

Inhibition of neuronal nitric oxide synthase prevents iron-induced cerebellar Purkinje cell loss in the rat

Sefa Gulturk¹, Ramazan Kozan^{2*}, M. Omer Bostanci³, Fatih Sefil³, and Faruk Bagirici³

Department of Physiology, Faculty of Medicine, ¹Cumhuriyet University, 58140 Sivas; ²Mustafa Kemal University, 31100 Hatay, *Email: drkozan@hotmail.com; ³Ondokuz Mayıs University, 55139 Samsun, Turkey

Iron plays an important role in maintaining normal brain function. However, in many neurodegenerative diseases abnormal iron accumulation in specific brain regions has been consistently reported. In this study, we investigated the neurotoxic effect of the intracerebroventricularly injected iron on the cerebellar Purkinje cells in the rat and the role of nitric oxide (NO) in this process. The role of NO in rats administered iron (FeCl₃·6H₂O) was examined with the use of a donor of NO, L-arginine (L-Arg), and a central selective inhibitor of NO synthase, 7-nitroindazole (7-NI). For this reason, rats were divided into 5 groups: control, iron-injected, iron plus L-Arg, iron plus 7-NI, and iron plus L-Arg plus 7-NI. Means (value ± standard deviation) of the total numbers of Purkinje cells in the cerebellum were estimated as 337 ± 23, 209 ± 16, 167 ± 19, 305 ± 26, and 265 ± 14 thousands in the control, iron, iron plus L-Arg, iron plus 7-NI, and iron plus L-Arg plus 7-NI groups, respectively. Iron treatment alone and the combination of iron and L-Arg caused a significant reduction in the total number of cerebellar Purkinje cells. Therefore, L-Arg increased the Purkinje cell loss induced by treatment with iron. These data show that inhibition of the neuronal NOS by 7-NI can prevent some of the deleterious effects of iron on cerebellar Purkinje cells. Presence of L-arginine decreased the neuroprotective effect of 7-NI.

Key words: iron, neurotoxicity, Purkinje cell, nitric oxide, stereology

INTRODUCTION

Iron plays an important role in maintaining normal brain function and is the most abundant transitional metal in the brain (Moos 2002). Iron deposition is a characteristic feature of common neurodegenerative diseases such as Parkinson's and Alzheimer's diseases as well as the much rarer disorders such as aceruloplasminemia, Hallervorden-Spatz disease (neurodegeneration with brain iron accumulation), Friedreich's ataxia, and neuroferritinopathy (Zecca et al. 2004). It is still not clear whether abnormal accumulation of iron leads to neurodegeneration or the accumulation follows neurodegeneration occurring due to other reasons.

The neuronal nitric oxide synthase (nNOS) is constitutively expressed in a fraction of brain neurons (Brown and Bal-Price 2003). Nitric oxide (NO) is an important

modulator of neuronal function in the central nervous system (CNS). However, under certain conditions its excessive formation may be an important mediator of the nervous tissue damage (Dawson and Dawson 1995). NO in high concentration is indirectly neurotoxic through various mechanisms, including iron-mediated lipid peroxidation. It also liberates iron from cell stores (Iadecola 1997, Bishop and Robinson 2001) and depletes cell energy by disruption of mitochondrial enzymes and nucleic acids. Thus, release of NO may also trigger neuronal apoptotic cell death (Iadecola 1997). Schulz and coworkers (1995) showed that a central selective inhibitor of nNOS, 7-nitroindazole (7-NI) produced significant neuroprotection against NMDA-mediated excitotoxic striatal lesions. In the rat model of focal cerebral ischemia, a significant neuroprotection was obtained with 7-NI. The effect was reversed by L-arginine (L-Arg) (Yoshida et al. 1994). Nevertheless, the mechanisms of NO neurotoxicity are still unclear.

Purkinje cells play a vital role in normal functioning of the cerebellum. They are highly susceptible to

Correspondence should be addressed to R. Kozan,
Email: drkozan@hotmail.com

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