ISSN 2218-6182 (online)

World Journal of *Anesthesiology*

World J Anesthesiol 2018 July 27; 7(2): 10-19

Published by Baishideng Publishing Group Inc

WJA World Journal of Anesthesiology

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World Journal of Anesthesiology is now indexed in China National Knowledge Infrastructure (CNKI).

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NAME OF JOURNAL
World Journal of Anesthesiology

ISSN
ISSN 2218-6182 (online)

LAUNCH DATE
December 27, 2011

FREQUENCY
Four-monthly

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World Journal of Anesthesiology
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8226 Regency Drive,
Pleasanton, CA 94588, USA
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E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
July 27, 2018

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World J Anesthesiol 2018 July 27; 7(2): 10-19

DOI: 10.5313/wja.v7.i2.10

ISSN 2218-6182 (online)

REVIEW

Targeting tumor necrosis factor in the brain relieves neuropathic pain

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Author contributions: Ignatowski TA initiated the literature review; Ignatowski TA and Spengler RN equally contributed to the writing and revision of the manuscript.

Conflict-of-interest statement: Tracey A Ignatowski and Robert N Spengler have served as unpaid expert witnesses for the Institute of Neurological Recovery (INR), a medical practice that utilizes perispinal etanercept and trains physicians in its use as a therapeutic modality. Tracey Ignatowski and Robert Spengler's professional activities include their work as Co-Directors of Neuroscience at NanoAxis, LLC, a company formed to foster the commercial development of products and applications in the field of nanomedicine that include novel methods of inhibiting TNF. This article represents the authors' own work in which NanoAxis, LLC was not involved.

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Manuscript source: Invited manuscript

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Received: March 27, 2018
Peer-review started: April 12, 2018
First decision: May 3, 2018
Revised: May 28, 2018
Accepted: June 2, 2018
Article in press: June 2, 2018
Published online: July 27, 2018

Abstract

Neuropathic pain is a chronic syndrome caused by direct damage to or disease of the somatosensory nervous system. The lack of safe, adequate and sustained pain relief offered by present analgesic treatments is most alarming. While many treatment options are available to manage chronic pain, such as antidepressants, non-steroidal anti-inflammatory agents, opioids, and anti-convulsants, chronic neuropathic pain remains largely unmanaged. Compounding the dilemma of ineffective chronic pain treatments is the need to provide relief from suffering and yet not contribute to the scourge of drug abuse. A recent epidemic of addiction and accidental drug prescription overdoses parallel the increased use of opioid treatment, even though opioids are rarely an effective treatment of relieving chronic pain. To make matters worse, opioids may contribute to exacerbating pain, and side-effects such as cognitive impairment, nausea, constipation, development of tolerance, as well as their potential for addiction and overdose deaths exist. Clearly, there is an urgent need for alternative, non-opiate treatment of chronic pain. Innovative discoveries of pertinent brain mechanisms and functions are key to developing effective, safe treatments. Pioneering work has revealed the essential effects of the pleiotropic mediator tumor necrosis factor (TNF) on brain functioning. These studies establish that TNF inhibits norepinephrine

release from hippocampal neurons, and show that excess TNF production within the hippocampus occurs during neuropathic pain, which mobilizes additional mechanisms that further inhibit norepinephrine release. Significantly, it has been verified that elevated levels of TNF in the brain are actually required for neuropathic pain development. Since TNF decreases norepinephrine release in the brain, enhanced TNF levels would prevent engagement of the norepinephrine descending inhibitory neuronal pain pathways. Increased levels of TNF in the brain are therefore critical to the development of neuropathic pain. Therefore, strategies that decrease this enhanced TNF expression in the brain will have superior analgesic efficacy. We propose this novel approach of targeting the pathologically high levels of brain TNF as an effective strategy in the treatment of the devastating syndrome of chronic pain.

Key words: Neuropathic pain; Tumor necrosis factor; Brain; Norepinephrine; Analgesia

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Core tip: Chronic pain is a widespread health problem. Current treatments, including opioids or non-steroidal anti-inflammatory drugs are inadequate as they lack sufficient efficacy, produce numerous side effects and hold the potential for addiction. Preclinical studies show that elevated brain tumor necrosis factor (TNF) levels during chronic pain are a novel target for producing analgesia. TNF can be practically targeted by non-invasive delivery of anti-TNF biologics directly to the ventricles of the brain *via* a peripheral perispinal injection. Herein we discuss decreasing TNF activity in the brain as a treatment to provide a superior analgesic strategy. Animal study results indicate potential benefit for patients with treatment-resistant pain.

