We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

The Use of Neurotoxins for Palliative Treatment of Chronic Joint Pain

Hollis Krug

Abstract

Osteoarthritis is a significant public health problem and is rapidly increasing in prevalence with the aging population. Pain is the most disabling consequence of osteoarthritis. Treatment for pain is inadequate and needs to be addressed with new therapeutic modalities. Chronic pain is often the result of peripheral and central pain sensitization which reduces the pain threshold and increases the perceived pain response to noxious and even non-noxious stimuli. Neurotoxins can reduce this sensitization by various mechanisms and are a fertile area of research for the treatment of chronic pain. Botulinum toxins, vanilloids, and conotoxin have all been studied for the treatment of chronic pain. Botulinum toxins and vanilloids have the greatest potential as analgesics for chronic joint pain thus far. Monoclonal antibodies directed against nerve growth factor have also been developed for the treatment of chronic joint pain due to osteoarthritis. These antibodies are not technically neurotoxins but have significant analgesic potential. However, they may have undesirable side effects and are still being evaluated as possible therapies for chronic osteoarthritis pain.

Keywords: osteoarthritis, chronic pain, arthritis, neurotoxins, anti-nerve growth factor

1. Introduction

Chronic joint pain is a world-wide problem. Osteoarthritis (OA) is the most common cause of chronic joint pain and is increasing in prevalence. In the United States alone, osteoarthritis affects approximately 27 million adults and is expected to exceed 67 million by the year 2030 [1, 2]. Although disability due to osteoarthritis varies, pain is the most disabling symptom affecting OA patients [3, 4]. To date, there are no disease modifying treatments for osteoarthritis. Treatment goals are focused on relief of symptoms and minimizing disability. The direct costs of treatment of OA combined with the indirect costs due to lost wages are substantial. According to one estimate, this cost accounts for 2% of the annual gross domestic product [5, 6]. Management of chronic pain from OA is challenging. Non-pharmacologic options include education, exercise, weight reduction, acupuncture, and joint protection, but these practices are generally insufficient to provide joint pain relief. Pharmacologic options include systemic and intraarticular therapies [7]. Insufficient pain relief, intolerable drug side effects and drug interactions increase the risk-benefit ratio for

available pharmaceutical therapies [8]. Even surgical therapies for degenerative joint disease may not be effective. Knee joint lavage has been shown to be no more effective for alleviation of pain than placebo [9, 10].

In particular, end stage disease provides challenges for effective therapy. Opioids can sometimes be effective when other therapies have lost efficacy, but the use of narcotics for chronic pain is undesirable due to eventual dependence and loss of efficacy, the need for dose escalation to maintain effectiveness, and the rising problem of opioid abuse and overdose that has occurred since the use of long-acting narcotics have been available [11]. In addition, unacceptable side effects, particularly in the elderly who are more likely to have end stage osteoarthritis pain, makes the use of opioids a poor choice [12]. Finally, opioids may not have any increased efficacy for chronic OA pain compared with non-narcotic therapies [13]. The efficacy of intra-articular treatments such as corticosteroids and hyaluronic acid preparations have not been clearly demonstrated. For this reason the American Academy of Orthopedic Surgeons recommends against viscosupplementation and felt the evidence to be inclusive regarding corticosteroid injections for osteoarthritis [14].

Surgical treatment for end stage osteoarthritis is limited. Total joint replacement is generally considered to be effective for short and long-term pain relief and usually achieves positive clinical and functional outcomes [15, 16]. However, surgical treatments are not without risk of complications. These include systemic complications such as pulmonary embolism, but also local complications such as dislocation of hips, wound and joint infection, periprosthetic fracture, aseptic loosening, patellar maltracking, rupture of the extensor mechanism, stiffness with reduced range of motion, heterotopic ossification, metal hypersensitivity, vascular injury or bleeding, or nerve palsy. Success rates vary but as many as 1 in 5 patients undergoing total knee arthroplasty (TKA) are not satisfied with the outcome [16]. Obese patients are at increased risk for complications following TKA. Pre-operative management including weight loss, optimization of diabetes treatment, venous thromboembolism prevention, and physical therapy can help to minimize these complications [17]. Even so, some individuals will not be surgical candidates. Clearly other options are needed for effective pain relief to minimize disability and optimize function in patients who are not candidates for surgery and for whom standard analgesics have not been helpful.

Palliative therapy is specialized medical care focused on providing relief from the symptoms and stress of a serious illness. The goal is to improve quality of life and enhance physical function, but without treating or attempting to cure the underlying disease. Palliative therapy for end stage osteoarthritis is a concept that has been explored but due to a lack of effective therapies has not been very successful [18].

2. Neurobiology of chronic pain

Pain is the result of nerves transmitting a noxious signal, usually the result of some sort of injury, to the brain where it is perceived as pain. This is an important signal for the organism experiencing the injury to withdraw or avoid the stimulus that is producing the pain. Chronic pain results when nociceptive systems are altered so that there is no longer a direct relationship between a noxious stimulus and pain perception. These alterations are due to plasticity of the nervous system whereby peripheral nerves become sensitized, or spinal cord neurons become increasingly excitable. Projections from the spinal cord to higher centers can result in changes to descending inhibitory controls that are initiated in the midbrain and brainstem. All these changes together tend to alter the perceived response to any

stimulus and thus lead to persistent pain states. This plasticity appears to be reversible and thus amenable to pharmacologic therapies [19].

