Review Article

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Cell based therapy for the management of chronic pain

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The management of chronic pain, particularly neuropathic pain, still has significant unmet needs. In addition to inadequate symptomatic relief, there are concerns about adverse effects and addiction associated with treatments. The transplantation of cells that secrete neuroactive substances with analgesic properties into the central nervous system has only become of practical interest in more recent years, but provides a novel strategy to challenge current approaches in treating chronic pain. This review covers pre-clinical and clinical studies from both allogeneic and xenogeneic sources for management of chronic refractory pain. (Korean J Anesthesiol 2011; 60: 3-7)

Key Words: Cell therapy, Chronic pain, Encapsulated cells, Gene therapy, Genetically modified cells.

Introduction

Chronic pain of different etiologies affects brain structure and function [1]. It may cause other symptoms or conditions, including depression and anxiety, and may also contribute to decreased physical activity given the apprehension of exacerbating pain [2]. Despite recent advances in our understanding of chronic pain mechanisms and normal nociceptive transmission, the management of chronic pain, particularly neuropathic pain, is still far from resolved with currently available therapeutic regimens. Although many effective treatments are available, a number of adverse effects that interfere with the quality of life may be associated with treatment, and a significant number of patients obtain no relief from these treatments. Therefore, chronic pain is a major medical and societal problems resulting in enormous financial costs [3].

Transplanting cells that secrete neuroactive substances with analgesic properties into the central nervous system (CNS) may have therapeutic potential for the long-term treatment of chronic pain [4-7]. Cell transplantation could provide analgesic effects similar to neuraxial drug delivery pumps such as the secretion of pain-reducing neuroactive substances at optimal sites and constant level, while overcoming problems of pump refilling and maintenance. In addition, these cell-based approaches targeted to the CNS could alleviate most systemic side effects. Therefore, the selection of appropriate bioengineered cells as biological mini pumps can provide permanent management of chronic pain. This review focuses on the role of cell-based therapy in the management of chronic pain.

The Mechanism of Cell Based Therapy for Pain

Cell transplants for pain are based on the concept of descending inhibitory modulation of sensory information. Descending inhibitory tracts from cell bodies in the periaqueductal

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gray, reticular formation, and nucleus magnus project to the dorsal horn. These inhibitory tracts contain a variety of neurotransmitters, including catecholamines and opioids, which play an important role in nociceptive responses [8,9]. Chromaffin cells [4-7], neural precursor cells [10], mesenchymal stem cells [11], and genetically engineered cells [12] can secrete neuroactive materials, including catecholamines, opioid peptides, and other neuropeptides with anti-nociceptive properties. Intrathecal transplantation of these cells induces analgesia in animal pain models.

Biomaterial Technology for Cell Implantation

One of the biggest issues for organ transplantation is the shortage of donor tissues or organs. The low number of available grafts requires the use of xenogenic non-human donors, but the transplants undergo immunological rejection, limiting their survival. In addition, the continuous use of immunosuppressive agents to prevent immunological rejection often causes side effects, such as bacterial or viral infection and carcinogenesis. Analgesic effects correlate with graft viability and output [6,7,13], and xenogenic grafts are frequently rejected. Therefore, protecting grafts from immunological responses by encapsulating them within a semipermeable membrane using biocompatible materials allows for immunoisolation, which permits the inward diffusion of small molecule nutrients and oxygen, and outward diffusion of therapeutic material produced by implants, but preventing host immune system responses and improving long-term graft survival without immunosuppressants [5-7].

One common design for microencapsulation involves enclosing cells within the lumen of a semipermeable membrane or flat sheet membrane of polyacrylonitrile/polyvinylchloride fiber [13]. For macroencapsulation, cells are usually suspended in a matrix within a hollow fiber membrane. The open ends of the hollow fiber are sealed, thereby forming a capsule within which the cells reside. The advantages of this technique include stability of the implant and ease of retrieval. However, the relatively thick fiber membrane is disadvantageous for cell viability and the efficient release of neuroactive materials, because there is a relatively large diffusion distance across the membrane. The loss of cell viability, in particular, severely limits the usefulness of macrocapsules [13]. This low grafting rate of cells transplanted and their consequent poor functions often cause low therapeutic efficacy of cell transplantation. Cells must have a suitable environment to overcome these problems. Microcapsules are much smaller, durable, and typically have a larger surface to volume ratio that is advantageous for the bi-directional diffusion of nutrients, oxygen, and bioactive materials, compared to macrocapsules. Therefore, microcapsules are more effective for the delivery of analgesic substances by transmembrane diffusion than macrocapsules [5-7]. In addition, the dimensions of microcapsules can be scaled easily to suit different species and implantation sites, although they are fragile and cannot be retrieved easily.

Application of Cell-based Therapies for Pain

Chromaffin cells

Chromaffin cells produce and release catecholamines, opioid peptides of various sizes, and other neuropeptides that produce analgesia in the spinal space [5-7,14]. Cerebrospinal fluid (CSF) in a neuropathic pain model induced by loose ligation of the sciatic nerve induces catecholamines release from chromaffin cells [15]. Long-term survival of intrathecally implanted encapsulated bovine chromaffin cells reduced mechanical and cold allodynia in a rat model of neuropathic pain [5-7]. In addition, norepinephrine and met-enkephalin levels of CSF were higher in the rats that received microencapsulated chromaffin cells [6]. However, due to concerns over the risk of prion transmission, the use of bovine adrenal medulla may be precluded in future clinical trials. Intrathecal porcine chromaffin cells also suppress nociceptive behavior in animal pain models [16,17].