Ignatowski TA, Spengler RN. Targeting tumor necrosis factor in the brain relieves neuropathic pain. *World J Anesthesiol* 2018; 7(2): 10-19 Available from: URL: http://www.wjgnet.com/2218-6182/full/v7/i2/10.htm DOI: http://dx.doi.org/10.5313/wja.v7.i2.10

INTRODUCTION

Neuropathic pain is a prevalent, chronic disease syndrome caused by injury to peripheral nerves, the spinal cord, or the brain. It affects over 20 million people and costs in excess of $500 billion per year in lost productivity and expenses[1,2]. In addition, it inflicts a tremendous amount of suffering and devastating effects on both the patient and loved ones. For those reasons, innovative breakthroughs are very much needed to replace current treatments, which have proven ineffective in treating this devastating health dilemma. The present therapeutic management of neuropathic pain with medications including opioids, non-steroidal anti-inflammatory drugs, antidepressants, and anticonvulsants is often ineffective in providing adequate as well as sustained pain relief. The next generation of analgesics (anti-pain medications) will be developed by exploiting the current knowledge of chronic inflammation, a pathophysiological response now known to direct fundamental mechanisms involved in the perception of pain. Novel treatment design will selectively target brain-mediators that are directly enhanced by nerve injury, are involved with the chronic inflammation, and very importantly are also localized to the brain regions associated with the perception of pain. Crucial to the understanding of the etiology of neuropathic pain is that many inflammatory mediators are also neuromodulators. A peripheral insult with its accompanying local inflammation produces an associated expression of inflammatory cytokines (inflammatory mediator proteins) in the brain, which subsequently directs profound neuromodulatory mechanisms that ultimately modify neurotransmitter release. It is becoming apparent that the effective treatment of neuropathic pain requires targeting the production of those brain (central nervous system, CNS) pleiotropic inflammatory cytokines. A particularly important cytokine that is also a neuromodulator target within the brain is tumor necrosis factor (TNF), because of its proximal function. In fact, TNF is often referred to as a pro-inflammatory cytokine; this implies that this protein mediator is a marker for inflammation since it sets into motion a myriad of events crucial in the inflammatory response. However, this pleiotropic mediator is involved in a myriad of physiologic processes including modifying release of neurotransmitters[3-7] and homeostatic regulation of the blood-brain barrier[8]. Yet, when it is increased in the level of expression or enhanced for an extended duration of time, TNF can instigate pathophysiologic changes; this is the case during neuropathic pain conditions. As a neuromodulator, TNF modifies both the perception of pain as well as brain-body communication directing the peripheral inflammatory loci[9,10]. Preclinical investigation and clinical case studies involving blocking the responses of this brain-derived protein and its mechanisms of action during neuropathic pain show great efficacy, with minimal side-effects, and has decreased or no apparent potential for drug abuse[9,11,12]. Accordingly, cutting-edge investigations into the role of brain-derived TNF in chronic pain etiology indicate that pioneering therapeutic approaches are on the horizon, and urgency in their development is paramount based on the rising epidemic of prescription opioid drug abuse and resurgence in heroin use by desperate and hopeless individuals. Current preclinical studies reveal an advanced breakthrough in treatment efficacy for the debilitating and life-threatening illness of neuropathic pain, by blocking the higher levels of TNF that are specifically within the brain during the onset, development and maintenance of this devastating disease[9,10,12-14].