Peripheral sensitization is thought to be the result of inflammation or nerve injury which alters nociceptive receptors causing increased intracellular calcium and activated intracellular protein kinase C and tyrosine kinases. These mediators phosphorylate sensory neuron-specific sodium channels and Transient Receptor Potential Vanilloid 1 (TRPV1) receptors causing a reduction in the depolarization threshold and reduced pain threshold. Nociceptive neurons themselves release chemical stimulants such as substance P (SP) and calcitonin gene-related peptide (CGRP) which amplify the local inflammatory response by interacting with local inflammatory cells and nearby blood vessels. This “neurogenic inflammation” causes vasodilation and edema, and increases local inflammation adding to peripheral sensitization [20]. Pharmacologic inhibition of this sensitization process is an attractive target for analgesia, as reducing sensitization would be expected to reduce the pain perception without eliminating the important pain defense mechanisms. Given the critical involvement of neuropeptides in the development of sensitization, the efficacy of neurotoxins was hypothesized for treatment of chronic pain.

3. Botulinum toxins as analgesics

3.1 Botulinum toxin background and human studies

There are eight serotypes of botulinum toxin. All are products of the bacterial genus *Clostridium*. Types A-G have been fully characterized and have varying durations of action, and enzymatic targets. They all cleave components of the soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptor (SNARE) proteins. The inability of the disrupted SNARE proteins to bring the synaptic vesicle membrane and the terminal plasma membrane of the peripheral nerve in close proximity results in an inability of the two membranes to fuse and failure of the nerve to release neurotransmitter such as acetylcholine (ACh). This produces the dramatic paralytic activity of botulinum toxin [21]. The eighth serotype, H, has been recently described, but its gene sequence has been withheld due to public safety concerns since it is considered the deadliest substance in the world [22].

Botulinum toxins A and B have been used for some time to treat painful muscle dystonias such as torticollis. It was thought that the paralytic effect of the toxin on motor units in the dystonic muscle was responsible for the pain relief that accompanied this treatment. But it was observed that pain relief preceded the muscle weakness that was expected with these treatments. This observation led to early studies of the use of intra-articular onabotulinum toxin (Type A) for end stage osteoarthritis [23]. Subsequent similar studies have been done and summarized in meta-analyses and systematic reviews. Their findings suggest that even for end stage arthritis pain, intra-articular botulinum toxin has modest beneficial effects in patients with refractory joint pain [24–27]. Studies of shoulders and knees predominated but one study treated refractory ankle osteoarthritis pain and one treated refractory pain after total knee arthroplasty. Doses used were between 100 and 200 IU onabotulinum toxin A (BOTOX), 200–500 IU abobotulinum toxin A (Dysport) and 2500 IU rimabotulinum toxin B (Myobloc). Controls in these studies were variable ranging from triamcinolone to saline to unspecified placebo. Some studies used botulinum toxin diluted with lidocaine and compared to saline with lidocaine. One small study of 75 patients compared intra-articular (IA) botulinum toxin A to injection with 2 ml sodium hyaluronate in patients with symptomatic ankle OA and found no difference in effectiveness between the two interventions [28]. Since the American

Academy of Orthopedic Surgeons has stated in their evidence based guidelines for the treatment of OA of the knee that viscosupplementation cannot be recommended, this comparison may be less than appropriate [29].

Studies of IA botulinum toxin use in humans have not reported significant safety issues. Although weakness was initially a concern, it was not found in extensive safety evaluations [23, 26]. Since a single injection provides pain relief for up to 6 months, fewer injections may be required as compared to corticosteroid or viscosupplementation injections and therefore, the risk of infection is minimized.