Neural precursor cells

Chromaffin cells stem from the neural crest, which plays a paradigmatic role in the mechanism that determines cell fate in the nervous system. Two types of fetal human chromaffin cells with an adrenergic phenotype between 7 and 10 gestational weeks could be obtained in vitro [18] through specific procedures, but these cells could be exploited for pain therapy [19]. Allodynia after injury may involve the pathological loss of inhibition in the spinal cord [20]. Following spinal cord or peripheral nerve injury, there is an apparent loss of γ-aminobutyric acid (GABA) ergic inhibitory interneurons in the spinal cord [21]. Bioreactor-expanded human neural precursor cells differentiated to a GABAergic phenotype prior to transplantation decreased allodynia in rat model of neuropathic pain induced by ligation of the spinal nerve [10].

Stem cells

Stem cells hold great potential for the regeneration of damaged tissues [22]. They limit neuronal damage in a wide variety of experimental neurologic injuries, including Parkinson's disease [23], spinal cord injury [24], and peripheral nerve damage [25]. Intra-brain microinjection of human

mesenchymal stem cells (hMSC) reduced the mRNA levels of the proinflammatory interleukin-1beta gene, as well as astrocytic and microglial cell activation in neuropathic mice [26]. In vitro, genetically engineered hMSCs transfected with the human preproenkephalin (hPPE) gene increased production of the opioid peptide, met-enkephalin [11]. In addition, hybrid cell fusions of chromaffin cells and hMSCs expressed some characteristics of the chromaffin cell phenotype, suggesting that novel cellular production could be developed by a "reprogramming" mechanism through the application of targeted cell fusion strategies [27]. Stem cells can provide a sufficient number of chromaffin cells due to the paucity of human adrenal tissue.

Cell lines

Immortalized cell lines are an alternative to chromaffin cells for cellular implantation, offering the advantage of shelf availability as well as a more detailed characterization of their phenotype and histocompatibility. The most useful cell lines are derived from chromaffin cells, with ongoing creation of human chromaffin cell lines that may be useful in treating traumatic and neurodegenerative disease [28-31]. Initially, the archetypal adrenal medullary cell lines were derived from spontaneous pheochromocytoma of the medulla, either from murine or human sources, such as the rat PC12 cell line and the human KNA and KAT45 cell lines [28-30]. Modern techniques use tumorigenesis and targeted oncogenesis in vivo, where isolation of specific populations of mouse endocrine cells allows exploration of the regulatory pathways in the chromaffin phenotype [31]. In addition, conditional immortalization with retroviral infection of chromaffin precursors has provided homogeneous and expandable chromaffin cells for transplant studies in animal models of pain [32]. This same strategy of immortalization with conditionally expressed oncogenes has been expanded to create the first disimmortalizable chromaffin cells, with an excisable oncogenic cassette, as might be envisioned for the creation of human chromaffin cell lines [33,34].

The use of monoamine-secreting cell lines for the continuous delivery of catecholamines and/or serotonin to the spinal cord may be an alternative strategy for the treatment of chronic pain. An encapsulated neuroblastoma cell line NB69 given intrathecally produced analgesia to neuropathic pain in rats by producing monoamines (dopamine and serotonin) [35]. Immortalized chromaffin cells of rats were genetically modified to improve opioid peptide expression through lipid-mediated gene transfer. When implanted into the spinal space, they reduced evoked c-fos protein expression in rat dorsal horn neurons in the formalin tonic pain model [36]. The use of such expandable cell lines for chronic spinal delivery of opiates could offer an attractive and safe alternative strategy based on ex vivo gene therapy for the control of opioid-sensitive chronic pain.

Macrophages

An ex vivo gene transfer of the human proenkephalin gene to autologous macrophages of rats was performed with a non-viral vector. Intrathecal implantation of these cells alleviated heat hyperalgesia and allodynia induced by sciatic nerve constriction for four weeks. The transplanted macrophages migrated into the spinal cord and expressed proenkephalin mRNA and met-enkephalin protein [37].

Clinical trial

Clinical trials with allografts consisting of whole-tissue fragments implanted into the subarachnoid space of the lumbar spinal cord showed that the allogeneic grafts could control cancer pain in two patients over 1 year based on patient reported pain scores, morphine intake, and CSF levels of met-enkephalin [38]. A Phase II open study in France showed the feasibility and the safety of chromaffin cell allografts administered intrathecally to cancer patients to relieve intractable pain [39]. The CNS is considered an immune privileged site. Non-human leukocyte antigen (HLA)-matched and unencapsulated tissue was grafted and analgesic efficacy was indicated by the reduction or stabilization in complementary opioid intake, although lymphocyte counts increased in CSF. Further work on the purification and/or the immunoisolation of tissues grafted in the CNS will be necessary, particularly for long-term or repeated grafting.

Conclusions

Cell based treatment offers certain benefits in controlled, safe, long-term delivery of analgesic molecules in experimental cell-based therapies. In addition, novel technologies such as encapsulation and engineered cell lines hold promise for future applications. Initial clinical trials have been generally encouraging, although evidence for translation into clinical use in humans is limited. Together, these studies suggest that cell transplantation is a potentially valuable complementary approach in the therapeutic management of chronic pain.

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