

Potential role of stem cells for neuropathic pain disorders

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Chronic neuropathic pain is a debilitating disease process associated with several medical disorders. Different from pain caused by inflammation, neuropathic pain is a diffuse pain disorder often found to be recalcitrant to the limited medical treatments available. Intractable nerve pain may benefit from other therapies capable of longer-lasting pain coverage or greater efficacy. A growing number of reports have emerged suggesting a role for stem cells as a cellular delivery source with neuroprotective agents opposing the effects of nerve damage. Here, the authors review the current experimental therapies examining the use of stem cells for the treatment of neuropathic pain disorders. (<http://thejns.org/doi/abs/10.3171/2013.6.FOCUS13235>)

KEY WORDS • stem cell • neuropathy • pain • nerve damage •
demyelination • myelin • oligodendrocyte • neurotrophic factor •
nerve growth factor

CHRONIC neuropathic pain is estimated to be on the rise, particularly with the expected increase in patients with diabetes within the US. Diabetic and nondiabetic patients were surveyed for sick days from work due to neuropathic pain; approximately two-thirds of these patients were found to consistently be taking days from work, and only one-fifth of those were satisfied with their current therapy.^{8,24} Unlike nociceptive pain (tissue-injury induced), neuropathic pain is specific to injury of either the central or peripheral nervous system and can be a combination of both. For this reason, several diseases manifest with neuropathy including SCI, stroke, multiple sclerosis, diabetes, infectious related, nutrient deficient, immune related, and oncological. Interestingly, adjuvant therapies for these disorders including chemotherapy and radiation therapy can also lead to chronic neuropathy. Treatments have largely depended on anticonvulsants and antidepressants because of their analgesic effects; however, the nature of neuropathic pain is its chronicity and as such often becomes recalcitrant to these pharmacological strategies. Intractable neuropathic pain has gained increasing awareness due to its prevalence and the technological advancements in surgical neuromodulation. Electrical stimulation via spinal cord, peripheral nerve,

and deep brain targeting has begun to show some early efficacy.¹⁸ To date, chronic neuropathic pain is largely considered a heterogeneous pain syndrome that remains with limited efficacious treatment modalities. Also, there is no treatment strategy that is effective for pain management while promoting nervous system repair.

Stem cell transplantation is a new approach to repairing damaged nervous system-induced neuropathic pain syndromes rather than simply providing palliation. Stem cells offer a totipotent cellular source for replacing injured or lost neural cells. They also represent a delivery modality for trophic factors for the injured nerve. We questioned whether experimental strategies examining repair of the injured nervous system is *sine qua non* for the long-lasting reduction or resolution of chronic neuropathic pain. Here, we review the literature for experimental strategies of examining stem cells for the repair and treatment of neuropathic pain in various disease models to begin to understand common translatable models, identify successes and limitations, and we speculate on these strategies for future directions.

Methods

The literature search was conducted on PubMed using the following 3 separate search queries: 1) stem cell AND neuropathic; 2) stem cell AND neuropathic pain; and 3) stem cell AND pain AND neuropathic. The search is estimated to have returned nearly 200 articles once

Abbreviations used in this paper: ASIA = American Spinal Injury Association; CCI = chronic constriction injury; MSC = mesenchymal stem cell; NCV = nerve conduction velocity; SCI = spinal cord injury.

redundancies were omitted. Articles were selected that focused on directly using stem cells to treat neuropathic pain syndromes in animal models. In particular studies, the references were reviewed for additional studies that were not originally identified. Pertinent studies with a direct hypothesis exploring the use of stem cells for a translatable chronic neuropathic pain disease were particularly reviewed. The results from the literature search were then grouped by disease processes.

Results and Discussion

A summary of the results of the review was assembled into Table 1.

Application of Stem Cells for Common Neuropathic Disorders

The studies demonstrated successful treatment of neuropathic pain associated with various neurological diseases through case reports and animal models (Fig. 1). These diseases include spinal cord injury, sciatic nerve injury, and diabetic neuropathy.

