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BRAIN RESEARCH

Research Report

Activation of cerebral peroxisome proliferator-activated receptors gamma exerts neuroprotection by inhibiting oxidative stress following pilocarpine-induced status epilepticus

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ABSTRACT

Status epilepticus (SE) can cause severe neuronal loss and oxidative damage. As peroxisome proliferator-activated receptor gamma (PPARγ) agonists possess antioxidative activity, we hypothesize that rosiglitazone, a PPARγ agonist, might protect the central nervous system (CNS) from oxidative damage in epileptic rats. Using a lithium-pilocarpine-induced SE model, we found that rosiglitazone significantly reduced hippocampal neuronal loss 1 week after SE, potently suppressed the production of reactive oxygen species (ROS) and lipid peroxidation. We also found that treatment with rosiglitazone enhanced antioxidative activity of superoxide dismutase (SOD) and glutathione hormone (GSH), together with decreased expression of heme oxygenase-1 (HO-1) in the hippocampus. The above effects of rosiglitazone can be blocked by co-treatment with PPARγ antagonist T0070907. The current data suggest that rosiglitazone exerts a neuroprotective effect on oxidative stress-mediated neuronal damage followed by SE. Our data also support the idea that PPARγ agonist might be a potential neuroprotective agent for epilepsy.

1. Introduction

Accumulating data from both laboratory and clinic have indicated that seizures can cause neuronal damage in certain brain regions. Such neuronal loss, in turn, may exacerbate the development of emergent epilepsy and result in cognitive impairments (Henshall and Murphy, 2007). Oxidative stress has been implicated in many human degenerative diseases, including epilepsy. It is well known that oxidative stress in the brain is able to increase the glutamate release in the hippocampus, affect

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Abbreviations: HO-1, heme oxygenase-1; SE, status epilepticus; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; ARE, antioxidant response elements; CNS, central nervous system; TZDs, thiazolidinediones; PPREs, PPAR responsive elements; SnPP, tin protoporphyrin; MDA, malondialdehyde; SOD, superoxide dismutase; GP, glutathione peroxidase; Nrf2, NF-E2 related factor 2; GSH, glutathione hormone; NF-κB, nuclear factor κB; DAB, diaminobenzidine; 15d-PGJ$_2$, 15-deoxy-Δ12,14-prostaglandin J$_2$

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ionic homeostasis and neurotransmission, where it leads to excessive activation of glutamate receptors producing intracellular acidification in neurons by Ca^{2+} entry which can be related to neuronal death (Costa et al., 2004). The recognition of the relationship between oxidative stress and neuronal loss in epilepsy has sparked an intensive interest in developing anti-oxidation strategy to protect neurons from oxidative damage following seizure activity (Ribeiro et al., 2005; Ilhan et al., 2005a; Chung and Han, 2003).

Heme oxygenase (HO) is a stress-related protein that catalyzes the rate-limiting step in heme degradation. Two active isoenzymes of HO have been identified, i.e., HO-1 (HSP32) and HO-2. While HO-2 is consistently active in normal condition, HO-1 is induced by various stresses and contributes to total HO activity predominantly. HO-1 expression induced by LPS is mediated via antioxidant response elements (ARE) of HO-1 gene promoter, which are activated through NF-E2 related factor 2 (Nrf2) (Alam et al., 1999; Camhi et al., 1998). HO-1 expression is also regulated by another two transcription factors, i.e., nuclear factor κB (NF-κB) and mitogen-activated protein kinase (Wijayanti et al., 2004). HO-1 degrades heme, a pro-oxidant, into carbon monoxide, biliverdin/bilirubin and free iron. Among these degraded products, biliverdin and bilirubin may act as physiological antioxidants and potent scavengers for oxygen radicals, while CO may confer neuroprotection via vasodilation and thus improve blood flow to an impaired region. HO-1 was

