available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Fluoxetine attenuates kainic acid-induced neuronal cell death in the mouse hippocampus

Yinchuan Jin[a], *Chae-Moon Lim*[a], *Seung-Woo Kim*[a], *Ju-Young Park*[b], *Ji-Seon Seo*[c], *Pyung-Lim Han*[c], *Sung Hwa Yoon*[b], *Ja-Kyeong Lee*[a,*]

[a]*Department of Anatomy and Center for Advanced Medical Education (BK21 project), Inha University School of Medicine, Incheon, Republic of Korea*
[b]*Division of Molecular Science and Technology, Ajou University, Suwon, Republic of Korea*
[c]*Division of Nano Sciences and Brain Disease Research Institute, Ewha Womans University, Seoul, Republic of Korea*

ARTICLE INFO

Article history:
Accepted 25 April 2009
Available online 7 May 2009

Keywords:
KA
Fluoxetine
Inflammation
Neuroprotection
NF-κB

ABSTRACT

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) and one of the commonly prescribed antidepressants. Numerous clinical observations and animal studies indicate that fluoxetine enhances the anticonvulsant potencies of several antiepileptic drugs. In the previous report, we showed that fluoxetine strongly protects against delayed cerebral ischemic injury. In the present study, the authors investigated whether fluoxetine has a beneficial effect on KA-induced neuronal cell death. An intracerebroventricular (i.c.v.) injection of 0.94 nmol (0.2 μg) of KA produced typical neuronal cell death both in CA1 and CA3 regions of the hippocampus. Although, there was no significant difference in the time course or severity of epileptic behavior, the systemic administration of fluoxetine 30 min before KA administration significantly attenuated this neuronal cell death. Fluoxetine was found to suppress neuronal cell loss when injected at 10 mg/kg and the effect was enhanced at 50 mg/kg. Furthermore, this fluoxetine-induced neuroprotection was accompanied by marked improvements in memory impairment, as determined by passive avoidance tests. KA-induced gliosis and proinflammatory marker (COX-2, IL-1β, and TNF-α) inductions were also suppressed by fluoxetine administration. It is interesting to note here that fluoxetine treatment suppressed NF-κB activity dose-dependently in KA-treated mouse brains, suggesting that this explains in part its anti-inflammatory effect. Together, these results suggest that fluoxetine has therapeutic potential in terms of suppressing KA-induced pathogenesis in the brain, and that these neuroprotective effects are associated with its anti-inflammatory effects.

1. Introduction

The administration of the excitatory amino acid L-glutamate analog, kainic acid (KA), in animals elicits characteristic patterns of epileptic behavior in a dose-dependent manner (Coyle, 1983; Sperk et al., 1985). KA-induced neuronal over-excitation triggers acute neuronal cell death in limbic structures, such as, CA1 and CA3 regions of the hippocampus

* *Corresponding author*. Department of Anatomy, Inha University School of Medicine, Jung-Gu Shinheung-Dong, 3 rd. St. 7-241, Incheon 400-712, Republic of Korea. Fax: +82 32 884 2105.
E-mail address: jklee@inha.ac.kr (J.-K. Lee).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.04.053

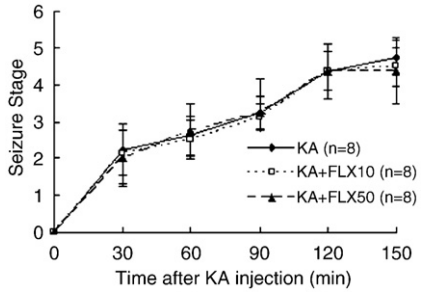

Fig. 1 – No changes in epileptic behavior by fluoxetine treatment. Fluoxetine (FLX, 10 or 50 mg/kg) was administered intraperitoneally (i.p.) 30 min before KA treatment (0.2 μg, i.c.v.). The seizure activity was scored by following the rating scale described by Sperk et al. (1985). Temporal seizure activity was presented as means ± SEMs of seizure scores of eight animals.

(Frederickson et al., 1989; Choi, 1990; Weiss et al., 2000). This process is followed by the activation of glial cells, and an insidious progress of cell death may occur over several days to weeks (Weise et al., 2005). Thus, this *in vivo* cell death model shows the features of both acute and delayed cell death within relatively limited areas in the brain. A number of recent studies have shown that the KA-induced delayed cell death is associated with the activation of microglia and astrocytes in the hippocampus, and with enhanced reactive oxygen species (ROS) production and cytokine expression (Cho et al., 2003; Kim et al., 2004; Penkowa et al., 2005).

