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Glatiramer acetate reverses cognitive deficits from cranial-irradiated rat by inducing hippocampal neurogenesis

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ABSTRACT

Patients received cranial-irradiation can be affected with cognitive deficits and decreasing hippocampal neurogenesis. In this work, we characterized the cognitive ability and immune-induced neurogenesis of the pre- and post-treated cranial-irradiated rats with Glatiramer acetate (GA), known as a weak CNS auto-antigen. The GA-treated rats displayed better cognitive abilities in Morris water maze (MWM). The numbers of Iba-I-positive microglia, $BrdU^+/DCX^+$ cells and $BrdU^+/NeuN^+$ cells in hippocampus increased, which are accompanied with increased IFN-γ and decreased IL-6, IL-4. Furthermore, GA reverted the Th1/Th2 balance. GA treatment can reverse the cognitive deficits caused by cranial irradiation through a mechanism that likely involves immunomodulation.

1. Introduction

Cranial radiotherapy is a necessary strategy widely used in systemic therapies of various cancers, such as primary brain tumors, metastatic brain tumors and certain head and neck malignancies. Patients who have received cranial radiotherapy can accompany with cognitive deficits, which appear several months to years after radiotherapy and worsen progressively (Monje, 2008). There has been no effective treatment until now. Cognitive processes are associated with the hippocampus (Kempermann et al., 1997; Gould et al., 1999). Hippocampus sustainably produces new neurons and may contribute to learning and memory. Cranial irradiation can induce extensive microglial inflammation and the release of pro-inflammatory cytokines such as Interleukin 6 (IL-6) (Monje et al., 2003), which can destroy the neurogenic microenvironment and subsequently block postnatal hippocampal neurogenesis (Monje et al., 2002).

It is known that the blood–brain-barrier (BBB) and environment of the central nervous system (CNS) guard the nervous tissue against peripheral immune cells; therefore, the CNS used to be considered an "immunological privileged site" (Barker and Billingham, 1977). However, more and more studies have recently provided accumulative evidence that the brain could not only be both involved in and affected by immune surveillance-monitoring but also be affected by the immune status of the periphery. On recognition of self-antigen (self-Ag), CD4+ memory T cells are activated to be self-recognizing T lymphocytes, which circulate in the cerebrospinal fluid (CSF) for immunosurveillance. Self-recognizing T cells in both the periphery and the CSF secrete growth/survival factors, such as insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF), and cross-talk with resident microglia to cause neural stem and progenitor cells (NPCs) to proliferate, migrate and differentiate (Ziv and Schwartz, 2008; Schwartz and Shechter, 2010). Under normal circumstances, the peripheral immune system and the CNS are maintained in a relatively stable state. If the immune activation is overwhelming, cytotoxic factors (such as tumor necrosis factor α (TNF-α) and IL-6) increase and growth factors (such as IGF-1 and BDNF) decrease, which could result in neurodegeneration. If the immune response could be regulated with proper timing, location and context, increasing cytotoxic factors and decreasing growth factors could result in neuroprotection (Schwartz et al., 2009).

T cells recognizing CNS antigens are implicated in the recovery of CNS from injuries through a phenomenon called "protective autoimmunity", which was formulated by Schwartz and her group (Ziv et al., 2006). T-cell immune responses caused by central nervous system (CNS) auto-antigens can restore the brain's immune microenvironment,

Abbreviations: GA, Glatiramer acetate; CNS, central nervous system; MWM, Morris water maze; IL-6, Interleukin 6; BBB, blood–brain-barrier; self-Ag, self-antigen; CSF, cerebrospinal fluid; IGF-1, insulin-like growth factor 1; BDNF, brain-derived neurotrophic factor; NPCS, neural stem and progenitor cells; TNF-α, tumor necrosis factor α; BrdU, 5-bromo-2′-deoxyuridine.

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which is capable of supporting CNS cell renewal. Numerous studies suggest that immune cells may play an essential role in various CNS-injury and age-related impairments by causing a decline in CNS neurogenesis (Monje et al., 2003; Ziv et al., 2006; Lewitus et al., 2009; Villeda et al., 2011).

Glatiramer acetate (GA) consists of acetate salts of synthetic polypeptides containing L-alanine, L-glutamate, L-lysine, and L-tyrosine. Known as a weak CNS auto-antigen, GA is an approved drug for the treatment of multiple sclerosis, and has been used to promote an immune-mediated neuroprotective response in various models of acute CNS injury (Kipnis et al., 2000).

Given that cranial irradiation can injure the local immune microenvironments which is mainly associated with hippocampal neurogenesis (Monje et al., 2003), in this work, we intended to evaluate whether irradiation-induced cognitive deficits and neurogenesis could be repaired by GA immune—restoring the neurogenic microenvironment in brain-irradiated rat models.

