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Non-invasive topical drug delivery to spinal cord with carboxyl-modified trifunctional copolymer of ethylene oxide and propylene oxide

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ABSTRACT

In this study the effect of oxidative modification on micellar and drug delivery properties of copolymers of ethylene oxide (EO) and propylene oxide (PO) was investigated. Carboxylated trifunctional copolymers were synthesized in the reaction with chromium(VI) oxide. We found that carboxylation significantly improved the uniformity and stability of polymeric micelles by inhibiting the microphase transition. The cytotoxicity of copolymers was studied in relation to their aggregative state on two cell types (cancer line vs. primary fibroblasts). The accumulation of rhodamine 123 in neuroblastoma SH-SY5Y cells was dramatically increased in the presence of the oxidized block copolymer with the number of PO and EO units of 83.5 and 24.2, respectively. The copolymer was also tested as an enhancer for topical drug delivery to the spinal cord when applied subdurally. The oxidized copolymer facilitated the penetration of rhodamine 123 across spinal cord tissues and increased its intraspinal accumulation. These results show the potential of using oxidized EO/PO based polymers for non-invasive delivery of protective drugs after spinal cord injury.

1. Introduction

Although a number of synthetic and biological substances were suggested as neuroprotectors, there is still a lack of available therapy for neurotrauma and particularly for spinal cord (SC) injury [1]. The only clinically accepted substance to cure the acute spinal cord injury is high-dose intravenous infusion of methylprednisolone, which is nevertheless controversial and related with serious side effects [2].

A line of potential agents with the neuroprotective activity has been studied over the last years, such as antioxidants [3], antagonists for glutamate excitotoxicity [4], and others. Recently polymers and colloids attract interest of researchers as promising neuroprotective agents and also a system for drug delivery.

Borgens and co-workers demonstrated that the administration of low molecular weight PEG to guinea pigs after severe spinal cord injury results in a significant recovery of nerve conduction and inhibition of consequences of secondary trauma [5,6]. Several mechanisms for PEG-assisted neuroprotection have been proposed, including direct sealing of the plasma membrane of damaged nerve cells, inhibition of calcium influx and oxidative stress, mitochondria protection and apoptosis inhibition [5,6]. The polymer-based therapy has been extended to PEG-related amphiphilic polymers, e.g. the block copolymer of ethylene oxide (EO) and propylene oxide (PO) Pluronic F68 (Poloxamer 188) [7] and PEG–polylactic acid (PLA) copolymer [8], which exhibited neuroprotective effect in SC injury at lower dose than that for PEG.

Other approaches to treating SC injury have been focused on the local polymer-assisted transfer of bioactive substances to the damaged spinal cord. Most studies in this field have reported gel and nanoparticle-based formulations with encapsulated drugs, which are intrathecally injected in the SC. Gupta et al. proposed fast-gelling hyaluronan/methylcellulose composite which exhibited

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