Spinal Cord Injury. The studies investigating spinal cord injury included 2 experimental mouse models. The stem cells were delivered directly into the spinal cord in the animal models.^{4,23}

Oligodendrocyte progenitor cells derived from an embryonic stem cell oligosphere culture selection protocol¹⁵ were used by one group to contribute to the remyelination of injured nerves and therefore inhibit neuropathic pain. When they downregulated neuregulin via small interfering RNA, a reduction in myelination was observed while functional measures of allodynia were increased. This effect was observed to 56 days post-SCI.²³ Another group used nanoparticles in coculture with human adipose tissue-derived stem cells, which led to increased stem cell expansion and self-renewal but also particularly to GABAergic neurons both in vitro and in vivo. This was found to correlate with reduced inflammatory mediators/cells and improvement at 4 weeks with allodynia and paw withdrawal tasks.⁴ Outcomes were assessed and resulting observations of tests of allodynia with hind paw

withdrawal ranging from 28 days to 56 days postinjury were done.

In a case report, Ichim et al.¹¹ transplanted a combination of CD34 and placenta-derived MSCs intrathecally into a 29-year-old man with ASIA Grade A SCI after a plane crash. Serial transplantations were performed and were observed to subsequently lead to an improvement in ASIA grade (from Grade A to D) and neuropathic pain (10/10 to 3/10 consistently) over a 1-year follow-up period.

Sciatic Nerve Lesion. A total of 7 animal models of neuropathic pain treated with stem cells were reviewed (4 mouse models and 3 rat models). In these studies, 4 groups administered the stem cells intravenously.^{6,14,19,22} Other sites to which stem cells were administered included the sciatic nerve,⁷ the L-4 dorsal root ganglion,⁵ and the lateral ventricle of the brain.²¹ After intravenous administration of these cells, migration to damaged nervous tissue was demonstrated.⁶ Administration into the L-4 dorsal root ganglion was the transplantation route used by Coronel et al. since the stem cells injected into the dorsal root ganglion migrate to lesioned cord areas.⁵ Administration of stem cells into the lateral ventricles of the brain was done by Siniscalco et al. to evaluate the role of supraspinal influence on neuropathic pain.²¹

Three different types of stem cells were used: MSCs, marrow mononuclear cells, and neural stem cells. Coronel et al. chose MSCs for their regenerative properties.⁵ Siniscalco et al. chose these cells for a variety of reasons including propensity for immunosuppression, migration to injured neural tissue, and the ability to differentiate into neural cells.^{21,22} Two studies used marrow mononuclear cells.^{7,14} These cells were used because they were easily obtained, they can differentiate into neural cells in an appropriate biological environment, and because remyelination has been previously demonstrated with intravenous administration with this cell type.⁷

Franchi et al. specifically selected neural stem cells to evaluate their use in the CCI model.⁶ Several properties of these cell types made them favorable to the authors, which included their role as direct precursors to neural cells, the role in maintaining nervous tissue, and in the collaboration with immune cells after nerve injury. Outcomes of allodynia and hyperalgesia were assessed pre-

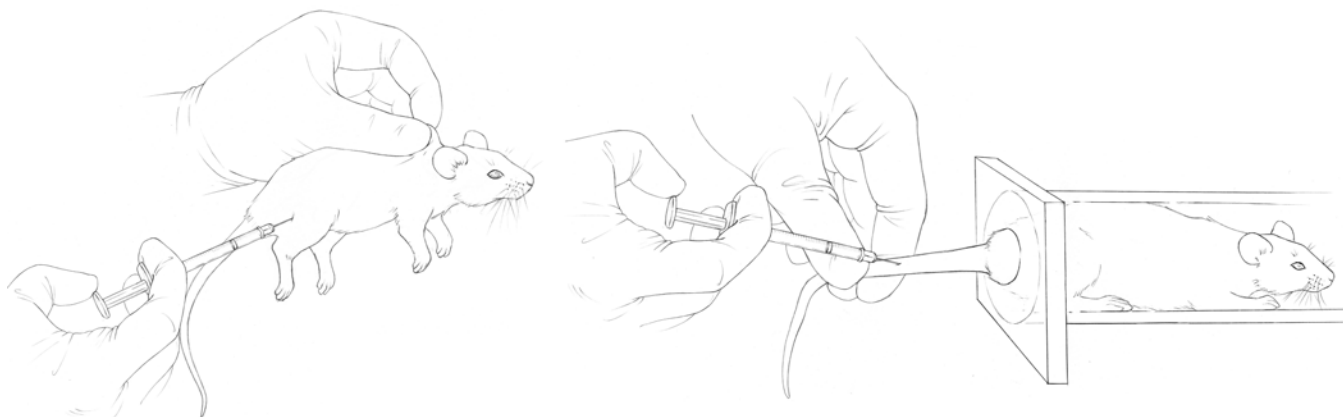


Fig. 1. Schematic representation of delivery routes for experimental stem cell strategies for the treatment of neuropathic pain. Copyright Katherine Relyea, M.S., C.M.I. Published with permission.

