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REGENERATIVE PAIN MEDICINE/INTERVENTIONAL PAIN MEDICINE (EC BRADLEY, SECTION EDITORS)

Modulatory Effects of Stem Cells on Opioid Receptors and Neuroinflammation

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Abstract

Purpose of Review This narrative review examines stem cell therapy and its effect on opioid therapy in neuropathic pain.

Recent Findings Stem cell therapy has shown promise in neuropathic pain and opioid tolerance, with a notable common pathway (the P2X4 receptor).

Summary Opioid therapy frequently has poor efficacy in patients who suffer from neuropathic pain. There is evidence that the presence of neuropathic pain itself causes changes to the opioid receptor, decreasing the therapeutic potential of this modality. The efficacy of opioid therapy is further decreased in this patient population after chronic opioid exposure, which leads to opioid tolerance and in some cases opioid-induced hyperalgesia. There is growing evidence that stem cell therapy has potential to treat neuropathic pain and may simultaneously decrease opioid tolerance and hyperalgesia. Opioid-induced hyperalgesia occurs via mu-opioid receptor-dependent expression of P2X4 receptors on microglia. Intrathecal stem cell therapy provides analgesic properties due to the significant reduction of P2X4R expression in spinal cord microglia, thereby directly decreasing chronic neuropathic pain.

Keywords Drug tolerance · Hyperalgesia · Neuralgia · Opioid analgesics · Opioid receptors · Pain management

Introduction

Recent data have shown that approximately 62% of the world's population has experienced chronic pain for more than 3 months [1]. Depending on the source of pain, various factors impact the effectiveness of the treatment and the patient's quality of life. Opioids are a commonly offered therapy to provide pain relief. These types of therapy work by interacting with the body's opioid receptors and have been used extensively to treat most types of pain with varying success. A patient treated with opioids generally experiences pain relief when this modality is started, but the relief typically decreases over time due to opioid tolerance (OT). In some cases, these patients experience opioid-induced hyperalgesia (OIH), where they note increased pain over time when experiencing static levels of noxious stimuli. Generally, patients with chronic pain need repetitive increased titrations of opioid therapy to control pain over time, which leads to a significant burden of opioid-induced side effects that can be life threatening. As a result, patients can experience physical dependency on opioid therapy, while their quality of life suffers due to the adverse effects of high-dose opioids, making it an imperfect long-term treatment plan in many patients. Neuropathic pain specifically responds poorly to opioid therapy due to its effect on the structure of the opioid receptor and additional mechanisms discussed in this review.

Stem cell therapy is currently an area of interest in treating a multitude of medical illnesses including chronic pain. This review discusses areas of focus for stem cell therapy in treating neuroinflammation, as well as its impact on opioid therapy and opioid receptors in the setting of neuropathic pain. Stem cell therapy has shown promise in decreasing the severity of neuropathic inflammation and symptoms by multiple mechanisms, as discussed below. Separately, it has shown promise in reducing the effects of OIH and improving the efficacy of opioid therapy in animal models of neuropathic pain. There is evidence that neuroinflammation itself

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plays a role in the structure and function of opioid receptors even in the absence of opioid therapy, leading to decreased opioid efficacy. Understanding these processes in totality has the potential to make advancements in combating the opioid epidemic while improving the quality of life of patients who suffer from chronic pain.

Opioid Therapy

Opioid receptors are located throughout the nervous system and have various effects. They exist in multiple locations in the brain, the dorsal horn of the spinal cord, and peripheral afferent nerves. To date, five receptors have been identified: mu receptor, delta receptor, kappa receptor, nociception receptor, and zeta receptor [2]. Each receptor contains several subtypes, each with their own clinical and physiologic effects. These receptors can be bound and activated by exogenous pharmacologic drugs (e.g., fentanyl) or by endogenous opioid compounds (e.g., enkephalins), which may result in pain relief. While pharmacologic agents and endogenous compounds provide pain relief through various opioid receptors in the central nervous system/peripheral nervous system, several challenges to opioid therapy in the treatment of chronic neuropathic pain remain as opioid resistance and opioid receptor modulation lead to increased treatment with high-dose opioids and increased opioid-related side effects. Stem cell therapy may diminish these effects of chronic opioid therapy and improve the overall efficacy of opioid therapy.

