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Advanced biomaterials for repairing the nervous system: what can hydrogels do for the brain?

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Newly developed hydrogels are likely to play significant roles in future therapeutic strategies for the nervous system. In this review, unique features of the central nervous system (i.e., the brain and spinal cord) that are important to consider in developing engineered biomaterials for therapeutic applications are discussed. This review focuses on recent findings in hydrogels as biomaterials for use as (1) drug delivery devices, specifically focusing on how the material can change the delivery rate of small molecules, (2) scaffolds that can modify the post-injury environment, including preformed and injectable scaffolds, (3) cell delivery vehicles, discussing cellular response to natural and synthetic polymers as well as structured and amorphous materials, and (4) scaffolds for tissue regeneration, describing micro- and macro-architectural constructs that have been designed for neural applications. In addition, key features in each category that are likely to contribute to the translational success of these biomaterials are highlighted.

Introduction

Recent advances both in our understanding of the nervous system and the availability of sophisticated biomaterials have significantly changed the landscape of potential strategies for repairing the nervous system. New imaging and staining techniques along with the development of novel materials have opened the possibility to directly design biomaterials tailored for a particular application. In this short review, recent advances in the use of hydrogels made from both natural and synthetic polymers are discussed (see Fig. 1 as reference) and their evaluations using *in vitro* and *in vivo* preclinical models are presented where applicable. This review is by no means a comprehensive review of biomaterials for nervous system repair: the readers are referred to a number of other excellent review articles for further studies [1–11]. This review introduces important obstacles to central nervous system (CNS) regeneration focusing on the unique characteristics of the CNS. Additionally, the injury environment and scarring are unique to the CNS in that a glial scar introduces a physical and chemical barrier to regeneration. Understanding the specific requirements and taking them into consideration in designing therapeutic platforms are likely to result in the successful development of next generation biomaterials. Briefly, the blood barriers, the endogenous immune system within the CNS, and the mechanical properties of CNS tissues are discussed. The focus of this review is on the use of hydrogels as scaffolds to aid regeneration within the central nervous system (CNS) (i.e., the brain and spinal cord). In particular, the following systems and applications are highlighted: (1) hydrogels as drug delivery platforms, (2) hydrogels to modify the post-injury environment, (3) hydrogels for cell delivery and (4) hydrogels for tissue regeneration.

Features of the central nervous system to consider for biomaterial development

There are a number of challenges that are unique to the CNS that must be considered for development of therapeutic biomaterials. First, the CNS is segregated from the circulating blood by the blood brain barrier (BBB) and the blood spinal cord barrier (BSCB). These barriers are made up of tight junctions between extracellular membranes of endothelial cells and astrocytes. In normal physiological

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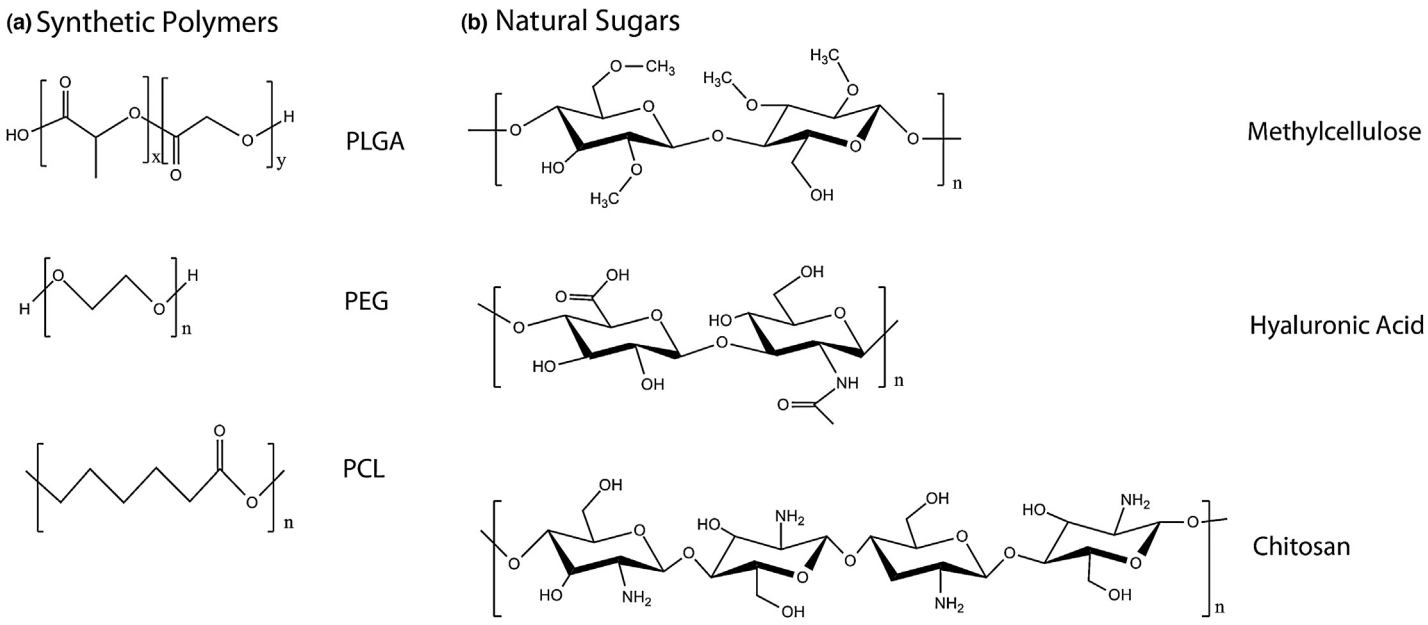