THERAPEUTIC TARGET LOCATED WITHIN THE BRAIN DURING THE ONSET AND DEVELOPMENT OF NEUROPATHIC PAIN

Improved therapeutic approaches require a greater understanding of the pathogenic mechanisms that create, develop, and propagate neuropathic pain. The perception and experience of pain manifests in select brain loci *via* molecular signaling; therefore, brain-derived protein mediators, such as pro-inflammatory cytokines (neuromodulators), along with neurotransmitters that are linked to neuropathic pain pose novel targets for analgesia. The functional interactive and mechanistic relationships that exist between the classical neurotransmitters and these protein neuromodulators (mediators) are being realized. In particular, how these relationships direct both normal as well as pathological brain functions is offering new insights into etiologies of disease syndromes. For instance, TNF produced either in the CNS or systemically has been implicated or has been shown to play a key role in the onset, development and maintenance of neuropathic pain. This is because increases in inflammatory cytokines occur rapidly after injury, and TNF as a proximal mediator initiates the cytokine cascade[15,16]. In fact, TNF drives the release of inflammatory cytokines, including IL-1β, IL-6, and itself, all of which are involved in chronic pain, and it robustly alters neurotransmission (glutamate and norepinephrine) in the CNS[5,13]. TNF levels rise locally and centrally after peripheral nerve injury[13,14,17-21]. Substantial data reveal pro-nociceptive roles for TNF in chronic pain[22-24], and increases in levels of TNF in the brain impact peripheral hypersensitivity[9,14,25,26]. Thus, whether the increase is central, peripheral or both, TNF facilitates pain[27,28], and lowering of TNF is antinociceptive[12,14,29-34]. Spread of inflammation occurs along the neuroaxis (CNS and peripheral nervous system, PNS) during neuropathic pain, providing an explanation for its chronicity[35]. The chronic pain state may exist from signal-induced TNF, IL-1β, and IL-6 production distant from the injury or from transport of cytokines to the CNS from the periphery. These cytokines induce neuroplasticity leading to chronicity of pain. In fact, chronic pain is centralized by maladaptive CNS functions that greatly alter brain systems, whether started in the PNS or CNS[36]. The enhanced production of TNF in the region of the brain known as the hippocampus, which is involved in memory formation and learning, is observed during sciatic nerve constriction-induced pain behavior[9,12-14]. In fact, it is now evident that enhanced TNF expression in specific brain regions is sufficient as well as necessary for the expression of pain behaviors. Ectopically enhanced expression of TNF (nanoparticle-bound TNF-expression plasmids) that is solely administered into and thus only found within the hippocampus generates a pain response that mirrors the hyperalgesia and allodynia that is normally associated with neuropathic pain[26]. This experimental study thus mimics the overexpression of brain TNF that occurs during the evolution of chronic pain, and results in peripheral hypersensitivity in the absence of nerve injury[9,13,14,26]. Based on these findings, it may be concluded that a treatment that exclusively or directly targets this increased production of TNF in the brain during neuropathic pain onset and development should provide greater therapeutic efficacy against this chronic disease syndrome. In addition, targeting CNS TNF activity would avoid the deleterious side effects associated with peripheral targets. In support of this therapeutic paradigm, alleviation of hyperalgesia occurs following intra-hippocampal injection of TNF-siRNA-complexed (bound) nanoparticles that prevent translation of TNF gene expression that is solely found within this brain region[12]. Thus, the therapeutic prevention of TNF expression that is specifically located in the hippocampus prevents the onset and development of peripheral hypersensitivity associated with peripheral nerve injury. These studies confirm that the overexpressed TNF that occurs in the hippocampus during the onset, development and maintenance of neuropathic pain is pathogenic and is a promising putative target for anti-nociceptive therapy[12,14,26].

NEUROTOXICITY MEDIATED BY TNF CONTRIBUTES TO THE CHRONIC PAIN PHENOTYPE

Patients with diverse chronic pain states have reduced brain region volumes, which highlights the linkage of the brain to chronic pain. The volume of the hippocampus is reduced with back pain, osteoarthritis, or complex regional pain syndrome. Similarly, mice with neuropathic pain have decreased hippocampal neurogenesis[37]. Prolonged, elevated TNF may reduce gray matter volume, since increased TNF appears to decrease neurogenesis in a neuropathic pain model[38] and enhances production of glutamate, which is neurotoxic when in excess[6,39]. Of note, even chronic low back pain patients treated with morphine show reduced gray matter volume[40]. Thus, ample evidence indicates TNF as a novel, non-opioid associated key mediator of chronic pain, and its dysregulated production in the CNS as vital to pain chronicity.

