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Research Report

Rifampicin attenuates the MPTP-induced neurotoxicity in mouse brain

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ABSTRACT

Rifampicin, an antibacterial drug, is highly effective in the treatment of tuberculosis and leprosy. Recently, it has been reported to have neuroprotective effects in in vitro and in vivo models. This study was designed to elucidate its neuroprotective effects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity (known as an in vivo mouse model of Parkinson's disease). Mice were injected intraperitoneally (i.p.) with MPTP (10 mg/kg) four times at 1-h intervals, and brains were analyzed 3 or 7 days later. Rifampicin at 20 mg/kg (i.p., twice) had protective effects against MPTP-induced neuronal damage (immunohistochemical changes in tyrosine hydroxylase) in both the substantia nigra and striatum. Rifampicin also protected against the MPTP-induced depletions of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) in the striatum. The maximal concentrations of rifampicin between 30 and 240 min after a single rifampicin injection (20 mg/kg, i.p.) were 2.6 μM (at 30 min) in plasma and 0.77 μM (at 60 min) in striatum. Next, the effects of rifampicin on oxidative stress [lipid peroxidation in mouse brain homogenates and free radical-scavenging activity against diphenyl-*p*-picrylhydrazyl (DPPH)] were evaluated to clarify the underlying mechanism. At 1 μM or more, rifampicin significantly inhibited both lipid peroxidation in the striatum and free radical production. These findings suggest that in mice, rifampicin can reach brain tissues at concentrations sufficient to attenuate MPTP-induced neurodegeneration in the nigrostriatal dopaminergic neuronal pathway, and that an inhibitory effect against oxidative stress may be partly responsible for its observed neuroprotective effects.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder whose cardinal features include tremor, slowness of movement, stiffness, and postural instability. These symptoms are primarily attributable to the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the consequent loss of their projecting nerve fibers in the striatum. Although several marketed drugs [such as L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine agonists, amantadine, selegiline, entacapone, budipine, and anticholinergics] are effective at alleviating PD symptoms, chronic use

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of these drugs is often associated with debilitating side effects, and none seems effectively to hinder the progression of the disease (Kostic et al., 1991). Hence, there is still a great need for a more efficacious treatment with fewer side effects that will halt or even reverse PD.

Although the exact cause of neuronal loss in PD remains unknown, current evidence points to the presence of ongoing oxidative stress and the generation of reactive oxygen species (ROS) as events occurring selectively in the SNpc of Parkinsonian brains (Gerlach et al., 1994; Jenner and Olanow, 1996). Human postmortem studies have also suggested that oxidative damage to lipids, proteins, and DNA occur in the SNpc of PD patients (Alam et al., 1997; Dexter et al., 1994; Zhang et al., 1999). Genes linked to familial PD include α-*synuclein* (Polymeropoulos et al., 1997), *Parkin* (Kitada et al., 1998), *UCH-L1* (Leroy et al., 1998), *PINK1* (Valente et al., 2004), *dardarin* (Paisan-Ruiz et al., 2004), and *DJ-1* (Taira et al., 2004). The genes *UCH-L1*, *DJ-1* are related to the clinical severity of PD in humans, and these genes may be closely involved in oxidative stress (Taira et al., 2004; Choi et al., 2004). Thus, the causal involvement of oxidative stress is a leading hypothesis for the pathogenesis of PD. Evidence of increased oxidative stress in autopsy samples of the substantia nigra in PD includes increased levels of malondialdehyde (MDA), lipid, and cholesterol hydroperoxides (Dexter et al., 1989, 1994) as well as increased levels of 8-hydroxy-2-deoxyguanosine, a marker of DNA oxidative damage (Sanchez-Ramos et al., 1994). These studies suggested

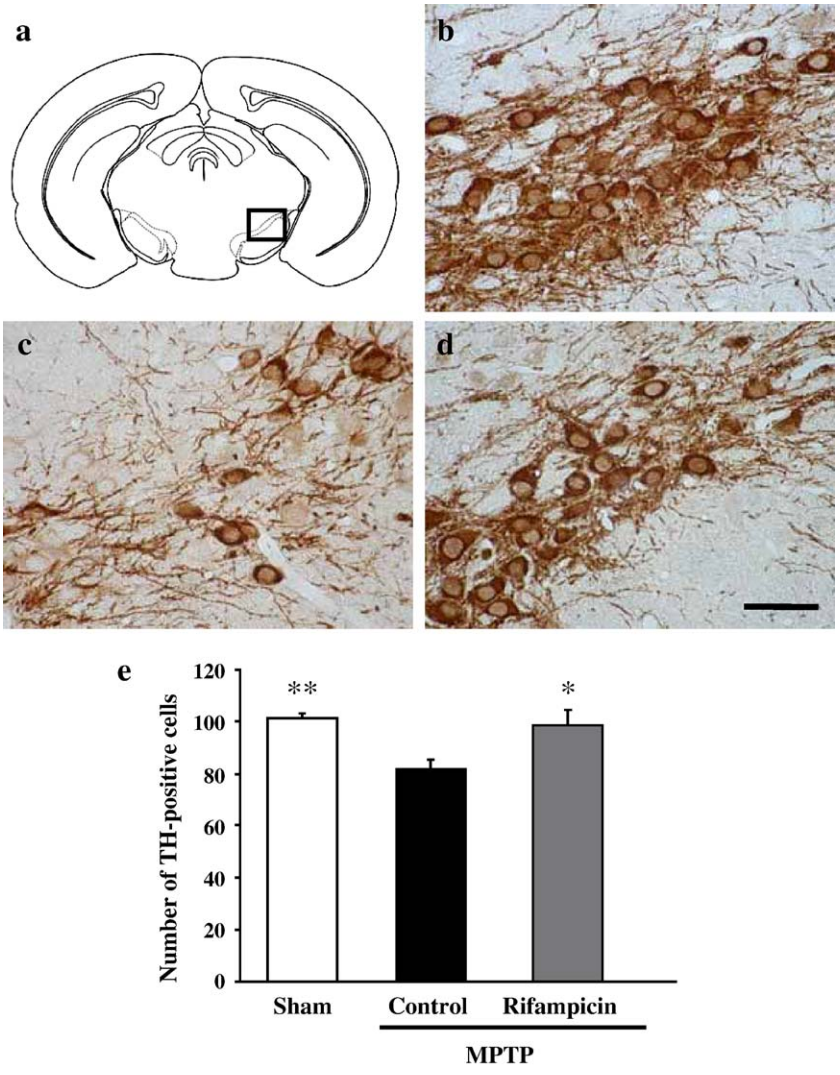

Fig. 1 – Rifampicin attenuated the immunohistochemical changes in tyrosine hydroxylase (TH) induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mouse substantia nigra. Mice were injected intraperitoneally with MPTP (10 mg/kg) four times at 1-h intervals, and twice with either rifampicin (20 mg/kg) or vehicle (at 1 h before the first administration of MPTP and 1 h after the last administration of MPTP). Brains were analyzed 7 days after the MPTP treatment. (a) Coronal section through the substantia nigra; square, area shown in the microphotographs. (b) Sham group (Sham). (c) Seven days after MPTP + vehicle treatment (Control). (d) Seven days after MPTP + rifampicin treatment (Rifampicin). (e) Number of TH-positive cells in substantia nigra. A decrease in the number of TH-immunopositive neurons in the substantia nigra was observed at 7 days after MPTP treatment (c, e). Rifampicin attenuated this decrease (d, e). Scale bar = 50 μm. Values are expressed as the mean ± S.E. *$P < 0.05$, **$P < 0.01$ vs. Control ($n = 6$ or 7).