Sánchez-Blázquez et al. describe a mechanism by which morphine administration decreases the efficacy of the opioid receptor [3]. They found that morphine administration caused an uncoupling of the activity of the glutamate ionotropic receptor (GluN) and the mu-opioid receptor. The proposed mechanism for this tolerance is morphine-induced upregulation of GluN receptor activity antagonizing the mu-opioid receptor signaling via nitric oxide synthase, calcium, and calmodulin-regulated kinase II. This induces phosphorylation and uncoupling of the mu-opioid receptor and causes OT.

OIH is thought to occur via a different mechanism, which is characterized by mu-opioid receptor-dependent expression of P2X4 receptors on microglia and the release of brain-derived neurotrophic factor (BDNF) by P2X4 receptors [4]. The release of BDNF, a potent signaling molecule expressed in neurons and immune cells, leads to a cascade of events that results in a switch from inhibitory to excitatory GABA transmission, as well as sensitization of lamina I neurons. This increase in excitatory GABA signaling in conjunction with neuronal hyperexcitability leads to a disinhibition of central pain regulatory mechanisms, which is thought to play a key role in the development of OIH [5]. This conclusion is further supported by the fact that blocking BDNF signaling has been shown to reverse hyperalgesia [4]. Additionally, researchers have also recently isolated a molecule that selectively antagonizes P2X4, which produces anti-allodynic effects in chronic pain models and further supports the regulatory importance of this receptor and its downstream counterparts [6]. As such, both P2X4 and BDNF are of great interest to pain researchers because they may offer a potential target for pharmacologic interventions, including novel stem cell therapies (Fig. 1).

In addition to OIH, it has also been demonstrated that patients who experience neuropathic pain and chronic inflammation have a high expression of P2X4, which leads to the development of mechanical hypersensitivity and allodynia [7]. Recently, several studies have shown promising results in the regulation of this receptor via stem cell-mediated mechanisms. For example, Teng et al. demonstrated the efficacy of stem cell therapy in treating chronic pain by injecting stem cells into the L4-L5 intrathecal interspace of rats that had medically induced chronic pain [8]. The study showed that the analgesic properties of stem cells were due to stem cell-derived factors and

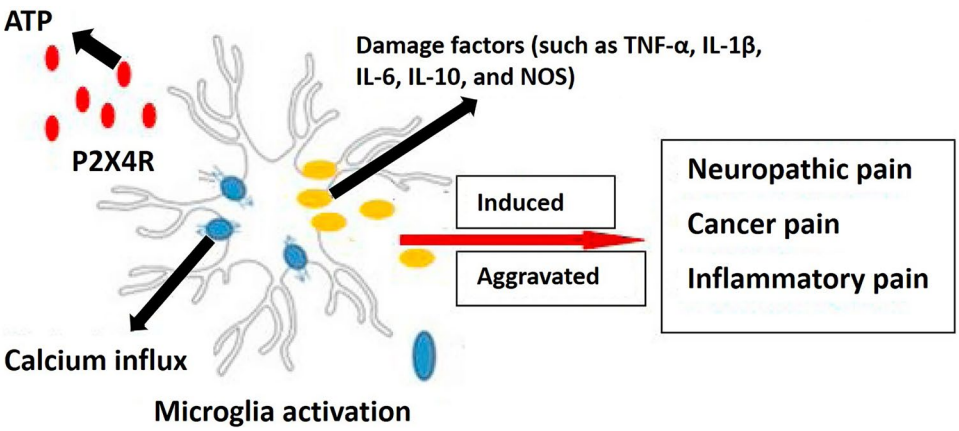

Fig. 1 P2X4R activates microglia and is involved in the development of chronic pain. ATP acts on P2X4R, P2X4R is activated, the ion channel is opened, calcium influx increased, further activates microglia and triggers the changes of molecular structure in microglia, releases damage factors (such as TNF-α, IL-1β, IL-10, and IL-6), and promotes the progression of chronic pain. Reprinted under Creative Commons license CC BY 4.0 from Zhang et al. [9•]

resulted in a significant reduction of P2X4R expression in spinal cord microglia, thereby directly decreasing chronic neuropathic pain [10]. Interestingly, reduction of P2X4 expression has been shown in animal studies to improve the efficacy of opioids [11].

