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Short communication

Induction of DNA repair proteins, Ref-1 and XRCC1, in adult rat brain following kainic acid-induced seizures

Nancy Quach[a], Tony Chan[a], Tony Au Lu[a], Steven S. Schreiber[b], Zhiqun Tan[a,*]

[a]Department of Neurology, UCI School of Medicine, ZOT 4275, 100 Irvine Hall, Irvine, CA 92612-4275, USA
[b]Department of Anatomy and Neurobiology, School of Medicine, University of California, Irvine, CA 92697-4275, USA

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Abstract

We evaluated the expression of DNA repair proteins, redox factor-1 (Ref-1) and X-ray repair cross-complementing protein 1 (XRCC1), relevant to neurodegeneration following kainic acid-induced seizures in rats. Neurons with oxidative DNA damage exhibited increased expression and colocalization of Ref-1 and XRCC1. Upregulation of DNA repair proteins was also associated with p53 induction and TUNEL. Coexpression of DNA repair proteins and cell death markers following seizures suggests that the DNA repair response may not be sufficient to prevent excitotoxin-induced neurodegeneration.

Theme: Development and regeneration
Topic: Neuronal death

Keywords: DNA damage repair; Ref-1; XRCC1; Seizures

Abnormal DNA repair has been implicated in the pathophysiology of a number of neurological disorders including stroke, traumatic brain injury and neurodegenerative diseases [2,26]. In this regard, base excision repair (BER) of DNA single-strand breaks plays a key role in the maintenance of genomic integrity and regulation of cell cycle checkpoints following DNA damage induced by oxidative stress or ionizing radiation [3,19]. Both redox factor-1 (Ref-1) and X-ray repair cross-complementing protein 1 (XRCC1) are critical components of the BER pathway [4,24]. Ref-1 functions primarily as an endonuclease that removes apurinic/apyrimidinic (A/P) lesions due to reactive oxygen species (ROS) [17]. In addition, by altering their redox state, Ref-1 is a potent activator of multiple transcription factors such as the tumor suppressor protein, p53, a major regulator of neuronal cell death [8,14]. Increasing evidence suggests that Ref-1 plays a crucial role in central nervous system (CNS) development as well as the pathophysiology of certain CNS diseases. Decreased Ref-1 expression correlates with neuronal cell death following transient ischemia and brain trauma, whereas Ref-1 induction may be neuroprotective [7,9,12,13,18]. Ref-1 protein has been shown to accumulate in vulnerable neurons and senile plaques in Alzheimer's disease (AD) [21], and a Ref-1 gene mutation causing loss of A/P endonuclease activity has been associated with oxidative DNA damage and neuronal cell death in amyotrophic lateral sclerosis [11,15]. XRCC1 plays a major role in the repair of single-strand breaks in mammalian DNA through interactions with modifying enzymes such as DNA ligase III, DNA polymerase β and poly(ADP-ribose) polymerase (PARP) [1,25]. Reduced levels of XRCC1 precede DNA damage and neuronal cell death following either transient ischemia or cold-induced brain injury in mice [5,6]. Interestingly, XRCC1 can physically interact with and stimulate Ref-1 in vitro [27]. Although studies have demonstrated that DNA

* Corresponding author. Fax: +1 949 824 2436.
E-mail address: tanz@uci.edu (Z. Tan).

