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Effects of AS2586114, a soluble epoxide hydrolase inhibitor, on hyperlocomotion and prepulse inhibition deficits in mice after administration of phencyclidine

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ABSTRACT

Accumulating evidence suggests that soluble epoxide hydrolase (sEH) plays a key role in controlling levels of lipid signaling molecules, and that the potent sEH inhibitors may be potential therapeutic drugs for a number of diseases associated with metabolism of epoxyeicosatrienoic acids (EETs). This study was undertaken to examine whether the potent sEH inhibitor AS2586114 could attenuate behavioral abnormalities (e.g., hyperlocomotion and prepulse inhibition (PPI) deficits) in male ddY mice after a single administration of the *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP). A single oral administration of AS2586114 (10, 30, or 100 mg/kg) attenuated the hyperlocomotion in mice after the administration of PCP (3.0 mg/kg, s.c.), in a dose dependent manner. Furthermore, a single oral administration of AS2586114 (10, 30, or 100 mg/kg) improved the PPI deficits in mice after the administration of PCP (3.0 mg/kg, s.c.), in a dose dependent manner. In addition, the atypical antipsychotic drug clozapine (10 mg/kg, p.o.) significantly attenuated hyperlocomotion and PPI deficits after the administration of PCP (3.0 mg/kg, s.c.). In conclusion, this study suggests that AS2586114 may have antipsychotic activity in PCP models of schizophrenia. Therefore, it is likely that the sEH inhibitors may be potential therapeutic drugs for neuropsychiatric diseases such as schizophrenia.

1. Introduction

Multiple lines of evidence suggest that a dysfunction in glutamatergic neurotransmission via the *N*-methyl-D-aspartate (NMDA) receptors might be involved in the pathophysiology of schizophrenia (Javitt and Zukin, 1991; Olney and Farber, 1995; Coyle, 1996; Krystal et al., 1999; Hashimoto et al., 2003, 2004, 2005a, 2005b; Hashimoto, 2006; Hashimoto et al., in press). The NMDA receptor antagonists such as phencyclidine (PCP), and ketamine are known to induce schizophrenia-like symptoms including positive symptom, negative symptoms, and cognitive deficits in healthy subjects (Javitt and Zukin, 1991; Krystal et al., 1994); consequently, PCP has been used widely in animal models of schizophrenia (Jentsch and Roth, 1999; Hashimoto et al., 2005a, 2005b, 2006, 2007, 2008a, 2008b; Hagiwara et al., 2008; Tanibuchi et al., 2009).

Prepulse inhibition (PPI) of the acoustic startle response is a form of sensorimotor gating, defined as an inhibition of the startle response when a low intensity stimulus, the prepulse, precedes the startling stimulus. Deficits in PPI have been reported in several psychiatric disorders including schizophrenia, suggesting that deficient PPI per se or abnormalities in neural circuits regulating PPI may cause some symptoms of schizophrenia (Braff and Geyer, 1990; Swerdlow et al., 1994; Perry et al., 1999; Geyer et al., 2001). Therefore, pharmacological models of PCP-induced PPI deficits are excellent predictors of antipsychotic activity (Bakshi et al., 1994; Javitt and Lindsley, 2001; Yee et al., 2004; Egerton et al., 2008; Shirai et al., 2012).

Epoxide hydrolases (EHs) have been traditionally regarded as detoxifying enzymes implicated in the defense against xenobiotic-derived compounds (Arand et al., 2005). Soluble EH (sEH) is known to catalyze the hydrolysis of epoxyeicosatrienoic acids (EETs) to the corresponding dihydroxyeicosatrienoic acids (DHETs), which are believed to be less biologically active than their parent molecules (Fig. 1). Accumulating evidence suggests that sEH plays a key role in controlling levels of lipid signaling molecules, most notably of EETs known for their role in a number of biological processes (Imig, 2012; Morisseau, 2013; Morisseau and Hammock, 2013). At present, the sEH inhibitors are expected to enhance the beneficial cardiovascular properties of EETs since the cardiovascular effects of EETs include vasodilation, anti-migratory actions on vascular smooth muscle cells and anti-inflammatory actions (Fang, 2006; Imig and Hammock, 2009). Studies showed that sEH immunoreactivity was detected in astrocytes throughout the brain (Marowsky et al., 2009), and that deletion of sEH gene was protective against ischemic brain damage (Zhang et al., 2007a, 2007b, 2008). In addition, EETs were also shown to suppress inflammation (Node et al., 1999) and oxidative stress (Yang et al., 2001). Taken all together, it is likely that sEH inhibitors could

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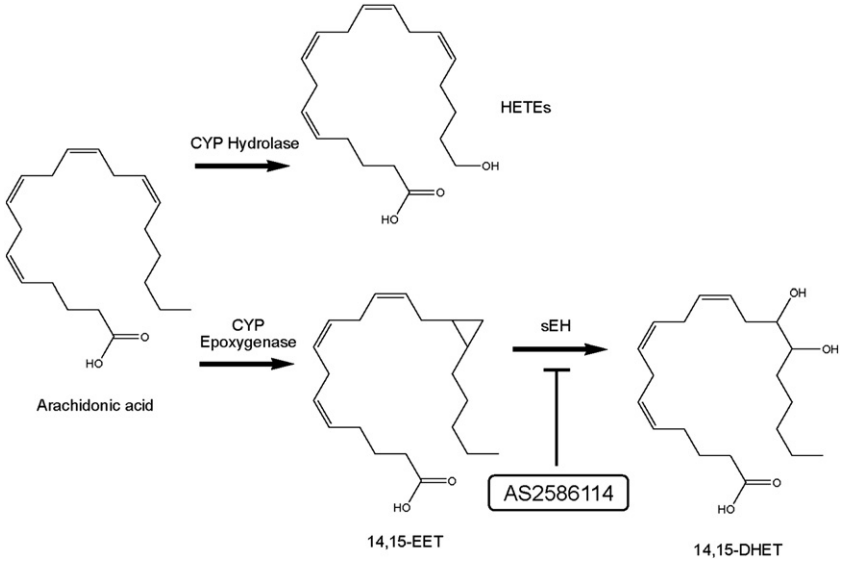