An interesting study by Guo et al. suggests that the analgesic properties of stem cells may be attributable, at least in part, to the effect on opioid receptors [12]. The team induced facial pain states in rats and administered intravenous or local injections of stem cells, which reliably decreased the animals' pain. The pain relief was long-lasting and hyperalgesia and allodynia decreased. The team administered naloxone at various time intervals after the stem cell injections. Interestingly, naloxone reversed the pain-relieving effects of stem cell treatment for several hours (the expected duration of action of naloxone) before the rats returned to their improved pain state. The animals continued to experience pain relief throughout the study, which lasted 5 months. The treatment effects were reversed by downregulating brainstem opioid receptors through RNA interference. This was done by inserting shRNAs into the rostral ventromedial medulla (RVM) on stem cells, which downregulated expression of mu opioid receptors in this area. Mechanical sensitivity was tested after the gene transfer. The authors concluded that stem cell therapy can provide long-term attenuation of hyperalgesia and allodynia via their modulatory effects on the endogenous opioid system. Further literature supports stem cell therapy to treat OT and OIH. Li et al. demonstrated that stem cell injection via the intravenous and intrathecal route affected OT and OIH [5]. This study involved injecting subcutaneous morphine in mice daily until maximum OT and OIH were reached. These variables were defined via behavior testing and observation of response to noxious stimuli. Specifically, pain-like behavior was evaluated by assessing paw withdrawal thresholds to mechanical or thermal stimulation. These data were then extrapolated to represent objective measurements of OIH and OT. After stem cell treatment, OIH was reversed by 70% to 80%. In animals with OT, mesenchymal stem cell (MSC) therapy restored sensitivity to morphine. The effects of OIH and OT treatment were observed throughout the study (34 days) and did not show any signs of waning. Interestingly, rats treated with stem cells before the administration of subcutaneous morphine did not develop OT or OIH. The mechanism that the study authors proposed is that stem cells modulate immune and glial cells. The functions of these cells are changed by the consistent administration of opioids, and post-study immunohistochemistry demonstrated that the cells largely returned to normal functioning after administration of stem cells. The study did not report any adverse effects of stem cell therapy, although walking pattern, food and fluid intake, and body weight gain were the only parameters evaluated.

Neuroinflammation

Injury and infection result in inflammation via a complex biological process involving the somatosensory, immune, autonomic, and vascular systems. This biological process affects the central and peripheral nervous system and results in the sensation of pain. Nociceptors are primary afferent neurons with cell bodies located in the dorsal root ganglia (DRG) and trigeminal ganglia and transmit the sensation of pain or noxious stimuli through their innervation of skin, muscle, joint, and visceral organs [13, 14]. Nociceptors can be directly activated via inflammatory mediators such as prostaglandins (e.g., prostaglandin E2), bradykinin and pro-inflammatory cytokines, and chemokines such as tumor necrosis factor α (TNF-α) and interleukin (IL) 1β [13, 15, 16]. This neurogenic inflammatory response is triggered through nociceptor activation via the release of the neuropeptide, Substance P, resulting in rapid plasma extravasation and edema. This may contribute to chronic pain conditions such as headache and complex regional pain syndrome [17]. Neuroinflammation is localized inflammation in the peripheral nervous system and central nervous system as a result of increased vascular permeability; leukocyte infiltration; activation of glial cells in the DRG, spinal cord, and brain; and increased production of proinflammatory cytokines and chemokines [18]. Neuroinflammation drives peripheral sensitization and central sensitization through the activation of various ion channels, contributing to the development of chronic pain [14, 16].

Several studies suggest that stem cells can provide analgesia in the setting of neuropathic pain [16, 19, 20]. Stem cells have been shown to suppress glial cell activation and, therefore, lead to decreased cytokine release and neuroinflammation [19]. Data suggest that neuropathic pain itself can change opioid receptor availability and potentiate OT; [21••] therefore, every mechanism that decreases inflammation may help reverse this problem.

As discussed above, there is growing evidence that the P2X4 receptor influences OT, OIH, and opioid efficacy [8, 10, 11, 22, 23]. The P2X4 receptor has also been identified as an important receptor that mediates neuropathic pain in the absence of opioids [9•]. This raises the potential of a compound effect when treating neuropathic pain. Specifically, if neuroinflammation augments OT, there is a possibility that the therapeutic effect of stem cell therapy on inflammation could unlock ways to decrease or reverse OT.

Stem cell therapy has modulating effects on neuroinflammation in the treatment of neuropathic pain [16]. One such effect is decreasing the mRNA and protein levels of

proinflammatory IL-1 at the lesion site, thereby significantly attenuating hyperalgesia. Stem cells may be anti-inflammatory or proinflammatory, depending on their environment [16]. When introduced into inflammatory conditions, stem cells become anti-inflammatory. They secrete transforming growth factor (TGF) β1, indole amine 2,3-dioxygenase, and prostaglandin E2 and can convert macrophages/microglia from the proinflammatory M1 to the anti-inflammatory M2 phenotype [16]. Accumulating evidence suggests that TGF-β is produced by stem cells, reduces the expression and secretion of proinflammatory cytokines, and inhibits nerve injury-induced activation and proliferation of microglia and astrocytes [16, 24–27].

