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Research Report

Ginsenoside Rb1 improves spatial learning and memory by regulation of cell genesis in the hippocampal subregions of rats

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ABSTRACT

Ginsenoside Rb1 (Rb1) is known to improve learning and memory in hippocampus-dependent tasks. However, the cellular mechanism remains unknown. Cell genesis in hippocampus is involved in spatial learning and memory. In the present study, Rb1 was orally administrated to adult rats for 30 days. The behavioral training tests indicated that Rb1 improved spatial cognitive performance of rats in Morris water maze (MWM). Furthermore, we investigated the effects of Rb1 on cell genesis in adult rats' hippocampus, using thymidine analog bromodeoxyuridine (BrdU) as a marker for dividing cells. It has been shown that hippocampal cell genesis can be influenced by several factors such as learning and exercise. In order to avoid the effects of the interfering factors, only the rats treated with Rb1 without training in MWM were used to investigate cell genesis in hippocampus. When BrdU was given to the rats 30 days prior to being killed, it was shown that oral administration of Rb1 significantly increased cell survival in dentate gyrus and hippocampal subregion CA3. However, when BrdU was injected 2 h prior to sacrifice, the results indicated that Rb1 had no significant influence on cell proliferation in the hippocampal subregions. Thus, an increase of cell survival in hippocampus stimulated by Rb1 may be one of the mechanisms by which ginseng facilitates spatial learning and memory. Our study also indicates that Rb1 may be developed as a therapeutic agent for patients with memory impairment.

1. Introduction

Hippocampus, a key brain region, plays a critical role in learning and memory, which is a complex biological process including the acquisition, consolidation and retrieval of information (Hou et al., 2004). Neurogenesis in the hippocampus, defined as the generation of new nerve cells, is involved in memory formation (Shors et al., 2001; Clelland, et al., 2009).

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Abbreviations: AD, Alzheimer's disease; BDNF, brain-derived neurotrophic factor; BrdU, bromodeoxyuridine; CA1, hippocampal subregion CA1; CA3, hippocampal subregion CA3; DG, dentate gyrus; MWM, Morris water maze; PBS, phosphate-buffered saline; Rb1, ginsenoside Rb1; SGZ, subgranular zone

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Recent studies have revealed the important roles of neurogenesis on hippocampal-dependent learning tasks (Gould et al., 1999b; Gage, 2002; Snyder et al., 2005; Dupret et al., 2008; Zhao et al., 2008). Increased neurogenesis is associated with improved spatial memory whereas impaired neurogenesis indicates depressive behaviors and poor cognitive function (Luo et al., 2007; Koo et al., 2010).

Various factors have been found to modulate neurogenesis in the hippocampus of rodents. For example, hippocampal-dependent learning enhances survival of adult generated neurons in the rat dentate gyrus (DG) (Gould et al., 1999a). Similarly, voluntary exercise such as running increases cell proliferation in the adult mouse DG (van Praag et al., 1999). Additionally, environmental enrichment also increases adult hippocampal neuron whereas neurogenesis declines with aging and stress (Kempermann et al. 1998; Cameron & Mckay, 1999; Donovan et al., 2006; Dranovsky and Hen, 2006).

Ginseng, the root of *Panax ginseng* C.A. *Meyer*, has been widely used in traditional oriental medicine for several thousand years. Ginsenosides, the main bioactive components in ginseng, play an important role in central nervous system (Liao et al., 2002; Yuan et al., 2007). They have been proved to be effective in the attenuation of learning deficits due to brain damage and aging in humans and animals (Petkov et al., 1993; Attele et al., 1999; Lee et al., 2008; Lee et al., 2010). The beneficial effects of ginseng root on learning and memory are often attributed to ginsenoside Rb1 (Rb1). It has been known that Rb1 enhances the stimulatory effect of neurite outgrowth (Nishiyama et al., 1994). Afterwards, it has been suggested that Rb1 protects hippocampal neurons against either ischemia (Lim et al., 1997) or glutamate-induced neurodegeneration (Kim et al., 1998). Recent studies have also revealed that Rb1 promotes neurotransmitter release by modulating phosphorylation of synapsins through a cAMP-dependent protein kinase pathway (Xue et al., 2006). However, there is little information available in literature regarding the effects of Rb1 on cell genesis in the hippocampus. Gao et al. (2010) first put forward that Rb1 increased neurogenesis by regulation of expression of brain-derived neurotrophic factor (BDNF) and caspase-3. Because it is more representative way of general human consumption, Rb1 was orally administrated to the rats in the present study to further clarify the cellular mechanism of memory enhancement. Furthermore, we investigated the effects of Rb1 on spatial cognitive performance and cell genesis in hippocampus of rats.