3.2 Botulinum toxin studies in preclinical models of joint pain

In an effort to better understand the mechanism of action of pain relief seen with botulinum toxin and to precisely define functional outcomes, a variety of animal studies have been done (**Table 1**). Botulinum toxins have been given intraarticularly for joint pain in mice, rats and dogs. IA botulinum toxin appears to be effective for chronic arthritis pain but not acute joint pain in mice, supporting the idea that botulinum toxin reduces peripheral sensitization by inhibiting neuropeptide release in the periphery [30, 31]. Only one study evaluated efficacy of rimabotulinum toxin for osteoarthritis pain in mice and found that it reduced both spontaneous and evoked pain behaviors [32]. In dogs with chronic lameness due to stifle, hip or elbow osteoarthritis IA onabotulinum toxin produced improvement in several force platform variables including vertical impulse, peak vertical force and in the Helsinki chronic pain index compared to the placebo group after 12 weeks. The secondary outcomes of subjective pain score and the need for rescue analgesics were not significantly improved in the botulinum toxin treated group compared to placebo. No major adverse events were detected [33]. A second study in dogs designed to detect adverse effects of IA botulinum toxin compared toxin injection to placebo in healthy beagle dogs. This study evaluated dynamic and static weight bearing, range of motion, joint tenderness, synovial fluid, neurologic function and electrophysiologic recordings, and histopathology of joint structures and adjacent muscles and nerves. Intra-articular botulinum toxin A did not produce significant clinical, cytological, or histopathological adverse effects in healthy dogs, but based on the electrophysiological recordings that found low compound muscle action potentials in 2 dogs in the botulinum toxin injected limb, the authors concluded that toxin may spread from the joint, but that its clinical impact is probably low [34]. In rats with inflammatory arthritis of the temporal mandibular joint (TMJ) produced by immunization with bovine serum albumin (BSA) and subsequent intra-articular challenge with BSA, injecting the joint with botulinum toxin A significantly reduced nociceptive behaviors that resulted from IA injection of low dose formalin into these inflamed joints. These authors demonstrated that the trigeminal ganglion of botulinum A treated arthritic animals released less substance P (SP) and calcitonin gene related peptide (CGRP) than saline treated arthritic animals but glutamate release was not affected. Glutamate receptors AMPA and NMDA were also unchanged in botulinum treated ganglia compared to saline treated controls. Periarticular tissues from the arthritic TMJs released increased amounts of interleukin 1- β (IL-1 β) and tumor necrosis factor α (TNF α). Treatment with botulinum toxin reduced IL-1 β release but had no effect on TNF α [35]. In another study of rats with adjuvant-induced arthritis induced in the tibial-tarsal joint, mechanical and thermal hyperalgesia and TRPV1 expression in the L4-5 dorsal root ganglia (DRG) were measured. DRGs were also stained for the presence of cleaved synaptosomal-associated protein of 25 kDa (SNAP-25)—the cleavage product of botulinum toxin A—and for transient receptor potential vanilloid 1 and put TRPV1 in parentheses TRPV1 and CGRP. TRPV1 expression increased significantly in

Arthritis model	Experiment	Results	Reference
Murine CFA, COL	IA BoNT/A vs. sham	Reduced spontaneous and evoked pain behaviors in CFA arthritis, reduced spontaneous pain behavior in COL arthritis	[30, 31]
Murine COL	IA BoNT/B vs. saline or sham injection	Improved visual gait analysis, improved joint tenderness	[32]
Dog, OA, multiple joints	IA BoNT/A vs. placebo Outcome measured after 12 weeks	Improved peak vertical force, improved Helsinki chronic pain index	[33]
Healthy beagles (safety study)	IA BoNT vs. placebo	No adverse clinical, cytological, or histopathological effects. Some EMG evidence for spread outside the joints to muscle	[34]
Rat BSA TMJ inflammatory arthritis	IA BoNT/A followed by pain induction with formalin injection	Significantly reduced pain behaviors, reduced SP and CGRP release, no change in glutamate release, reduced release of IL-1 β but not TNF α	[35]
Rat CFA tibiotarsal joint	IA BoNT/A (dose ranging) compared to CFA alone and saline control	All pain outcomes improved in a dose dependent fashion. (Mechanical and thermal hyperalgesia) TRPV1 expression reduced but not transcription, thought due to the observed reduced movement of TRPV1 to the cell membrane	[36]
Rat CFA ankle arthritis Plantar injection of capsaicin and formalin and plantar incision as standardized pain models. Also included SNI model	BiTox—unique nonparalyzing botulinum toxin molecule	CFA induced swelling reduced, mechanical hyperalgesia but not thermal hyperalgesia reduced. No effect on acute pain from capsaicin or formalin but reduced secondary mechanical hyperalgesia after plantar capsaicin injection. Plantar incision pain response reduced after day 2. Reduced neuropathic pain in the SNI model	[37]
ACIA model in mice	Genetic modification of mice to express the conotoxin ω -conopeptide MVIIA vs. wild type	Pain was suppressed but joint inflammation was increased and more destructive in genetically modified mice	[55]

CFA—complete freund's adjuvant induced arthritis, COL—collagenase-induced osteoarthritis, BoNT/A—onabotulinum toxin type A, BoNT/B—rimabotulinum toxin type B, BSA—bovine serum albumin, TMJ—temporal mandibular joint, SNI—spared nerve injury, ACIA—antigen and collagen-induced arthritis.

Table 1.
Preclinical studies of botulinum and other toxins as analgesics for arthritis pain.

the arthritic animals' DRGs and arthritic animals demonstrated mechanical and thermal hyperalgesia. Botulinum toxin A increased the paw withdrawal threshold and latency to both mechanical and thermal stimuli and reduced TRPV1 expression in a dose-dependent manner. TRPV1 transcription was likewise increased with Complete Freund's Adjuvant (CFA) induced arthritis but botulinum toxin A did not alter this increased transcription. Using immunofluorescent staining, these authors found that the increase in TRPV1 and CGRP co-expressing neurons which was the result of CFA arthritis was reduced by botulinum toxin in a dose dependent manner. Since botulinum toxin exerts its effects by cleaving SNAP-25 and thus preventing

