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BRAIN RESEARCH

Research Report

The alterations of oligodendrocyte, myelin in corpus callosum, and cognitive dysfunction following chronic cerebral ischemia in rats

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ABSTRACT

Although the white matter lesions, so called leuko-araiosis, often seen in elderly people have been gaining attention due to their association with cognitive dysfunction (CD) and high risk of incident stroke, the pathological significance of these lesions still remains controversial. Therefore, in the present study, we investigated the alterations in oligodendrocytes (OLG), including oligodendrocytes progenitor cells (OPCs), myelin, and CD following chronic cerebral ischemia in rats. SD rats were subjected to bilateral common carotid artery occlusion. Immunohistochemical staining was performed at 2, 4, 6, 8, and 12 weeks after the induction of ischemia with anti-NG2 (OPCs), anti-GST-π (OLG), and anti-MBP antibodies in paramedian corpus callosum (CC). CD was assessed by the Morris water maze test. There was a significant decrease in the number of GST-π positive cells at 2 weeks after the start of ischemia compared with that seen in the sham group. There was a significant increase of the number of NG2 positive cells at 4 weeks in the ischemia group compared with the sham group. In the ischemic group, the amount of MBP was observed to have decreased significantly at each time point compared with the sham group. CD was observed in the ischemic group than that in the sham group at all time points. Our results indicate that remyelination is strongly correlated with the recovery of cognitive dysfunction following chronic cerebral ischemia.

1. Introduction

The white matter lesions, so called leuko-araiosis (Hachinski et al., 1987), often seen in elderly people have been gaining attention due to their association with cognitive dysfunction and high risk of incident stroke (Pantoni and Garcia, 1995). Although we are currently able to diagnose these common lesions by MR imaging, which demonstrate hyper-intensity on T2-weighted and FLAIR images, the clinical significance and pathogenesis of these lesions still remain controversial. For example, patients with white matter lesions do not always suffer from cognitive dysfunction, and the degree of dysfunction might depend on the extent or location of these lesions in individual patients. Regarding the mechanisms of white matter lesions, both chronic cerebral ischemia and aging are considered to be possible causes at present. There is a need to

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gain insight into the pathophysiology of leukoaraiosis in order to reduce the potential burden of disability associated with these lesions, and to devise a method for preventing their development.

There have been reports that have suggested that oligodendrocytes and/or myelin were damaged, and cognitive function was compromised following chronic cerebral ischemia in a rat model. We therefore turned our attention to the alterations of oligodendrocytes, myelin, and cognitive function in chronic cerebral ischemia. In previous reports, the number of oligodendrocytes was observed to decrease in the paramedian corpus callosum after 14 days (Tomimoto et al., 2003) and demyelination was observed in the corpus callosum after 7 or 14 days, which persisted for at least 90 days (Tomimoto et al., 2003; Wakita et al., 1994; Wakita et al., 2002), following chronic cerebral ischemia in rats. Cognitive dysfunction, as evaluated by the Morris water maze test, was observed after 14 days and persisted until at least 1 year following chronic cerebral ischemia (De Jong et al., 1999; Pappas et al., 1996). However, the correlation among oligodendrocyte loss, myelin damage, and cognitive dysfunction remains unclear.

It is also important to investigate whether the restoration of oligodendrocytes and myelin can occur following chronic cerebral ischemia. Other investigators have reported the restoration of oligodendrocytes and myelin after transient

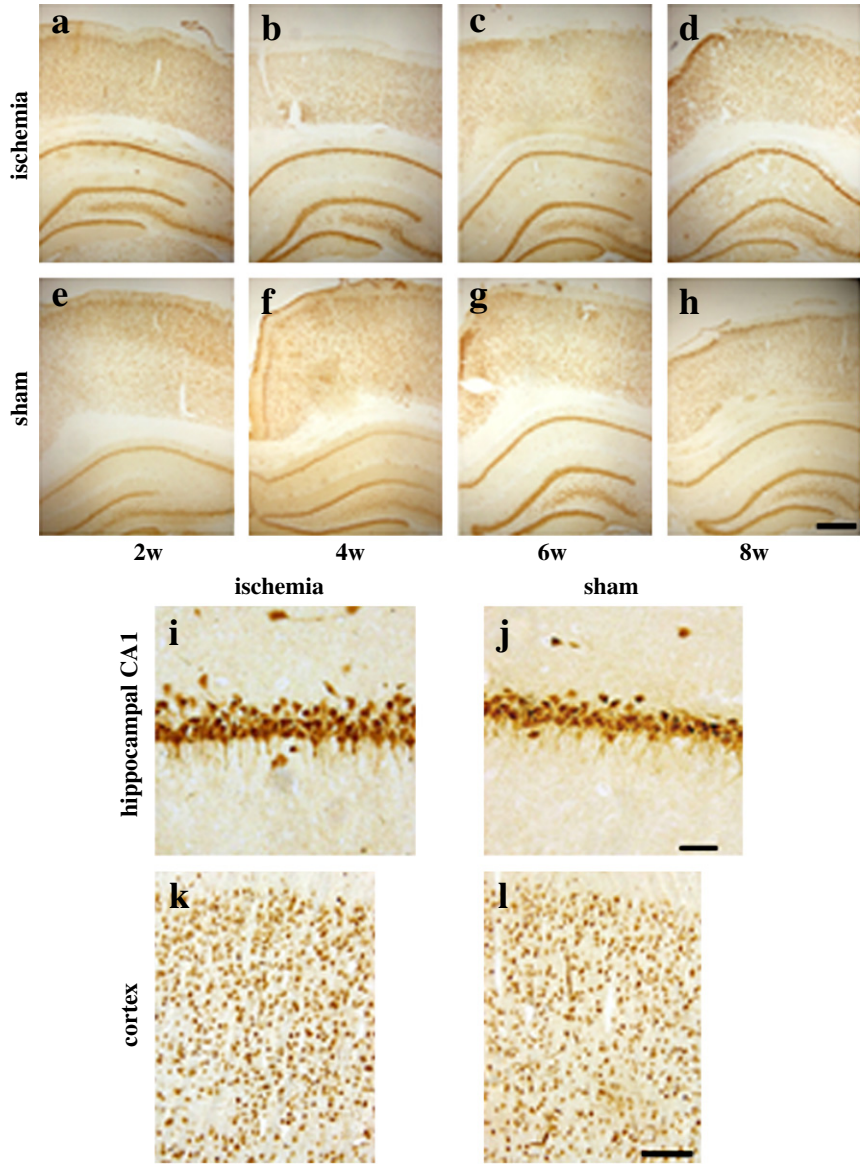

Fig. 1 – Representative photographs of immunohistochemical staining of NeuN in the cortex and hippocampal CA1 region at 2, 4, 6, and 8 weeks after chronic cerebral ischemia. Photographs (a–h) show 2 w (a), 4 w (b), 6 w (c), and 8 w (d) in the ischemic group and 2 w (e), 4 w (f), 6 w (g), and 8 w (h) in the sham group. Original magnification ×40 Scale bar = 500 μm. There was no loss of NeuN positive cells in the hippocampal CA1 and cerebral cortex following chronic cerebral ischemia.