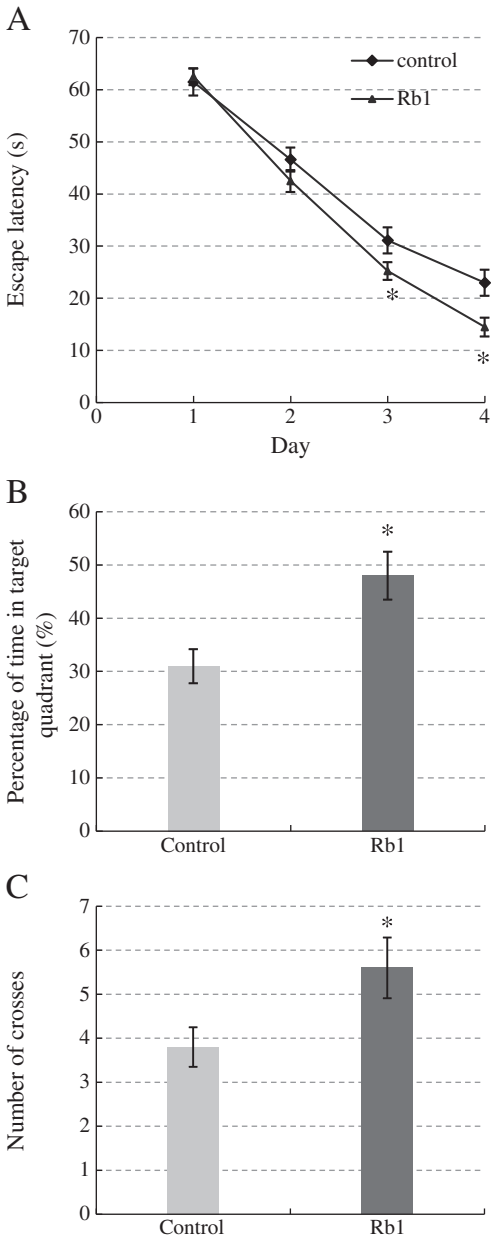

Fig. 1 – The effects of Rb1 on cognitive performance in Morris water maze test. Rb1 decreased the escape latency (A) and increased the percentages of time in target quadrant (B) and the number of crosses (C).

2. Results

2.1. *Behavioral test in MWM*

Fig. 1 shows the results of training in the MWM. The rats in two groups (control and Rb1) showed a general decrease in overall latency throughout the acquisition phase (Fig. 1A). It indicated that learning itself can improve memory. Compared to the control group, Rb1 group spent significantly less time in finding the hidden platform with repeated training ($p<0.001$). The shorter escape latency to the hidden platform may be resulted from faster swimming speed but not the amelioration of spatial memory. Therefore, we compared the swimming speed of rats on the fourth test day. However, Student's *t*-test showed that there was no significant difference in swimming speed between two groups ($p>0.40$) (data not shown).

In the water maze probe trails, the percentage of time in target quadrant of Rb1 group was significantly higher than that of control group ($p<0.01$) (Fig. 1B). In addition, the number of crossing over the previous site of the platform was measured at the same time. The number of crosses of Rb1 group rats significantly increased ($p<0.01$) (Fig. 1C).

In the visible version of the water maze, it was found that there was no significant difference between the escape