release of neuropeptide by preventing fusion of vesicles with the terminal membrane, the presence of cleaved SNAP 25 localized with TRPV1 in the DRG was analyzed. Co-localization of cleaved SNAP-25 with TRPV1 in the botulinum toxin A group was clearly seen 5 days after botulinum toxin injection. This was not seen in the sham and CFA saline control groups. These authors speculated that botulinum toxin A may prevent TRPV1 expression on DRG neurons by inhibition of TRPV1 trafficking to the cell membrane after retrograde transport of botulinum toxin from the periphery to the DRG since the expression of the TRPV1 receptor has been shown to be dependent on exocytosis that requires interactions with proteins of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex consisting of SNAP-25 [36]. The presence of botulinum toxin in the DRG would prevent the SNARE complex from functioning normally to move TRPV1 to the cell membrane. A botulinum toxin A based molecule—BiTox—has been synthesized that is reported to retain neuronal silencing capacity without causing paralysis. This molecule reduces plasma extravasation and inflammatory edema but is not transported to the DRG ganglia or dorsal horn and does not inhibit pain behaviors in response to formalin or capsaicin and does not inhibit formalin-induced c-Fos expression in the dorsal horn. It was found to strongly reduce A-nociceptor mediated secondary mechanical hyperalgesia due to CFA joint inflammation or capsaicin injection and decreased hypersensitivity from nerve injury. The authors concluded that this botulinum toxin based molecule could reduce local release of neuromodulators from C fibers without impairing C nociceptive signaling function [37].

4. Vanilloids as analgesics

4.1 Vanilloids and their receptors background

Vanilloids such as capsaicin (the active ingredient in hot chili peppers) and resiniferatoxin (a product of the plant *Euphorbia resinifera*) were first notable for their ability to produce burning pain when administered topically. Later, both molecules were found to have analgesic potential and subsequent work identified the non-selective cation channel to which these compounds bind. This receptor was found to be located on the dorsal root and trigeminal ganglia of various species. Subsequent work identified the channel, allowed cloning and cDNA characterization, and revealed that the channel could be activated not only by vanilloids but also by heat suggesting a role in thermosensation. The receptor was named transient receptor potential vanilloid 1 (TRPV1) and other ligands were identified making it a transducer of many types of noxious stimuli [38].

Because of the variety of ligands, TRPV1 was considered a likely target for analgesia. Agonists such as vanilloids were noted to cause desensitization of these channels and in rodents as well as humans, pain behaviors could be alleviated with vanilloid treatment. TRPV1 knockout mice demonstrated reduced thermal hypersensitivity with inflammation. TRPV1 antagonists were shown to reverse pain behavior in rodents with a wide variety of painful conditions including inflammation, osteoarthritis and cancer. Both agonists and antagonists have been considered as analgesic therapies. Although systemic administration of vanilloids demonstrated analgesic efficacy in preclinical pain models, because of the undesirable systemic side effects of these compounds, most therapeutic trials have focused on local or topical administration of these compounds. Undesirable effects include hypotension, respiratory compromise and other negative effects on reflex pathways. Less pungent analogs were found to be less efficacious with respect to analgesia [38].

4.2 Vanilloids as analgesics—Human and pre-clinical studies

In humans, current treatment of joint pain with vanilloids is limited to topical therapies. Pain relieving creams such as Zostrix® and patches such as Salonpas Hot Capsicum Patch® are available over the counter and contain capsaicin as the active ingredient. Multiple clinical trials have found modest benefit for osteoarthritis from low dose topical capsaicin [39–41]. More recently, a high dose 8% capsaicin patch has been approved for the treatment of post-herpetic neuralgia. According to the package insert, application of the patch requires careful adherence to application instructions by the health care professional and local anesthesia for the patient prior to application and systemic analgesics as needed in the post-application period. Interestingly, results from clinical trials of this drug for treatment of painful HIV neuropathy did not show clinical benefit [42, 43].

Resiniferatoxin (RTX) is an ultra-potent capsaicin (CAP) analogue [44], that is several thousand-fold more potent than CAP [45]. RTX in low concentrations produces a slow and sustained depolarization of membrane potential, preventing the generation of action potentials but causing less toxicity. A single IA injection in rats has been found to reduce hyperalgesia due to carrageenan induced joint pain [46].

RTX has been studied in clinical trials for other painful conditions. When given intravesicularly for interstitial cystitis and painful bladder syndrome, it did not improved overall symptoms of pain, urgency, frequency or nocturia [47, 48]. Adlea™ (4975) is another CAP analogue under development for the treatment of post-operative musculoskeletal pain, osteoarthritis and tendinopathy. Phase II trials of intra-articular injection of this compound were encouraging but no further clinical trials appear to have been performed [38]. Zucapsaicin (Civamide) is the cis-isomer of capsaicin, and functions as a TRPV1 blocker. Phase III trials have been done with topical civamide for OA knee pain [49]. This topical therapy is not absorbed systemically, is well tolerated, and produced significant improvement in Western Ontario and McMaster Universities Arthritis Index (WOMAC) physical function score, pain score and subject global evaluation. Improvement was maintained for a year. This drug has not yet been approved by the US FDA.

4.3 TRPV1 antagonists as analgesics

Several TRPV1 antagonists have also been identified that act as analgesics [50]. Some are more selective than others, complete nonselectivity producing inhibition of all modes of TRPV1 activation (protons, heat and capsaicin). More selectivity

Arthritis model	Experiment	Results	Reference
Rat carrageenan-induced acute joint pain	IA RTX vs. vehicle given 24 hours after arthritis induction in a dose ranging study	Significant reduction in pain behavior with RTX treatment	[46]
Rat MIA model—early phase	A-425619 given IP in a dose range during acute inflammatory phase	47% reduction in weightbearing asymmetry. Prolonged benefit	[50, 51]
Rat MIA model—late phase	A-889425 and A-995662 given orally	Reduced loss of grip force within 1 hour and maintained up to 8 hours	[50, 52, 53]

IA—intra-articular, RTX—resiniferatoxin, MIA—monosodium iodoacetate.

