Neurochem Res
DOI 10.1007/s11064-014-1470-4

ORIGINAL PAPER

Hyaluronan Tetrasaccharide Exerts Neuroprotective Effect and Promotes Functional Recovery After Acute Spinal Cord Injury in Rats

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Received: 25 June 2014 / Revised: 11 September 2014 / Accepted: 30 October 2014

Abstract The objective of this study was to explore the therapeutic efficiency of hyaluronan tetrasaccharide (HA_4) treatment after spinal cord injury (SCI) in rats and to investigate the underlying mechanism. Locomotor functional and electrophysiological evaluations revealed that the behavioral function of rats in the HA_4-treated group was significantly improved compared with the vehicle-treated group. The expression of brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), cluster determinant (CD44) and Toll-like receptor-4 (TLR-4) was obviously upregulated in the HA_4-treated group than that in the sham and vehicle-treated group. Furthermore, HA_4 could induce BDNF and VEGF expression in the astrocytes in vitro. In addition, the high expression of BDNF and VEGF could be inhibited by blocking CD44 and TLR-4. These findings indicate that HA_4 could be useful as a promising therapeutic agent for SCI and might exert the effect by interaction with the CD44 and TLR-4.

Keywords Spinal cord injury · Hyaluronan tetrasaccharide · Astrocytes · Neurotrophic factor

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Introduction

Spinal cord injuries (SCI) are highly disabling and deadly injuries. With the modern traffic development, the incidence and prevalence of spinal injuries have been increasing, with the incidence rate of traumatic SCI estimated at 15–40 cases per million worldwide, although injury prevention initiatives have tried to reduce the occurrence of SCIs [1]. The adult central nervous system (CNS) has limited regenerative capacity and is unable to achieve full functional recovery after traumatic injury. Thus, the patients with complete SCI always have poor outcomes and the problem causes a huge economic burden to society and family.

Hyaluronan (HA) was first described by Meyer and Palmer and composed of repeating units of disaccharides [-D-glucuronic-acid-b1, 3-*N*-acetyl-D-glucosamine b1, 4-]n [2]. It has been reported that different molecular weight HA has distinct biological function [2–4]. In the literature, Many studies have showed that low molecular weight (LMW)-HA has the neuroprotective effect on the nervous system. The previous study has demonstrated that NMDA-induced neuronal cell death was partially blocked by hyaluronan tetrasaccharide (HA_4) in vitro, and HA_4 promotes motor function recovery after SCI in vivo [5]. It has been reported that, at an optimal dose, HA_4 promotes neural regeneration and axonal outgrowth [6].

In our previous study, it has been reported that HA_4 in the cerebrospinal fluid was associated with self-repair of rats after chronic spinal cord compression. Furthermore, HA_4 could induce the neurotrophic factor expression in the astrocytes in vitro and these phenomenons illustrated that LMW-HA_4 could exert positive influence on the SCI [7]. Thus, we performed this experiment to assess the neuroprotective effect of HA_4 on the injured spinal cord in the rats.

Published online: 06 November 2014