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI), and is commonly prescribed for treating major depression due to its tolerability and safety. Furthermore, it has been reported that chronically administered fluoxetine enhances the anticonvulsant effects of conventional antiepileptic drugs in a mouse maximal electroshock model (Borowicz et al., 2007), and that dietary fluoxetine supplementation abolishes handling-induced seizure susceptibility in epileptic mice via neural

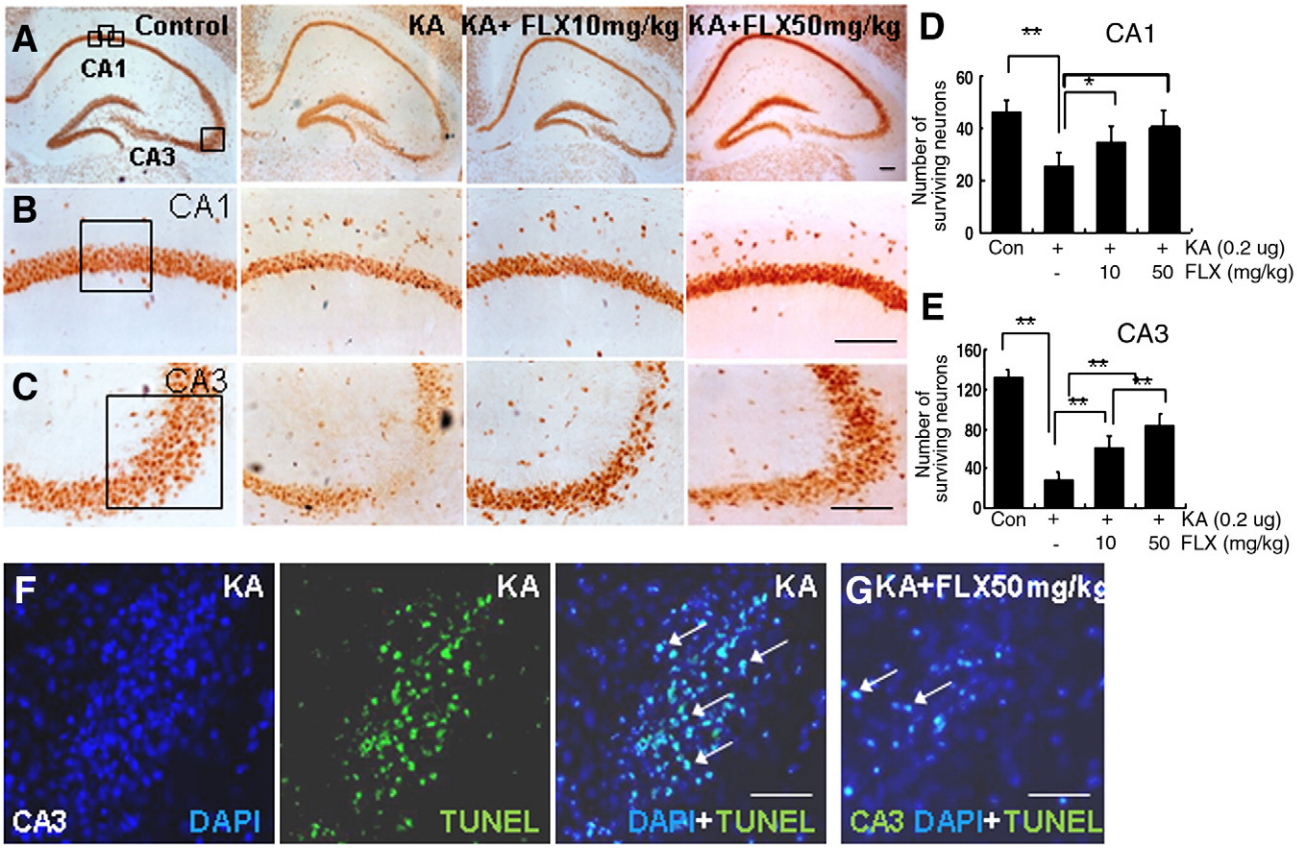

Fig. 2 – Systemic fluoxetine administration dose-dependently attenuated KA-induced neuronal death in the hippocampus. Fluoxetine (10 or 50 mg/kg) was administered intraperitoneally (i.p.) 30 min before KA (0.2 μg, i.c.v.) injection, and extents of KA-induced neuronal losses in the hippocampus were evaluated at 2 days post-KA treatment by staining with anti-Neu N^+ antibody (A–C). Representative pictures from three independent experiments are shown. Numbers of Neu N^+ cells in CA1 (0.01 mm^2, 0.1 × 0.1 mm) (D) and CA3 (0.018 mm^2, 0.13 × 0.13 mm) (E) regions in ipsilateral hippocampus, indicated as black boxes in (A), were counted from 12 photographs taken from three independent experiments and are presented as means ± SEMs. Representative confocal laser-scanning microscopic images of double staining for TUNEL (green) and DAPI (blue) in CA3 region were presented. TUNEL staining was carried out 1 day post-KA treatment with (G) and without (F) fluoxetine (50 mg/kg) administration. *, $p < 0.05$; **, $p < 0.01$. Scale bars represent 100 μm in A, B, C and 50 μm in F, G.