Table 2.
Preclinical studies of vanilloid agonists and antagonists as analgesics for arthritis pain.

appears to improve the side effect profile. Centrally active TRPV1 antagonists appear to provide greater analgesia when given systemically or intrathecally in preclinical models of OA pain. Most preclinical studies of OA have been done in the monosodium iodoacetate (MIA) model in the rat (**Table 2**). Rats with MIA-induced arthritis pain demonstrate reduced weightbearing of the affected limb, pain with movement of the joint and hypersensitivity of uninjured tissues (secondary allodynia of the hind paw). These pain behaviors are thought to be due to both central and peripheral sensitization. TRPV1 antagonists appeared to be analgesic during both the acute inflammatory phase of MIA pain and later during the chronic phase [50–53]. Analgesia appears to improve with repeated dosing and side effects such as hyperthermia abate with some of the investigational TRPV1 antagonists. The potency of hyperthermia induction seems to relate most closely to the blockade of proton-induced TRPV1 activation [50].

Only a few TRPV1 antagonists have been used in clinical trials. ADZ1386 given orally in two different doses did not reduce OA pain more than placebo. A study in dogs with hip OA using oral ABT116 did not improve the total pain score, pain severity or pain interference score, but did reduce rescue medication use, increased night time activity levels and briefly produced an acute hyperthermic effect. NEO 6860, which is specific for blocking capsaicin activation of the target, with little or no effect against pH or heat activation, underwent a first-in-human phase I trial of the safety and efficacy of the drug in healthy human subjects [54]. The dose ranging study included 64 subjects and measured pharmacodynamics with an intradermal capsaicin test as well as pharmacokinetics. The drug was rapidly absorbed with a half-life of between 4 and 8 hours. Side effects included headache, paresthesia, nausea, and dizziness. Study participants were monitored specifically for increase in temperature and heat pain threshold/tolerance, but these were not noted. At all doses, most subjects reported a rapid onset, transient sensation of “feeling hot”. The authors concluded that this compound had potential for development for treating OA-associated pain and future clinical studies were planned but have not yet been initiated.

5. Other potentially analgesic neurotoxins

5.1 Conotoxin

Ziconotide (ω -conopeptide MVIIA) is a synthetic compound of the neurotoxin ω -conopeptide derived from the *Conus Magus* fish hunting marine snail found in the Pacific Ocean. It selectively binds to the N-type voltage-gated calcium channels found in the laminae of the spinal cord’s dorsal horn and blocks these channels. This blockade prevents calcium influx and halts neurotransmission thereby preventing nociceptive signaling. Pain transmission messages are prevented from arriving at the brain. It is FDA approved for intrathecal use for severe chronic pain in individuals who are intolerant of or refractory to other treatments including intrathecal (IT) morphine, but has demonstrated some serious side effects such as suicidal ideation and psychosis [55].

In a study of transgenic mice bred to express a membrane-tethered form of the conotoxin ω -conopeptide MVIIA under control of a nociceptor-specific gene, who were subjected to unilateral induction of joint inflammation with the antigen- and collagen- induced arthritis (ACIA) model, pain was effectively suppressed, but joint inflammation became persistent and more destructive. The authors concluded that blockade of $\text{Ca}_v2.2$ -mediated calcium influx and nociceptive signaling by this toxin impaired recovery from induced inflammatory arthritis. They concluded that this

blockade could lead to potentially deleterious and devastating effects if used during inflammation [55].

5.2 Tetrodotoxin

Another neurotoxin studied as a potential analgesic is tetrodotoxin (TTX). Voltage-gated sodium channels (VGSCs) are critical for neuronal function and dysfunctional VGSCs have been implicated in several pain states. There are nine isoforms of the sodium channel alpha-subunit (Nav1.1–1.9 in mammals). Only Nav1.1–1.4 and Nav1.6–1.7 subtypes (TTX-sensitive channels) can be blocked by nanomolar concentrations of tetrodotoxin. Micromolar concentrations are required to block Nav1.5 and Nav1.8–1.9 subtypes (TTX-resistant channels) [56]. Although it appears to have little effect on acute pain further studies are needed. Analgesic efficacy in preclinical inflammatory pain models demonstrated promising effects of systemic administration for mechanical hyperalgesia and the neurogenic inflammatory response to injury. There are contradictory results for TTX efficacy for neuropathic pain. Effectiveness in preclinical models of neuropathic pain varied depending on dose, route of application, and appeared more effective in acute neural injury than in chronic neuropathic pain. In one clinical trial of tetrodotoxin for chemotherapy-induced neuropathic pain, injected TTX did not have a significant effect on pain [57]. There have been no specific studies evaluating tetrodotoxin for the treatment of chronic joint pain.

