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Review

Polymer and nano-technology applications for repair and reconstruction of the central nervous system

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ABSTRACT

The hydrophilic polymer PEG and its related derivatives, have served as therapeutic agents to reconstruct the phospholipid bilayers of damaged cell membranes by erasing defects in the plasmalemma. The special attributes of hydrophilic polymers when in contact with cell membranes have been used for several decades since these well-known properties have been exploited in the manufacture of monoclonal antibodies. However, while traditional therapeutic efforts to combat traumatic injuries of the central nervous system (CNS) have not been successful, nanotechnology-based drug delivery has become a new emerging strategy with the additional promise of targeted membrane repair. As such, this potential use of nanotechnology provides new avenues for nanomedicine that uses nanoparticles themselves as the therapeutic agent in addition to their other functionalities. Here we will specifically address new advances in experimental treatment of Spinal Cord and Traumatic Brain injury (SCI and TBI respectively). We focus on the concept of repair of the neurolemma and axolemma in the acute stage of injury, with less emphasis on the worthwhile, and voluminous, issues concerning regenerative medicine/nanomedicine. It is not that the two are mutually exclusive — they are not. However, the survival of the neuron and the tissues of white matter are critical to any further success in what will likely be a multi-component therapy for TBI and SCI.

This review includes a brief explanation of the characteristics of traumatic spinal cord injury SCI, the biological basis of the injuries, and the treatment opportunities of current polymer-based therapies. In particular, we update our own progress in such applications for CNS injuries with various suggestions and discussion, primarily nanocarrier-based drug delivery systems. The application of nanoparticles as drug-delivery vehicles to the CNS may likely be advantageous over existing molecular-based therapies. As a "proof-of-concept", we will discuss the recent investigations that have preferentially facilitated repair and functional recovery from breaches in neural membranes via rapid sealing and reassembly of the compromised site with silica or chitosan nanoparticles.

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Introduction

The injuries to the central nervous system (CNS; brain and spinal cord), are one of the most challenging fields of medical development. Those that have suffered from traumatic spinal cord and brain injuries endure life-long paralysis and other significant losses to their quality of life. In the latter, TBI is the leading cause of death in the US among children and young adults (the mode, or most frequent age at injury, is 19 years of age). Over a quarter of a million persons are hospitalized each year and estimates are 80–90,000 of these persons survive but with significant functional losses including cognitive disruption, memory, and sometimes even suffer significant changes in personality. Most require considerable medical care over the course of their lifetime (Thurman et al., 1999). Estimates of chronically injured SCI patients suggest about 250,000 persons in the United States; the average age at injury is 31, and the most frequent age at injury (the mode) is again 19 (Berkowitz et al., 1998; DeVivo et al., 1995).

The overall mission of this Research Center for 25 years has been to develop new therapies for spinal cord injury (SCI), traumatic brain injury (TBI), and other neurological-related pathologies in human medicine. After more than 60 years, SCI and TBI have no "standard of care" treatment that can significantly prevent or restore the loss of behavior after the injury. The use of 4-AP (dalfampridine or alternately ampyra) to treat chronic SCI and Multiple Sclerosis originated in this group and is now commercialized by Acorda Therapeutics (for the treatment of MS), as is the use of Oscillating Field Stimulation (OFS; Shapiro et al., 2005; Walters, 2010) by NeuroMetrix Corporation. We have developed these modalities as CNS therapies, stewarding them through their initial human clinical trials, and securing corporate sponsorship in partnership with our University. Our latest "invention" to reach the threshold of human testing is intravenous administration of polyethylene glycol in TBI and SCI as will be discussed below. The Purdue licensee, Medtronics/Sofamor Danek Corporation, successfully completed phase one "safety" trials using uninjured volunteers which now brings the intravenous use of PEG to the very door of human SCI and TBI clinical trials.

Though we emphasize CNS injury — we are certainly not limited in this area, but feel that the most catastrophic of injuries provide the best "proof of concept" investigations possessing the most serious human need. The passage above is meant to reveal our dedication to turn the technologies discussed here into actual, practical, and clinical therapies — moving them through the initial human clinical trials, so these issues will be emphasized.

A self-propagating catastrophe: CNS trauma

The degenerative process in the injured nervous system begins instantly after damage coincident with the deterioration of the barrier function of the plasma membrane. Subsequently, necrosis and apoptosis of cells, and eventually cell and tissue death occur. Under these circumstances, rapid and acute sealing of the initial impairment of the cell membrane is critical to reduce progressive collapse of the plasma membranes and thus inhibits severe cell and tissue deterioration at the site of an injury and immediately adjacent to it. As the permeability in the plasma membrane generated by such pathological damage facilitates the movement of intracellular and extracellular ions and molecular substances across the affected membrane, irreversible conduction loss in nerve processes and apparent nerve failure is inevitable. Occasionally, natural and spontaneous resealing, a passive process, is typical at the injury site in cases of minor membrane disruption. In moderate to severe cases, lethal phospholipid membrane disruption is a part of an auto-catalytic destructive pageant called "secondary injury". As a consequence, even normal healthy cells may be particularly susceptible to the production of highly reactive oxygen species (ROS) and later, lipid peroxidation of the membrane (LPO) (Liu-Snyder et al., 2006a,b). This leads to the production of potent endogenous toxins such as acrolein that are the poisonous agents of secondary injury to cells and tissues (Fig. 1) (Liu-Snyder et al., 2006a,b).

Fusogens/sealants

The term "fusogen" has been applied to some polymers (PEG, Poloxamers, and Poloxamines) denoting their ability to fuse the membranes of several cells (producing giant ones). Their initial notoriety came with the fabrication of monoclonal antibodies from so-called fused "hybridomas". Below we provide the history and details