TABLE 1: Experimental stem cell strategies for the treatment of neuropathic pain*

| Authors & Year | Methods | | | | Outcome | | |
|-------------------------|---|--------------------------|---------|---|--|---|---|
| | Cell Source | Delivery Site | Species | Model† | Mechanism | Description | Observation Length |
| SCI | | | | | | | |
| Tao et al., 2013 | embryonic stem cell–derived oligodendrocyte progenitor cells | spinal cord | mouse | contusion SCI ⁹ | ↑ neurotrophin-1; ↑ epidermal growth factor receptor; ↑ myelination; presence of oligodendrocytes differentiated from transplanted cells | improved mechanical allodynia | 56 days |
| Choi et al., 2013 | hATSCs w/ core shell nanoparticles (superparamagnetic iron oxide core w/ photonic zinc oxide shell) | spinal cord | mouse | modified SCI model | ↑ GABAergic neurons; ↑ antiinflammatory markers (TGFβ1 and IL-10); ↑ SOD1, GPx3 expression; maintenance of functional neural cells (NF160 cells, MAP2ab, GAP43, GABA, Tuj+, MBP+); ↓ inflammatory cells (ED1+/-/Iba1+) | improved mechanical allodynia; improved heat hyperalgesia | 4 wks |
| sciatic nerve lesion | | | | | | | |
| Klass et al., 2007 | marrow mononuclear cells | IV (tail vein) | rat | sciatic nerve CCI ^{1†} | not evaluated | improved allodynia; improved thermal hyperalgesia | 10 days |
| Coronel et al., 2009 | MSCs | L-4 dorsal root ganglion | rat | ligature nerve constriction of sciatic nerve ³ | ↓ neuropathic pain markers (galanin & NPY); ↑ NPY Y1 receptor | not evaluated | not evaluated |
| Franchi et al., 2012 | neural stem cells | IV (tail vein) | mouse | sciatic nerve CCI ^{1†} | ↓ Fos-positive neurons; ↑ substance P; ↓ inflammatory cytokines; ↑ myelination | improved allodynia; improved heat hyperalgesia | 28 days |
| Goel et al., 2009 | marrow mononuclear cells | sciatic nerve | rat | severed sciatic nerve | ↑ axonal regeneration; ↑ remyelination; ↓ Schwann cell proliferation | not evaluated | not evaluated |
| Siniscalco et al., 2011 | hMSCs | IV (tail vein) | mouse | spared nerve injury ² | ↑ antiinflammatory cytokines (IL-10); ↓ inflammatory cytokines (IL-1β, IL-17); ↑ antiinflammatory macrophages (CD206); hMSCs accumulated at L4–5 & prefrontal cortex | improved allodynia; improved thermal hyperalgesia | 90 days |
| Siniscalco et al., 2010 | hMSCs | lat ventricle | mouse | spared nerve injury ² | ↓ inflammatory cytokine (IL-1β); ↓ neural β-galactosidase (in pre-/infralimbic cortex); ↑ hMSC accumulation near injection site; ↓ astrocytes & Iba-1 microglia activation | improved allodynia; improved thermal hyperalgesia | 21 days |
| Sacerdote et al., 2013 | hASCs | IV | mouse | sciatic nerve CCI ^{1†} | ↑ antiinflammatory cytokines (IL-10); ↓ inflammatory cytokines (IL-1β); replenishes NOS | improved mechanical allodynia; improved heat hyperalgesia | acute effect POD 1 & cont w/ repeat treatment |
| diabetic neuropathy | | | | | | | |
| Shibata et al., 2008 | MSCs | IM (hind leg) | rat | STZ-induced diabetes | ↑ VEGF & bFGF mRNA; ↑ blood flow; ↑ capillary density | improved sensory perception scores; ↑ NCV | not evaluated |
| Kim et al., 2011 | MSCs | IM (hind leg) | mouse | STZ-induced diabetes | ↑ NGF & NT-3 mRNA | ↑ NCV | 12–16 wks |

(continued)