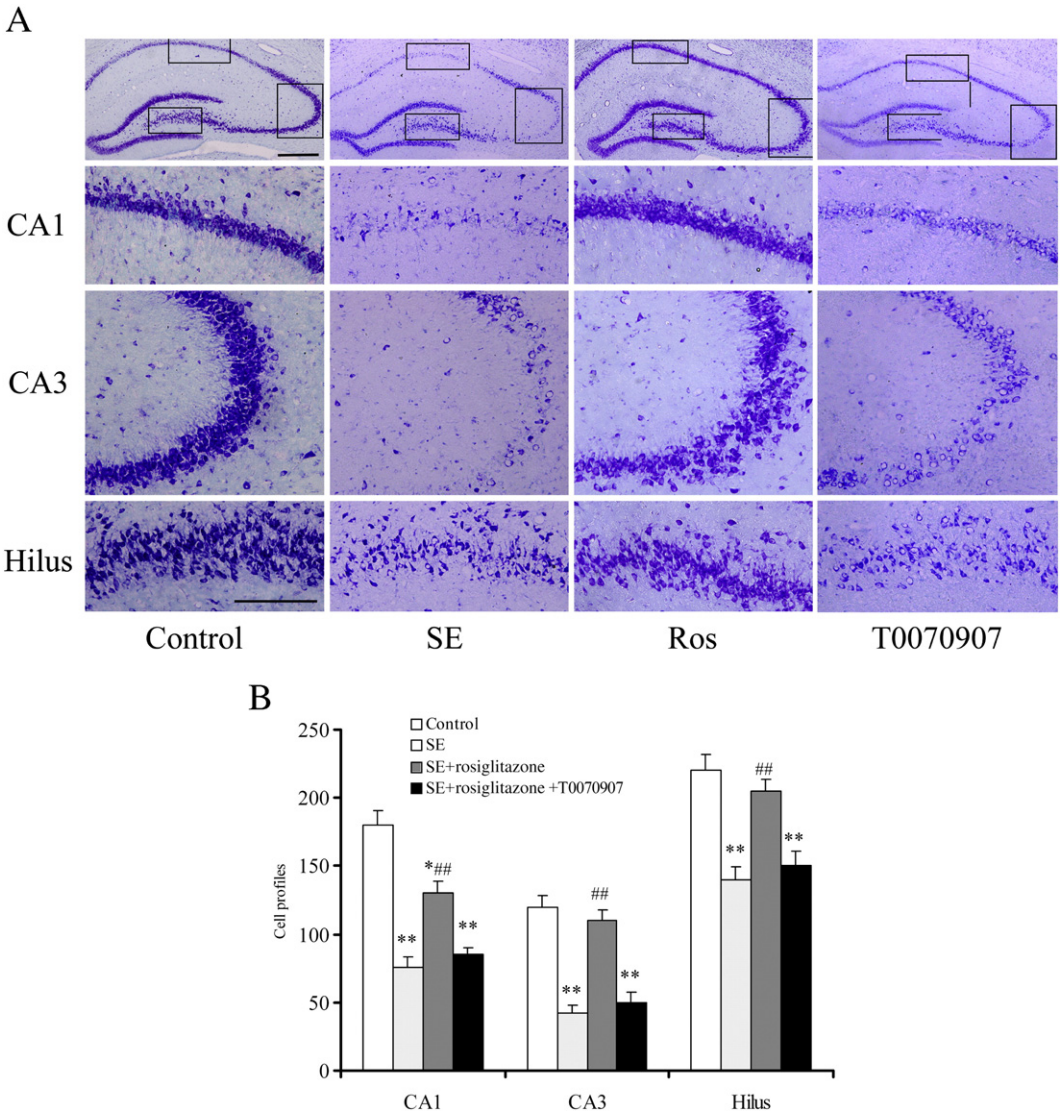

Fig. 1 – A) Neuronal loss assessed histologically by Nissl staining in the dorsal hippocampus and subfields CA1, CA3 and hilus 1 week after SE. (1) control group; (2) SE group; There is severe neuronal loss in the CA1, CA3 and hilus of hippocampus compared with the control group. (3) SE+rosiglitazone group; neuronal loss is attenuated markedly by rosiglitazone. (4) SE+rosiglitazone+T0070907 group. Obvious neuronal loss is observed after co-treatment with T0070907. Scale bar: the first row: 500 μm; the rest: 200 μm. B) Quantitative analysis of neuronal loss in the subfields demonstrates that rosiglitazone prevents the neuronal loss after SE while T0070907 reverses this protective effect. Data are expressed as mean±SEM; $^{*}P<0.05$, $^{**}P<0.01$ *vs.* control group; $^{\#\#}P<0.01$ *vs.* SE group ($n=4$, ANOVA with Dunnett's post test).