulted in an anticonvulsive effect, reducing the seizure score and increasing the latencies to onset of seizure. This is in line with previous studies, which showed that bupropion at a dosage of 15–30 mg/kg produces anticonvulsant activity and enhances the anticonvulsant potency of various anti-epileptic drugs in a mouse maximal electroshock model (Barczynski et al., 2011; Tutka et al., 2004). However, there have been reports of clonic convulsions in mice at 100–150 mg/kg of bupropion (Tutka et al., 2004, 2005). Therefore, the role of bupropion on epilepsy is apparently dependent on the administered dosage; a low dosage results in anticonvulsant activity, whereas high dosage causes convolution. In a clinical setting, bupropion is well-known to produce seizures in both patients who exceed the recommended dosage, and in patients taking it at or below the recommended dosage (450 mg/d) (Pesola and Avasarala, 2002). Further clinical testing is needed to determine whether a lower dosage of bupropion can be safely administered to patients with epilepsy.

Systemic KA administration causes neuronal death in specific brain regions, such as the hippocampus, piriform cortex, thalamus, and amygdala (Ben-Ari, 1985). In the hippocampus, CA3 pyramidal cells are most severely damaged after KA administration (Bahn et al., 1994; Friedman et al., 1994; Park et al., 2008; Pollard et al., 1993). Such a phenomenon may be attributed to the highest density of KA receptors in the CA3 region (Bahn et al., 1994). Similarly, KA-induced hippocampal damage in this study was restricted to CA3 pyramidal cells. Bupropion pretreatment (10 or 50 mg/kg) reduced this KA-induced neuronal loss, suggesting that bupropion acts as a potent neuroprotective agent in addition to being an anticonvulsant agent.

Considerable evidence suggests that KA-induced hippocampal neurodegeneration is associated with microglial activation (Avignone et al., 2008; Kim et al., 2010). Preventing microglia activation protects the hippocampus from neurodegeneration caused by KA-induced seizures (Penkowa et al., 2005). In our study, we also observed that the number of activated microglia immunostained by OX-42 antibodies in the hippocampus was significantly higher in KA-treated rats. Bupropion pretreatment reduced the number of activated microglia. Thus, bupropion can be supposed to have an anti-inflammatory function, and that this action underlies, at least in part, its neuroprotective effects. However, how bupropion affects microglial activation remains unclear. Microglial activation and the consequent production of various neurotoxic factors (including free radicals and pro-inflammatory cytokines) are believed to contribute to neuronal damage (Klegeris et al., 2007). Thus, a direct interaction between bupropion and these factors should be considered when determining the possible mechanism for the anti-inflammatory effect of bupropion.

Following KA-induced seizures, c-Fos protein is highly expressed in the hippocampus (Jynjent et al., 2009; Shin et al., 2009). This is supported by our data, which showed a significant increase in c-Fos expression in the CA3 region of the hippocampus following 4 h after KA injection. This phenomenon was found to be reduced by pretreatment with bupropion. In addition, it has been shown that the activation of MAPKs (i.e., ERK1/2, p38, and JNK) is associated with KA-induced seizures and neuronal death (Lemos et al., 2010; Mielke et al., 1999; Park et al., 2008; Spigolon et al., 2010). In the present study, we showed that KA administration activated all three kinases in rat hippocampus. However, the durations of their activation were different. Activation of ERK1/2, JNK, and p38 in hippocampus were only observed at 0.5 h after KA treatment, but, in contrast to ERK1/2

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<th>p-ERK1/2</th>
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<td>KA</td>
<td>127.8 ± 5.3***</td>
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<td>124.4 ± 2.9***</td>
<td>124.0 ± 2.3***</td>
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<td>102.8 ± 4.6*</td>
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<td>103.4 ± 4.9*</td>
<td>100.5 ± 2.2*</td>
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<tr>
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<td>107.3 ± 6.1*</td>
<td>97.1 ± 2.4*</td>
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<tr>
<td>KA</td>
<td>130.2 ± 3.5***</td>
<td>135.1 ± 9.8***</td>
<td>116.3 ± 5.5**</td>
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<tr>
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Values are percentage change of control group and expressed as mean ± SEM (n = 4 for each). Data were analyzed by one-way ANOVA followed by post hoc LSD comparison. * No detection. ** P < 0.01. *** P < 0.001, as compared with control group. * P < 0.05, as compared with the KA-treated group.
activation, which lasted for up to 4 h, the activation of JNK and p38 were transient. Our results are consistent with the findings of Jeon et al. (2000). Furthermore, we found that bupropion pretreatment reduced only the KA-induced phosphorylation of ERK1/2. Thus, these results suggest that bupropion reduces not only KA-induced seizures, but also cell death in the hippocampal CA3 region, thus reducing seizure-induced c-Fos expression and ERK1/2 phosphorylation.

5. Conclusion

Our data demonstrate that bupropion has significant anticonvulsant, anti-inflammatory, and neuroprotective effect in KA-injected rats, a well-characterized model of temporal lobe epilepsy. The relevance of our findings to in vivo clinical situations remains to be determined. However, these findings may allow us to further understand the cellular mechanisms of the action of bupropion in the brain, and to provide new avenues for the treatment of epilepsy and other neurodegenerative disorders.

Contributors

Kao-Chang Lin performed the experiments, undertook the statistical analysis; Chia-Chuan Wang was involved in data interpretation and generation of the manuscript; Su-Jane Wang designed the study, performed the experiments, undertook the statistical analysis and wrote the paper.

Acknowledgments

This work was supported by a grant from the Chi-Mei Medical Center (CMFJ10001).

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