Brain Research Bulletin 121 (2016) 48–58

Contents lists available at ScienceDirect

Brain Research Bulletin

journal homepage: www.elsevier.com/locate/brainresbull

Research report

Involvement of BDNF/ERK signaling in spontaneous recovery from trimethyltin-induced hippocampal neurotoxicity in mice

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ARTICLE INFO

Article history:
Received 6 October 2015
Received in revised form
28 December 2015
Accepted 4 January 2016
Available online 6 January 2016

Keywords:
Trimethyltin
Hippocampus
BDNF
ERK
Spontaneous recovery

ABSTRACT

Trimethyltin (TMT) toxicity causes histopathological damage in the hippocampus and induces seizure behaviors in mice. The lesions and symptoms recover spontaneously over time; however, little is known about the precise mechanisms underlying this recovery from TMT toxicity. We investigated changes in the brain-derived neurotrophic factor/extracellular signal-regulated kinases (BDNF/ERK) signaling pathways in the mouse hippocampus following TMT toxicity. Mice (7 weeks old, C57BL/6) administered TMT (2.6 mg/kg intraperitoneally) showed acute and severe neurodegeneration with increased TUNEL-positive cells in the dentate gyrus (DG) of the hippocampus. The mRNA and protein levels of BDNF in the hippocampus were elevated by TMT treatment. Immunohistochemical analysis showed that TMT treatment markedly increased phosphorylated ERK1/2 expression in the mouse hippocampus 1–4 days after TMT treatment, although the intensity of ERK immunoreactivity in mossy fiber decreased at 1–8 days post-treatment. In addition, ERK-immunopositive cells were localized predominantly in doublecortin-positive immature progenitor neurons in the DG. In primary cultured immature hippocampal neurons (4 days *in vitro*), BDNF treatment alleviated TMT-induced neurotoxicity, via activation of the ERK signaling pathway. Thus, we suggest that BDNF/ERK signaling pathways may be associated with cell differentiation and survival of immature progenitor neurons, and will eventually lead to spontaneous recovery in TMT-induced hippocampal neurodegeneration.

1. Introduction

The organotin compound trimethyltin (TMT) induces selective neurodegeneration in the mammalian central nervous system, particularly the hippocampus (Geloso et al., 2011). TMT-treated animals show neuronal death and glial activation in the hippocampus (Fiedorowicz et al., 2001; Kim et al., 2014b). They also exhibit cognitive deficits and behavioral changes, including memory loss, learning impairment, hyperactivity, aggression, and seizures (Besser et al., 1987; Fabrizi et al., 2015; Kim et al., 2013).

Previous studies in experimental animals have reported spontaneous recoveries from various brain injuries, including traumatic brain injury, stroke, seizure, and chemical insults (Blaiss et al., 2011; Lee et al., 2011; Park et al., 2014; Wachter et al., 2010). Mice also recover spontaneously from TMT-induced hippocampal lesions and seizure behaviors (Kim et al., 2014a, 2015; Yang et al., 2012). One hypothesis to explain this recovery emphasizes that neural stem cells (NSCs) and neural progenitor cells (NPCs) in the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone of the anterior lateral ventricle, where adult neurogenesis takes place, replace the damaged neurons and glial cells after TMT toxicity (Ogita et al., 2005). However, the precise intracellular mechanisms of this endogenous and spontaneous recovery remain unclear.