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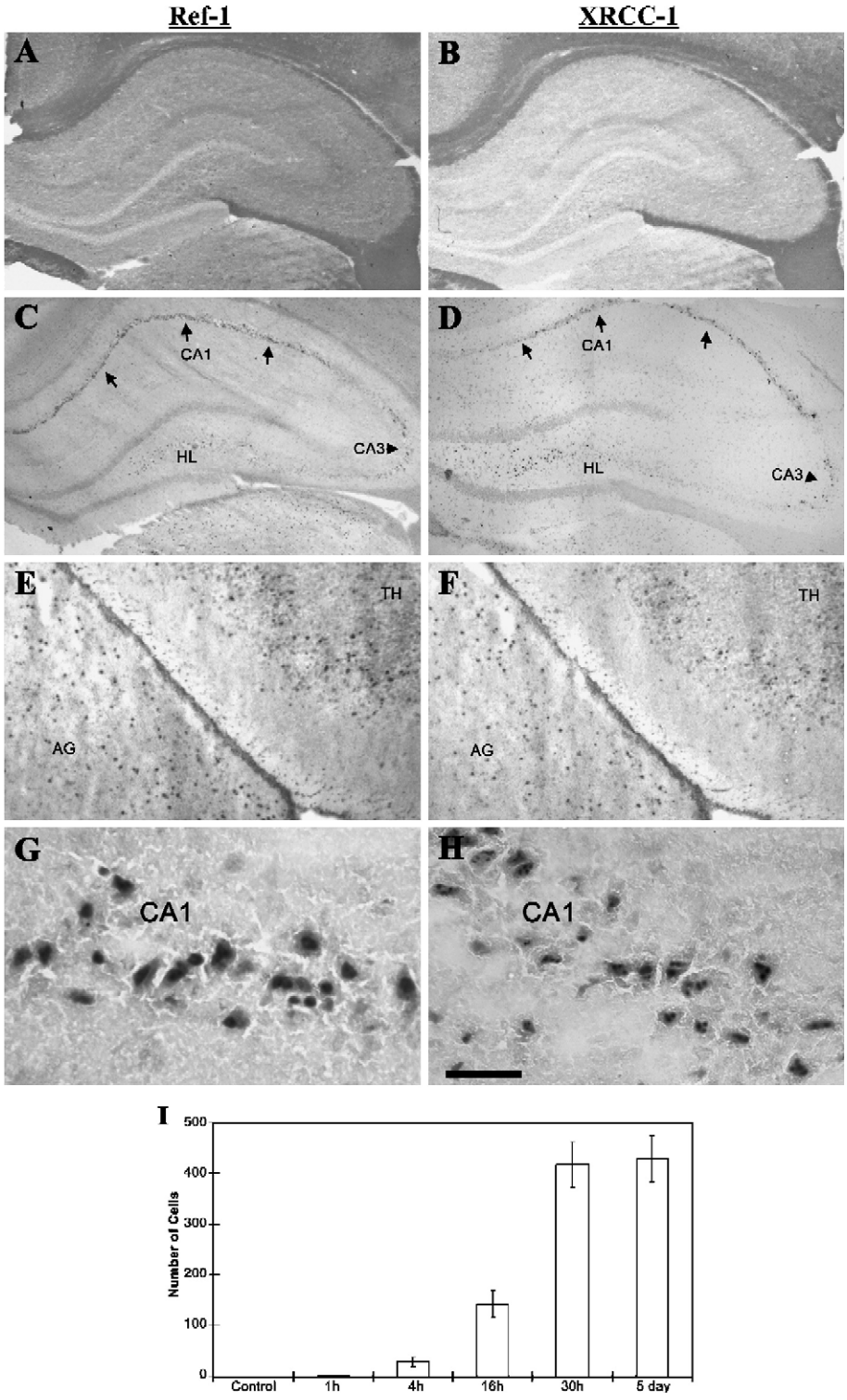

Fig. 1. Increased expression of Ref-1 and XRCC1 in rat brain following KA-induced seizures. Immunohistochemistry using Ref-1 (A, C, E and G) or XRCC1 (B, D, F and H) antibody and diaminobenzidine (DAB) reveals low level of staining in untreated control hippocampus (A, B). Representative section from a rat sacrificed 16 h after KA treatment shows increased Ref-1 (C, E) and XRCC1 (D, F) immunoreactivity in hippocampal pyramidal cell layers (CA1 and CA3, arrows), hilus (HL), thalamus (TH) and amygdala (AG). At higher magnification, the nuclear localization of both Ref-1 (G) and XRCC1 (H) in hippocampal CA1 pyramidal neurons is evident. (I) Quantification of XRCC1-positive cells in rat hippocampus at each time point is expressed as mean ± SEM. Scale bar represents 400 μm in A–D, 300 μm in E and F and 30 μm in G and H.