FIGURE 1

Synthetic and natural materials can be used to deliver small molecules or cells to the nervous system. Micro and macro architecture can also be introduced to these hydrogels to alter injury environments and direct cell behavior. Chemical structures of some common polymers are presented here. *Abbreviations*: PLGA – poly(lactic-co-glycolic acid), PEG – poly(ethylene glycol), PCL – polycaprolactone.

conditions, few molecules can passively move from the circulating blood to the CNS extracellular fluid. This makes it difficult, if not impossible, to deliver drugs and small molecule therapeutics to the CNS intravenously. It has been suggested that hydrogels made from both natural and synthetic polymers that can be intrathecally placed into localized areas show great promise to deliver therapeutics into the brain and spinal cord.

Under normal conditions, the BBB and BSCB also isolate the CNS tissue from the circulating immune cells. Thus, the CNS is considered an 'immune privileged' organ. Major immune cells within the CNS include (1) microglia, which are resident immune cells that are distributed throughout the brain and the spinal cord, and (2) perivascular macrophages that are located in the capillaries. After injury or in response to disease, microglia, astroctyes, macrophages, oligodendroctyes and even neurons to an extent, can all respond and release inflammatory cytokines [12]. Therefore, for biomaterials to modify the injury environment, the materials must interact with the resident cells' immune response in a positive manner [13].

The brain and spinal cord are some of the softest tissues in the body with compressive moduli around 2000 Pa [14–16]. Matching the mechanical properties of an implanted biomaterial to that of the host tissue can significantly affect the success of the implanted material *in vivo* [2,17]. *In vitro* studies of neural progenitor cell (NPC) differentiation showed that hydrogels that best matched the stiffness of the brain provided the most optimal results for neuronal differentiation [16,18]. Hence, determining the appropriate mechanical property is a key factor to consider when using biomaterials in the CNS.

Injury environment of the nervous system

A major difference between the peripheral nervous system (PNS) and CNS is the capacity for peripheral nerves to regenerate; CNS axons do not regenerate appreciably in their native environment. After injury in the CNS, macrophages infiltrate the site of injury much more slowly than they do in the PNS. This delays the removal of inhibitory myelin associated proteins from the injury site. Macrophage recruitment is also limited because cell adhesion molecules in the distal end of the injured spinal cord are not appreciably up-regulated. Additionally, astrocytes in the CNS become 'reactive', and produce glial scar tissue.

Astrocytic response after injury is characterized by cellular hypertrophy, astrocyte proliferation, process extension, and increased production of the intermediate filament proteins glial fibrillary acidic protein (GFAP), vimentin, and nestin [19]. This response of astrocytes to injury is known as reactive gliosis. When an injury does not involve penetrating the dura mater, the scar tissue formed is mainly composed of astrocytes; however, when the dura is broken there is infiltration of meningeal fibroblasts in addition to reactive astrocytes [20]. Most glial scar tissue is thought to include, in addition to the reactive astrocytes, $NG2^+$ oligodendrocyte precursor cells, meningeal cells, infiltrating macrophages, and activated microglia. Schwann cells from adjacent dorsal roots have also been found within the CNS scar tissue in experimental injuries where the dura was broken. The mature glial scar includes proteoglycans such as neurocan, phosphocan, versican, and brevican along with secreted proteins including Semaphorin 3A and 3D [21]. One notable component of glial scar tissue is chondroitin sulfate proteoglycans (CSPGs). CSPGs have been shown to inhibit axonal outgrowth in many neuronal systems [22]. In sites distant from traumatic injury, astrocytes can also become larger in size and transform into a more pronounced stellate shape. These 'activated astrocytes' have been known to produce soluble trophic factors that enhance the survival of neurons and glial cells in the vicinity of the astrocytes [23]. Therefore, the effects of activated astrocytes after injury on axonal regeneration and neuronal plasticity is unclear. Moreover, myelin-related glycoproteins have long been implicated in creating a non-hospitable environment for the