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http://dx.doi.org/10.1016/j.brainresbull.2016.01.002
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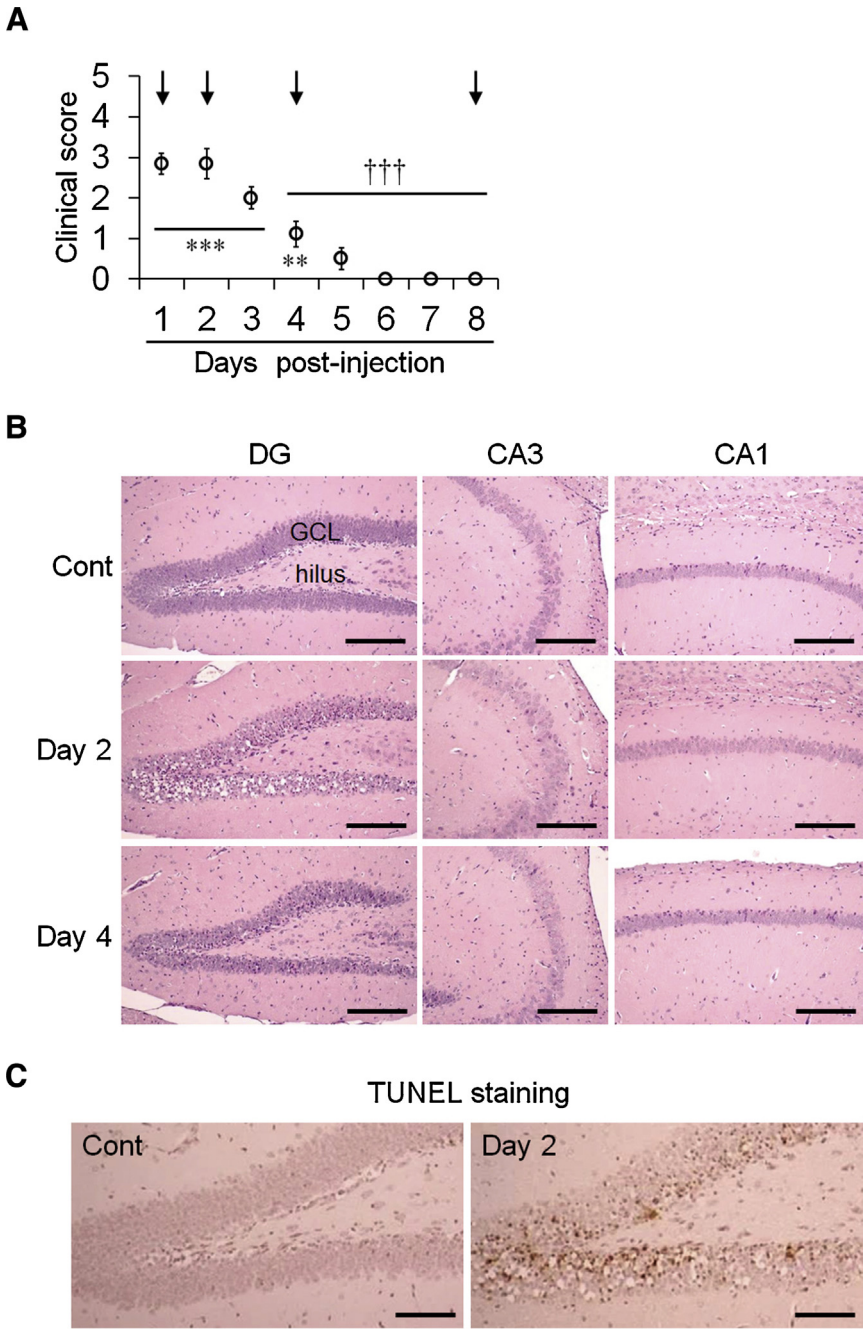

Fig. 1. Clinical seizure scores and histological findings in the hippocampus of mice treated with TMT. (A) Clinical symptoms were scored (0–5) for 8 days after TMT injection. Mice were sacrificed at the times indicated by the arrows. The data are reported as the means ± SEs ($n = 10$ per group). ** $p < 0.01$, *** $p < 0.001$, *vs.* vehicle-treated controls; ††† $p < 0.001$, *vs.* peak stage of seizure scores (day 2 post-injection). (B) Histopathological analysis was performed using H&E staining at 2 and 4 days post-treatment. (C) Apoptotic neuronal cell death was determined by TUNEL staining in the hippocampus 2 days post-treatment. DG, dentate gyrus; CA, *cornu ammonis*; GCL, granular cell layer; Cont, controls. Scale bars represent 180 μm (B) and 130 μm (C).

Extracellular signal-regulated kinases (ERK) 1 and 2, members of the mitogen-activated protein kinase (MAPK) superfamily, are activated when extracellular stimuli, such as neurotransmitters, neurotrophic factors, and growth factors, bind to the upstream receptors of ERK1/2 under physiological conditions (Grewal et al., 1999; Segal and Greenberg, 1996). Translocation of the activated ERK1/2 to the nucleus then leads to diverse cellular responses, including gene transcription, protein synthesis, ion channel modulation, dendritic spine stabilization, cell cycle progression, and cell survival, through cell-specific combinations of downstream substrates (Garcia et al., 2002; Khokhlatchev et al., 1998). ERK1/2 activation is not only found in normal states, but is also found in pathological conditions, such as viral infection, DNA injury, oxidative stress, epilepsy, and ischemic stroke (Adderley and Fitzgerald, 1999; Berkeley et al., 2002; Lannuzel et al., 1997; Slevin et al., 2000). Likewise, the roles of ERK1/2 activation following brain insults seem to be complex and implicated in both neurodegeneration and neuroprotection. In certain brain injuries, including damage elicited by H_2O_2, amyloid beta, and 6-hydroxydopammine, ERK activation may lead to cell death (Bhat and Zhang, 1999; Kulich and Chu, 2001; Rapoport and Ferreira, 2000). Alessandrini et al. (1999) reported that increased ERK phosphorylation was seen in infarct areas of the brain cortex in mice following occlusion of the middle cerebral artery, and pre-treatment with the MAPK kinase