Fig. 1. Role of sEH in the metabolism of arachidonic acid. Arachidonic acid is metabolized by two cytochrome P450 (CYP) pathways; CYP hydrolase and CYP epoxygenase. The hydrolase CYP enzymes convert arachidonic acid to hydroxyeicosatetraenoic acid (HETEs). The epoxygenase CYP enzymes generate epoxyeicosatrienoic acid (EETs), by catalyzing the epoxidation of arachidonic acid olefin bond, resulting in the production of four regioisometric EETs: 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. The soluble epoxide hydrolase (sEH) converts 14,15-EET to 14,15-DHET.

produce the neuroprotective and anti-inflammatory actions in the brain, and that the sEH inhibitors would be potential therapeutic drugs for neuropsychiatric diseases.

AS2586114, 3-cyclopropyl-4-{4-[2-({[(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]methyl}amino)-2-oxoethyl]piperidin-1-yl}benzoic acid monohydrochloride (Fig. 2), is a potent sEH inhibitor (IC_{50} = 16 nM for human sEH and 5.9 nM for rat sEH) (Miura et al., 2011). A single oral administration of AS2586114 inhibited more than 99% of the activity of sEH in the blood, indicating that this compound showed a very potent sEH inhibition (Miura et al., 2011). Considering the physiological functions of sEH in the brain, we have a hypothesis that sEH inhibitor may possess antipsychotic activity in animal models of schizophrenia. The present study was, therefore, undertaken to study whether AS2586114 could attenuate hyperlocomotion and PPI deficits in mice after the administration of PCP.

2. Materials and methods

2.1. Animals

Male ddy mice (8 weeks old) weighing 25–30 g were purchased from SLC Japan (Hamamatsu, Shizuoka, Japan). The mice were housed in clear polycarbonate cages (22.5 × 33.8 × 14.0 cm) in groups of 5 or 6 per cage under a controlled 12/12-h light–dark cycle (lights on from 7:00 AM to 7:00 PM), with room temperature at 23 ± 1 °C and humidity at 55 ± 5%. The mice were given free access to water and food pellets. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, USA. The protocol was approved by the Committee on the Ethics of Animal Experiments of the Chiba University.

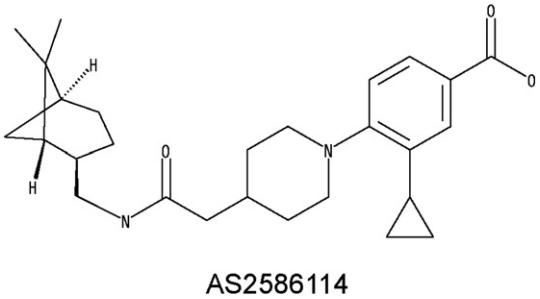

Fig. 2. Chemical structure of AS2586114.

2.2. Drugs

AS2586114, 3-cyclopropyl-4-{4-[2-({[(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]methyl}amino)-2-oxoethyl]piperidin-1-yl}benzoic acid monohydrochloride (compound Ex33 in the patent; Miura et al., 2011) (Fig. 2), was obtained from Astellas Pharma Inc. (Tsukuba, Japan), and was dissolved in 0.5% carbomethoxycellulose (CMC) (Wako Pure Chemical Co., Tokyo, Japan). Clozapine (Sigma-Aldrich Co., St Louis, MO) was dissolved in 0.5% CMC. PCP hydrochloride was synthesized in our laboratory, and the dose (3.0 mg/kg) of PCP was expressed as a hydrochloride salt. Other drugs were purchased from commercial sources.

2.3. Effects of AS2586114 and clozapine on PCP-induced hyperlocomotion in mice

Locomotor activity was measured as reported previously (Shirai et al., 2012; Zhang et al., 2007a, 2007b; Hashimoto et al., 2010; Chen et al., 2012). After habituation (60 min) in the cage, AS2586114 (10, 30 or 100 mg/kg) or vehicle (0.5% CMC, 10 ml/kg) was administered orally to mice. Sixty minutes after a single oral administration of AS2586114 or vehicle, PCP (3.0 mg/kg) or vehicle (physiological saline; 10 ml/kg) was administered s.c. to the mice. Locomotor activity was measured using an animal movement analysis system (SCANET MV-40, Melquest, Toyama, Japan). The system consisted of a rectangular enclosure (560 × 560 mm). The side walls (height, 60 mm) of the enclosure were equipped with 144 pairs of photosensors located at 6-mm intervals at a height of 30 mm from the bottom edge. An animal was placed in the observation cage 120 min from injection of vehicle or PCP. A pair of photosensors was scanned every 0.1 s to detect the animal's movements. The intersection of paired photosensors (10 mm apart) in the enclosure was counted as one unit of locomotor activity. Data collected for 4 h were used in this study.

After habituation (60 min) in the cage, clozapine (10 mg/kg) or vehicle (0.5% CMC, 10 ml/kg) was administered orally to mice. Sixty