6. Anti-nerve growth factor

Though not technically neurotoxins, several monoclonal antibodies have been developed against nerve growth factor (NGF) specifically for the treatment of chronic pain, and specifically for pain from OA. Tanezumab was the first of these to be developed. Three other companies have now created similar antibodies. Tanezumab was in phase III studies when the US FDA placed a hold on further clinical trials after an increase in joint destruction was observed in patients who had been given this drug. After that, preclinical studies suggested that this class of drugs could damage the autonomic nervous system, which delayed further research [58]. Since the hold was released in 2015, phase III clinical trials are being repeated. Results from those that have been published show that these biologic therapies appear to be effective with acceptable side effect profiles [59–61]. These therapies are administered parenterally, and therefore are systemically active. These antibodies have significant potential to improve analgesia for chronic arthritis pain. Alternative routes of administration such as IA will be of interest.

7. Conclusions

Chronic joint pain is a significant public health problem that will only increase along with the aging population. In the absence of disease modifying treatments for OA, the need for better pain therapies will continue to increase. Neurotoxins can be helpful as adjunct treatments for pain, particularly in cases where peripheral sensitization has lowered pain thresholds and increased pain perception. Advances in understanding of the pathophysiologic mechanisms of nociception and sensitization and elucidation of the specific functions of the various neurotoxins will allow more advanced development of toxins that may avoid potential side effects and more specifically reduce pain perception.

Acknowledgements

Thanks to Maren Mahowald who first introduced me to the concept of neurotoxins as therapy for joint pain.

Conflict of interest

The author has no conflict of interest to declare.

Author details

Hollis Krug
Minneapolis VA Health Care System, University of Minnesota, Minneapolis,
Minnesota, USA

*Address all correspondence to: hollis.krug@va.gov

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Hootman JM, Helmick CG, Barbour KE, Theis KA, Boring MA. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among US adults, 2015-2040. *Arthritis & Rheumatology*. 2016;**68**(7):1582-1587
- [2] Hootman JM, Helmick CG. Projections of US prevalence of arthritis and associated activity limitations. *Arthritis and Rheumatism*. 2006;**54**(1):226-229
- [3] Malfait AM, Schnitzer TJ. Towards a mechanism-based approach to pain management in osteoarthritis. *Nature Reviews Rheumatology*. 2013;**9**(11):654-664
- [4] Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage*. 2013;**21**(9):1145-1153
- [5] Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Osteoarthritis and absenteeism costs: Evidence from US National survey data. *Journal of Occupational and Environmental Medicine*. 2010;**52**(3):263-268
- [6] Yelin E, Murphy L, Cisternas M, Foreman A, Pasta D, Helmick C. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons to 1997. *Arthritis and Rheumatism*. 1997;**56**(5):1397-1407
- [7] Wenham CY, Conaghan PG. New horizons in osteoarthritis. *Age and Ageing*. 2013;**42**(3):272-278
- [8] Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis and Cartilage*. 2010;**18**(4):476-499
- [9] Kirkley A, Birmingham TB, Litchfield RB, Giffin JR, Willits KR, Wong CJ, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *The New England Journal of Medicine*. 2008;**359**(11):1097-1107
- [10] Mosely JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, David H, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *The New England Journal of Medicine*. 2002;**347**:81-88
- [11] Manchikanti L, Helm S 2nd, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;**15**(3 Suppl):ES9-E38
- [12] Rolita L, Spegman A, Tang X, Cronstein BN. Greater number of narcotic analgesic prescriptions for osteoarthritis is associated with falls and fractures in elderly adults. *Journal of the American Geriatrics Society*. 2013;**61**(3):335-340
- [13] Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *Journal of the American Medical Association*. 2018;**319**(9):872-882
- [14] Jevsevar D, Brown GA, Jones DL, Matzin EG, Manner P, Mooar P, et al. *Treatment of Osteoarthritis of the Knee: Non-Arthroplasty Treatment*. 2nd ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2013
- [15] Varacallo M, Johanson NA. Hip, replacement. In: *Treasure Island*. FL: StatPearls Publishing LLC; 2018