2. Materials and methods

2.1. Animal models and treatment

Sprague–Dawley rats were obtained from the Experimental Animal Center of Sun Yat-sen University. All animal handling and procedures were approved by the institutional animal care and use committee at Sun Yat-sen University. Six weeks old male SD rats were randomly divided into five groups: the control group, control GA, 'pre-GA Rad', 'post-GA Rad', and 'Rad alone' (six rats per group). The control group was treated with PBS; the control GA was treated with GA alone; two weeks later after GA treatments, the pre-GA Rad group received cranial irradiation; the post-GA Rad group was post-treated with GA just one day after irradiation; and the Rad group was treated with radiation alone. GA-treated animals were all s.c. injected five times with a total of 100 μg high-molecular-weight GA (Batch No. 538659, Teva Pharmaceutical Industries, Petah Tiqva, Israel) dissolved in 200 μL of PBS;

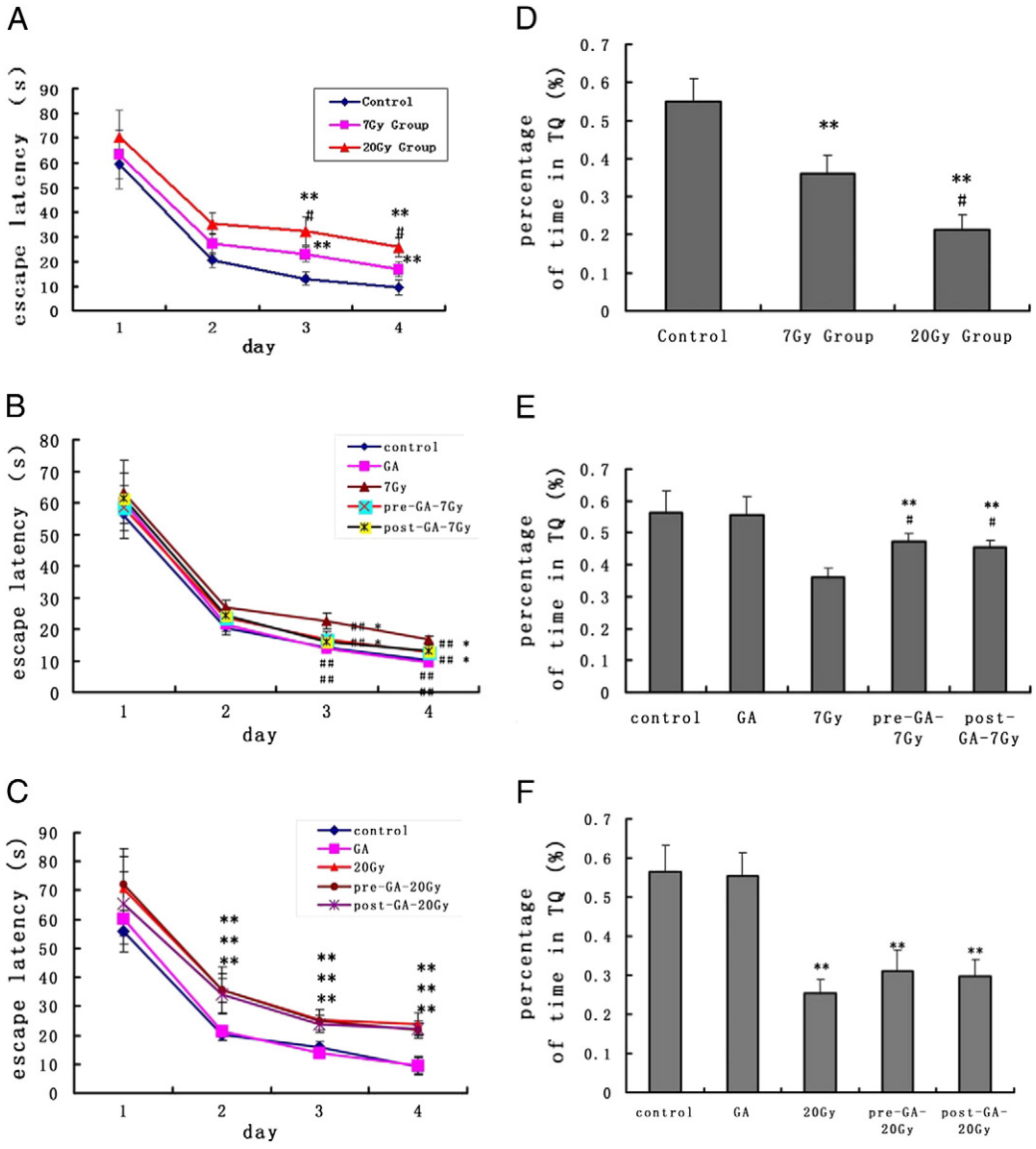

Fig. 1. The effects of GA vaccination on radiation-induced cognitive deficit were assessed in a Morris water maze. (A), (B), and (C) Learning curve showing the escape latency at days 1–4. $^{**}p < 0.01$ compared with the control; $^{\#}p < 0.05$ compared with irradiation alone. (D) Percentage of time spent in the target quadrant (TQ) in probe trials in 7Gy group and 20Gy group. $^{**}p < 0.01$, compared with the control; $^{\#}p < 0.05$ compared with 7Gy group. (E) Percentage of time spent in the target quadrant (TQ) in probe trials in 7Gy GA-treated groups. $^{**}p < 0.01$, compared with 7Gy alone group; $^{\#}p < 0.05$ compared with the control. (F) Percentage of time spent in the target quadrant (TQ) in probe trials in 20Gy GA-treated groups. $^{**}p < 0.01$, compared with the control.