Stem cells also have an anti-inflammatory role through the mitogen-activated protein kinase (MAPK) pathway. Nerve injury results in signals from damaged axons, which activate the extracellular signal-related MAPK signal pathway in Schwann cells. This process plays a role in inflammatory regulation [28]. Intrathecal injection of stem cells has been shown to inhibit the expression of DRG phosphorylated extracellular signal-regulated kinase 1/2 (p-ERK1/2), which is upstream in the MAPK pathway [20].

Stem cells have cannabinoid (CB) receptors type 1 and type 2, which have been shown to alleviate neuropathic pain. AM1241 is a selective CB2 receptor agonist, and intrathecal administration of AM1241-treated MSCs has shown a positive effect on analgesia, likely through the molecular signaling pathway involving TGF-β1 and p-ERK1/2 [20].

Another mechanism is glial cell accumulation and activation, which occur after an injury and lead to the release of inflammatory cytokines. This process results in glutamate receptor upregulation and pain hypersensitivity. Stem cells have been shown to suppress glial cell activation [16, 29].

Yang et al. explored an additional mechanism of anti-inflammatory effects of stem cells [30]. In rats, intrathecal injection of stem cells ameliorated chronic constriction injury (CCI)-induced mechanical allodynia and heat

Table 1 BMSC effect on pain under different injury and injection conditions

Year	Reference	Disease (model) and species	Cell type (source)	Number of cells	Delivery site	Effect on pain and mechanism
2015	Chen et al. [24]	CCI of the sciatic nerve, mice	BMSCs (mice)	1.0×10^5 or 2.5×10^5	Intrathecal	Improved mechanical allodynia and thermal hyperalgesia. Reduced neuropathic pain via TGF-β secretion
2019	Xie et al. [20]	CCI, mice	AM1241-pretreated BMSCs (SCB)	2×10^5	Intrathecal	Inhibited CCI-induced p-ERK1/2 expression in the DRGs and increased the amount of TGF-β1 protein in the DRGs TGF-β1 attenuated NP through inhibition of p- ERK1/2
2020	Yang et al. [30]	CCI, rats	BMSCs (rat)	5×10^6	Intrathecal	Inhibited the activation of the TLR2/MyD88/NF-κB pathway by secreting TSG-6, which attenuates the production of pro-inflammatory cytokines
2017	Forouzanfar et al. [29]	CCI, rats	AD-MSCFGF1	1×10^6	Intravenously into the caudal vein	Attenuated the CCI-induced mechanical and thermal hypersensitivity. Led to a decrement in the level of CCI-induced TNF-α and GFAP expression

AD-MSCs, adipose-derived mesenchymal stem cells, successfully transfected by a pCMV6-Entry vector with Myc-DDK-tagged ORF clone of *Rattus norvegicus* (rat FGF1) AD-MSCFGF1 fibroblast growth factor 1; *BMSC,* bone marrow stem cell; *CCI,* chronic constriction injury; *DRG,* dorsal root ganglion; *GFAP,* glial fibrillary acidic protein; *p-ERK1/2,* phosphorylated extracellular signal-regulated kinase 1/2; *SCB,* Stem Cell Bank (Chinese Academy of Sciences); *NP,* neuropathic pain; *TGF,* transforming growth factor; *TNF,* tumor necrosis factor