- [16] Varacallo M, Johanson NA. Total knee arthroplasty. In: Treasure Island. FL: StatPearls Publishing LLC; 2018
- [17] Feng JE, Novikov D, Anoushiravani AA, Schwarzkopf R. Total knee arthroplasty: Improving outcomes with a multidisciplinary approach. *Journal of Multidisciplinary Healthcare*. 2018;**11**:63-73
- [18] Pavelka K. Treatment of pain in osteoarthritis. *European Journal of Pain*. 2000;**4**(Suppl A):23-30
- [19] Dickenson A. The neurobiology of chronic pain states. *Anaesthesia and Intensive Care Medicine*. 2016;**17**(9):436-439
- [20] Mahowald ML, Krug HE. Chronic musculoskeletal pain. In: Firestein GS, Budd RC, Harris ED Jr, McInnes IB, Ruddy S, Sargent JS, editors. *Kelly's Textbook of Rheumatology*. I. 8th ed. Philadelphia, PA: Saunders Elsevier; 2009. pp. 963-992
- [21] Montecucco C, Molgo J. Botulinal neurotoxins: Revival of an old killer. *Current Opinion in Pharmacology*. 2005;**5**(3):274-279
- [22] Barash JR, Arnon SS. A novel strain of clostridium botulinum that produces type B and type H botulinum toxins. *The Journal of Infectious Diseases*. 2014;**209**(2):183-191
- [23] Mahowald ML, Singh JA, Dykstra D. Long term effects of intra-articular botulinum toxin A for refractory joint pain. *Neurotoxicity Research*. 2006;**9**(2-3):179-188
- [24] Wu T, Fu Y, Song HX, Ye Y, Dong Y, Li JH. Effectiveness of botulinum toxin for shoulder pain treatment: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*. 2015;**96**(12):2214-2220
- [25] Wu T, Song HX, Dong Y, Ye Y, Li JH. Intra-articular injections of botulinum toxin a for refractory joint pain: A systematic review and meta-analysis. *Clinical Rehabilitation*. 2017;**31**(4):435-443
- [26] Singh JA, Fitzgerald PM. Botulinum toxin for shoulder pain: A cochrane systematic review. *The Journal of Rheumatology*. 2011;**38**(3):409-418
- [27] Kheniouia H, Houvenagel E, Catanzaritia JF, Guyota MA, Agnania O, Donzea C. Usefulness of intra-articular botulinum toxin injections. A systematic review. *Joint, Bone, Spine*. 2016;**83**:149-154
- [28] Sun SF, Hsu CW, Lin HS, Chou YJ, Chen JY, Wang JL. Efficacy of intraarticular botulinum toxin A and intraarticular hyaluronate plus rehabilitation exercise in patients with unilateral ankle osteoarthritis: A randomized controlled trial. *Journal of Foot and Ankle Research*. 2014;**7**(1):9
- [29] Sanders JO, Murray J, Gross L. Non-arthroplasty treatment of osteoarthritis of the knee. *The Journal of the American Academy of Orthopaedic Surgeons*. 2014;**22**(4):256-260
- [30] Krug HE, Frizelle S, McGarraugh P, Mahowald ML. Pain behavior measures to quantitate joint pain and response to neurotoxin treatment in murine models of arthritis. *Pain Medicine*. 2009;**10**(7):1218-1228
- [31] Blanshan N, Mahowald ML, Dorman C, Frizelle S, Krug HE. The analgesic effect of intraarticular OnabotulinumtoxinA in a female murine model of collagenase induced chronic degenerative monoarthritis. *Toxicon*. 2018;**158**:8-15
- [32] Anderson S, Krug H, Dorman C, McGarraugh P, Frizelle S, Mahowald M. Analgesic effects of intra-articular

botulinum toxin type B in a murine model of chronic degenerative knee arthritis pain. *Journal of Pain Research*. 2010;**3**:161-168

[33] Heikkila HM, Hielm-Bjorkman AK, Morelius M, Larsen S, Honkavaara J, Innes JF, et al. Intra-articular botulinum toxin A for the treatment of osteoarthritic joint pain in dogs: A randomized, double-blinded, placebo-controlled clinical trial. *Veterinary Journal*. 2014;**200**(1):162-169

[34] Heikkila HM, Jokinen TS, Syrja P, Junnila J, Hielm-Bjorkman A, Laitinen-Vapaavuori O. Assessing adverse effects of intra-articular botulinum toxin A in healthy beagle dogs: A placebo-controlled, blinded, randomized trial. *PLoS One*. 2018;**13**(1):e0191043

[35] Lora VR, Clemente-Napimoga JT, Abdalla HB, Macedo CG, Canales GT, Barbosa CM. Botulinum toxin type A reduces inflammatory hypernociception induced by arthritis in the temporomandibular joint of rats. *Toxicon*. 2017;**129**:52-57

[36] Fan C, Chu X, Wang L, Shi H, Li T. Botulinum toxin type A reduces TRPV1 expression in the dorsal root ganglion in rats with adjuvant-arthritis pain. *Toxicon*. 2017;**133**:116-122

[37] Mangione AS, Obara I, Maiaru M, Geranton SM, Tassorelli C, Ferrari E, et al. Nonparalytic botulinum molecules for the control of pain. *Pain*. 2016;**157**(5):1045-1055

[38] Wong GY, Gavva NR. Therapeutic potential of vanilloid receptor TRPV1 agonists and antagonists as analgesics: Recent advances and setbacks. *Brain Research Reviews*. 2009;**60**(1):267-277

[39] Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, et al. Treatment of arthritis with topical

capsaicin: A double-blind trial. *Clinical Therapeutics*. 1991;**13**(3):383-395

[40] Kosuwon W, Sirichatiwapee W, Wisanuyotin T, Jeeravipoolvarn P, Laupattarakasem W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. *Journal of the Medical Association of Thailand*. 2010;**93**(10):1188-1195

[41] McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *The Journal of Rheumatology*. 1992;**19**(4):604-607

[42] Brown S, Simpson DM, Moyle G, Brew BJ, Schifitto G, Larbalestier N, et al. NGX-4010, a capsaicin 8% patch, for the treatment of painful HIV-associated distal sensory polyneuropathy: Integrated analysis of two phase III, randomized, controlled trials. *AIDS Research and Therapy*. 2013;**10**(1):5

[43] Clifford DB, Simpson DM, Brown S, Moyle G, Brew BJ, Conway B, et al. A randomized, double-blind, controlled study of NGX-4010, a capsaicin 8% dermal patch, for the treatment of painful HIV-associated distal sensory polyneuropathy. *Journal of Acquired Immune Deficiency Syndromes*. 2012;**59**(2):126-133