TABLE 1: Experimental stem cell strategies for the treatment of neuropathic pain* (continued)

| Authors & Year | Methods | | | | Outcome | |
|---------------------------------|---------------------------------------|---------------|---------|----------------------|---|--|
| | Cell Source | Delivery Site | Species | Model† | Mechanism | Observation Length |
| diabetic neuropathy (continued) | | | | | | |
| Naruse et al., 2011 | bone marrow–derived mononuclear cells | IM (hind leg) | rat | STZ-induced diabetes | ↑ NT-3; ↑ blood flow; ↑ capillary density | 2 wks for ↑ NCV; 5 wks for hyperalgesia; improved cold allodynia |

* bFGF = basic fibroblast growth factor; cont = continued; GABA = γ -aminobutyric acid; hASC = MSC from adipose tissue; hATSC = human adipose tissue-derived stem cell; hMSC = human MSC; IL = interleukin; IM = intramuscular; IV = intravenous; NF = neurofilament; NGF = nerve growth factor; NOS = nitric oxide synthase; NPY = neuropeptide Y; NT-3 = neurotrophin-3; POD = postoperative day; STZ = streptozotocin; TGF = transforming growth factor; VEGF = vascular endothelial growth factor; ↑ = increased; ↓ = decreased.

† Superscripted numbers in this column cite the study whose method was used for injury.

dominantly via the plantar stepping test and behavioral locomotion assessments. Nerve conduction velocities and sensory perception scores were also collected. Observations were identified ranging, collectively, from 1 to 90 days postoperatively.

Diabetic Neuropathy. Three papers were reviewed that investigated the use of stem cells to treat diabetic neuropathy. All 3 studies were animal models (2 rat and 1 mouse) and all administered stem cells intramuscularly into the hind leg. Two of the studies used MSCs. These cells were also chosen by Shibata et al. for their ability to differentiate into a wide variety of cell types and to secrete cytokines, such as vascular endothelial growth factor and basic fibroblast growth factor.²⁰ Kim et al. used MSCs since recent research has suggested that these stem cells promote neurotrophic factors and that loss of neurotrophic factors might be partly responsible for diabetic neuropathy.¹² Naruse et al. instead used marrow mononuclear cells and mentioned that an advantage of these cells was that they are easily acquired.¹⁷ Outcomes were measured commonly with either sensory perception scoring or NCV. Collectively, the studies reported improvement from 2 to 16 weeks postinjury.

Limitations

Despite the fact that stem cell transplantation strategies have shown good benefit, these approaches are questioned for long-term survival, induced inflammatory responses, tumorigenic formation, and quiescent cells versus active or differentiated cells, and long-term outcome effect. The difficulty in clinical interpretation here is limited to a few animal models with rare functional outcome measures. The heterogeneous differentiation potential of stem cells may limit the ascribed benefit observed in functional assessments. For example, few studies have reported a negative association with stem cell transplantation and neuropathic pain outcomes. Olson's group identified aberrant axonal sprouting to have possibly contributed to increased allodynia-like hypersensitivity despite myelination, motor, and sensory response improvement.¹⁰ This cautions clinical interpretation and translation. Kurpad's group¹⁶ suggested that studies particular to certain neurotrophic factors, in this case glial-derived neurotrophic factor, may have a protective effect when upregulated or provided via stem cell transplantation. However, without it, stem cell transplantation alone into SCI, for example, may be associated with increased allodynia.¹⁶ A case-control study performed in Cairo, Egypt, with 64 total patients participating as either receiving intrathecal marrow mesenchymal cell transplantation monthly or serving as controls (those who did not consent to treatment). Unfortunately, no significant differences were found in primary or secondary end points examining motor, sensory, bladder, bowel, ASIA grade, or somatosensory evoked potential recovery. Furthermore, this group did carefully note that adverse reactions were quite prevalent, as 24 of 43 patients developed neuropathic pain.¹³

Careful experimental studies in the laboratory in appropriate models may advance the understanding of the role of stem cells in pain disorders. The side effects ob-

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served previously are important impediments to patients' daily living with neuropathy, and further preclinical studies directly testing neuropathy are warranted before translation to direct patient care.

Conclusions

The experimental studies reviewed here suggest early encouraging observations in favor of exploring the potential of stem cell application for the treatment of neuropathic pain disorders. The key elements that need to be evaluated include the longevity of stem cell efficacy on treating pain, restoration of nerve injury by repair with cell replacement, and neurotrophic factor delivery.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Vadivelu, Curry, McDonald. Acquisition of data: Vadivelu, Willsey. Analysis and interpretation of data: Vadivelu. Drafting the article: Vadivelu, Willsey. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Vadivelu. Study supervision: Vadivelu, Curry.

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