Table 2 Current clinical trials

Trial title	Location	Estimated enrollment	Dates	Status	ClinicalTrials.gov identifier
Autologous Culture Expanded Adipose Derived MSCs for Treatment of Painful Hip OA	Mayo Clinic, Rochester, MN	24	Start: November 2018 Estimated completion: December 2021	Recruiting	NCT03608579
Neurologic Bone Marrow Derived Stem Cell Treatment Study	Margate, FL: The Healing Institute; Sharjah, United Arab Emirates: Euro-Arabian Hospital	300	Start: June 2016. Estimated completion: June 2023	Recruiting	NCT02795052
Use of adipose-derived cellular stromal vascular fraction (AD-cSVF) parenterally in post-concussion injuries and traumatic brain injuries (TBI)	Stevensville, MT: Regenevita LLC	0	Start: November 2016. Estimated completion: March 2024	Withdrawn	NCT02959294
Efficacy of Intradiscal Injection of Autologous BM-MSC in Worker Patients Affected by Chronic LBP Due to Multilevel IDD (ACTIVE)	Campus Bio-Medico University of Rome	52	Start: July 2021; Estimated completion date: June 2022	Recruiting	NCT04759105
Bone Marrow Concentrate (BMC) Injection in Intervertebral Discs	Stem Cures, Cincinnati, OH	80	Start: November 2018. Estimated completion: April 2021	Active, not recruiting	NCT04559295
Impact of Mesenchymal Stem Cells in Knee Osteoarthritis	University Hospitals Cleveland Medical CenterStudy	16	Start: November 2018. Estimated completion: July 2022	Recruiting	NCT03477942
Safety & Effectiveness of Autologous Regenerative Cell Therapy on Pain & Inflammation of Osteoarthritis of the Hip	VivaTech International, Inc. Grove City, PA	4000	Start: July 2015. Estimated completion: July 2022	Recruiting	NCT02844764
Stem Cells vs. Steroids for Discogenic Back Pain	Johns Hopkins University	106	Start: November 2021. Estimated completion: November 2025	Suspended	NCT04735185
The Safety/Efficacy Study of Human Umbilical Cord Mesenchymal Stem Cells Therapy for Lumbar Discogenic Pain	Sclnow Biotechnology Co., Ltd	242	Start: November 2021. Estimated completion: November 2025	Recruiting	NCT04104412

hyperalgesia. The analgesic effect and anti-inflammatory property of stem cells were attenuated when TNF-α-stimulated gene 6 protein (TSG-6) expression was silenced, thus showing the significant role that TSG-6 plays. Moreover, stem cells inhibited the activation of the TLR2/MyD88/NF-κB pathway in the ipsilateral spinal cord dorsal horn by secreting TSG-6 and downregulating the production of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, in primary microglia. Intrathecal injection of exogenous recombinant TSG-6 also effectively attenuated CCI-induced neuropathic pain, indicating that this may be an effective treatment option for CCI-induced neuropathic pain [30]. Table 1 provides an overview of the effects of stem cells on pain under various injury and injection conditions.

Limitations

This was not a systematic review, which means that we have not included all pertinent references. Furthermore, we have not included all possible mechanisms or neuroinflammatory pathways of stem cell therapy and the effect on reducing chronic pain. We have included relevant studies and promising results in clinical trials or those being studied in human subjects in protocols that are ongoing, based on the ClinicalTrials.gov database. We could not explain in great detail the effect of stem cell therapy for all of the various routes of administration or all chronic pain pathology due to space limitations.

Conclusions

With the large number of ongoing and completed clinical trials, there are promising data highlighting the positive effects of stem cells on neuroinflammation and opioid therapy. The route of administration and the environment are important considerations. Stem cells may be either anti-inflammatory or proinflammatory depending on the environment [17], which should be considered by a medical professional before recommending a stem cell therapy for a specific condition. Stem cell therapy appears promising in offering a variety of treatment options, each with stem cell lines that secrete unique factors that vary in risk and benefit. Each line may be considered a separate form of therapy, which may provide multiple treatment avenues to achieve a common goal.

There remains much to discover regarding the mechanisms and pathways in which stem cells reduce neuroinflammation. The future of stem cell therapy in reducing neuroinflammation looks bright because of technological advances and an increasing body of experimental and clinical evidence. Several human clinical trials are underway or will be soon (Table 2), although to our knowledge, there are none focusing specifically on OT or OIH.

In conclusion, multiple mechanisms impact neuropathic pain, opioid efficacy, tolerance, and hyperalgesia. Among these, the P2X4-receptor pathway has been shown to be upregulated in neuropathic pain states, as well as in the setting of opioid therapy. Neuropathic pain has been shown to induce opioid resistance by destabilizing the opioid receptor, leading to decreased opioid efficacy. This phenomena has made chronic pain a difficult to treat condition that is in need of efficacious alternative approaches. Stem cell therapy has shown promise in limiting neuropathic inflammation, as well as limiting OIH and improving the pain-relieving effects of opioids. As the understanding of the plasticity of the opioid receptor in response to opioid therapy and the role of OIH advances, MSC therapy can be tailored to patients with neuropathic pain who have had a decreased response from opioid therapy. Stem cell therapy may not only provide an additional treatment modality for neuropathic pain, but it may also improve opioid therapy, decrease opioid resistance, and reduce OIH through the P2X4 receptor pathway. Additional mechanisms may also reduce neuropathic pain through decreased neuroinflammatory cytokines, glial cell activation, and leukocyte infiltration.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest.

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