[44] Rosenbaum T, Simon SA. TRPV1 receptors and signal transduction. In: Liedtke WB, Heller S, editors. *TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades*. Frontiers in Neuroscience. Boca Raton, FL: CRC Press/Taylor & Francis; 2007

[45] Szolcsanyi J, Szallasi A, Szallasi Z, Joo F, Blumberg PM. Resiniferatoxin: An ultrapotent selective modulator of capsaicin-sensitive primary afferent neurons. *The Journal of Pharmacology*

and Experimental Therapeutics. 1990;**255**(2):923-928

[46] Kissin EY, Freitas CF, Kissin I. The effects of intraarticular resiniferatoxin in experimental knee-joint arthritis. *Anesthesia and Analgesia*. 2005;**101**(5):1433-1439

[47] Chen TY, Corcos J, Camel M, Ponsot Y, Tu le M. Prospective, randomized, double-blind study of safety and tolerability of intravesical resiniferatoxin (RTX) in interstitial cystitis (IC). *International Urogynecology Journal and Pelvic Floor Dysfunction*. 2005;**16**(4):293-297

[48] Payne CK, Mosbaugh PG, Forrest JB, Evans RJ, Whitmore KE, Antoci JP, et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: A randomized, double-blind, placebo controlled trial. *The Journal of Urology*. 2005;**173**(5):1590-1594

[49] Schnitzer TJ, Pelletier JP, Haselwood DM, Ellison WT, Ervin JE, Gordon RD, et al. Civamide cream 0.075% in patients with osteoarthritis of the knee: A 12-week randomized controlled clinical trial with a longterm extension. *The Journal of Rheumatology*. 2012;**39**(3):610-620

[50] Kelly S. TRPV1 antagonists in the treatment of osteoarthritis pain. *International Journal of Clinical Rheumatology*. 2015;**10**(3):161-175

[51] Honore P, Chandran P, Hernandez G, Gauvin DM, Mikusa JP, Zhong C, et al. Repeated dosing of ABT-102, a potent and selective TRPV1 antagonist, enhances TRPV1-mediated analgesic activity in rodents, but attenuates antagonist-induced hyperthermia. *Pain*. 2009;**142**(1-2):27-35

[52] Chu KL, Chandran P, Joshi SK, Jarvis MF, Kym PR, McGaraughty S. TRPV1-related modulation of spinal neuronal activity and behavior in a

rat model of osteoarthritic pain. *Brain Research*. 2011;**1369**:158-166

[53] Puttfarcken PS, Han P, Joshi SK, Neelands TR, Gauvin DM, Baker SJ, et al. A-995662 [(R)-8-(4-methyl-5-(4-(trifluoromethyl)phenyl)oxazol-2-ylamino)-1,2,3,4-tetrahydro naphthalen-2-ol], a novel, selective TRPV1 receptor antagonist, reduces spinal release of glutamate and CGRP in a rat knee joint pain model. *Pain*. 2010;**150**(2):319-326

[54] Brown W, Leff RL, Griffin A, Hossack S, Aubray R, Walker P, et al. Safety, pharmacokinetics, and pharmacodynamics study in healthy subjects of oral NEO6860, a modality selective transient receptor potential vanilloid subtype 1 antagonist. *The Journal of Pain*. 2017;**18**(6):726-738

[55] Brookes ME, Eldabe S, Batterham A. Ziconotide monotherapy: A systematic review of randomised controlled trials. *Current Neuropharmacology*. 2017;**15**(2):217-231

[56] Nieto FR, Cobos EJ, Tejada MA, Sanchez-Fernandez C, Gonzalez-Cano R, Cendan CM. Tetrodotoxin (TTX) as a therapeutic agent for pain. *Marine Drugs*. 2012;**10**(2):281-305

[57] Kavoosi M. The Purpose of this Study Is to Determine if Tetrodotoxin (TTX) Is Effective in the Treatment of Pain Resulting from Chemotherapy Treatment (TTX-CINP-201). Bethesda, MD: U.S. National Library of Medicine; 2012. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT01655823?term=tetrodotoxin&rank=2> [Accessed: June 1, 2019]

[58] Mullard A. Drug developers reboot anti-NGF pain programmes. *Nature Reviews. Drug Discovery*. 2015;**14**(5):297-298

[59] Mayorga AJ, Wang S, Kelly KM, Thippawong J. Efficacy and safety of

fulranumab as monotherapy in patients with moderate to severe, chronic knee pain of primary osteoarthritis: A randomised, placebo- and active-controlled trial. *International Journal of Clinical Practice*. 2016;**70**(6):493-505

[60] Tiseo PJ, Kivitz AJ, Ervin JE, Ren H, Mellis SJ. Fasinumab (REGN475), an antibody against nerve growth factor for the treatment of pain: Results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee. *Pain*. 2014;**155**(7):1245-1252

[61] Ekman EF, Gimbel JS, Bello AE, Smith MD, Keller DS, Annis KM, et al. Efficacy and safety of intravenous tanezumab for the symptomatic treatment of osteoarthritis: 2 randomized controlled trials versus naproxen. *The Journal of Rheumatology*. 2014;**41**(11):2249-2259