TNF is produced not only by immune/inflammatory cells, but also by brain neurons and glial cells[41]. Since microglia and neurons express both TNF receptor-1 (p55) and TNF receptor-2 (p75) (TNFR1 and TNFR2), and neuropathic pain development and maintenance is linked to signaling through TNFR1[38,42], it is likely that microglial activation by TNF through TNFR1 mediates persistent TNF production that contributes to the ongoing neuroinflammation and neuropathological consequences including synaptic transmission deficits and decreased neurogenesis[13,43-46]. Since the initial characterization of the roles of TNF in both normal physiology as well as in pathological settings as a pro-inflammatory mediator, TNF was labeled as functioning as a double-edged sword.

Quite interesting, this also holds true with its role now as a neuromodulator. Physiologic levels of brain TNF control proliferation and are neuroprotective; conversely, at high pathologic levels, TNF creates neuron dysfunction and disorder[41]. Thus, much attention is directed toward TNF as it drives the production/release of cytokines, directly causes nociception, and regulates neurotransmission.

INHIBITS NOREPINEPHRINE RELEASE FROM BRAIN NORADRENERGIC NEURONS

Neuromodulation is the process whereby autocrine, paracrine or hormonal mediators will control the ability of a neuron to release its neurotransmitter; thus, the physiological levels of classic neurotransmitters are regulated by such neuromodulators and accordingly modify the function of neurons. This is, in fact, a classic neuro-immune response, showing how immune effector cells orchestrate the nervous system. Neuromodulators, including cytokines, function as a paracrine by diffusing through large regional areas of the brain (CNS), affecting multiple neurons and glial cells and consequently are a communication signal between the nervous and immune system. This neuro-immune communication has a major impact on brain function. Unlike the specific targeting of an individual neuron by its own neurotransmitter, which is rapidly degraded or reabsorbed, a neuromodulator controls the neuronal circuitry of an entire brain region. The neuro-immune mediator, TNF, and its communication network have a major impact on brain function, and the elevated levels of brain-TNF during neuropathologies provide a therapeutic target. Targeting these elevated levels of TNF within the brain, and thus its impact on numerous neurotransmitter systems, will revolutionize medicine by treating numerous disorders as an aberrant inflammatory response of the brain.

One of the neuromodulator functions of TNF is to inhibit the release of the neuron-derived monoamine neurotransmitter, norepinephrine, as shown in the isolated median eminence[47]. TNF also inhibits the release of norepinephrine from field-stimulated tissue slices of the hippocampus, a region rich in noradrenergic nerve terminals[3,4]. Neuropathic pain, while directed by enhanced TNF production in the hippocampus, is also associated with reduced norepinephrine release within the brain[9,13,48]. Thus, this finding offers credibility to propose that a mechanism by which TNF directs neuropathic pain is through its enhanced and profound inhibitory effect on norepinephrine release. Overproduction of TNF in the hippocampus during neuropathic pain modifies signaling pathways to overwhelmingly inhibit norepinephrine release. Since supra-spinal descending noradrenergic inhibition of pain (endogenous analgesic pathway) occurs when norepinephrine is released in the brain[49,50], the overproduction of TNF during neuropathic pain, with its enhanced inhibition of norepinephrine release, would elevate pain to a chronic state by reducing central inhibition, thereby establishing a central component[9,13,48]. This mechanism explains how engagement of the descending inhibitory neuronal pain pathways is prevented as shown within the hippocampus. In fact, due to its direct sensory input from the spinal cord, indirect sensory input from other brain regions, and complex network connections to thalamic and parabrachial regions, the hippocampus is well-situated to participate in both pain processing and modulation[51]. Hence, the development of neuropathic pain is dependent upon the neuromodulatory role of the pathologically elevated levels of TNF in the hippocampus. In fact, the therapeutic mechanism by which antidepressant drugs provide analgesia during neuropathic pain is most possibly due to their ability to inhibit TNF production in the brain, and in particular in the hippocampus[10], as they do for the alleviation of depressive behaviors[52,53]. It follows then, strategies that decrease TNF expression in the hippocampus would be expected to produce greater therapeutic efficacy. It is becoming increasingly evident that there are clear functional links between brain production of TNF and the development of neuropathic pain[51]. More importantly, it is imperative to elucidate the mechanisms that are involved in the pathogenesis of neuropathic pain and which are secondary to the enhanced expression of TNF in the hippocampus. The development of novel therapeutic approaches that specifically target the increased levels of TNF in the brain of patients promises superior treatments for hard-to-treat chronic pain, such as neuropathic pain.

TRICYCLIC ANTIDEPRESSANT DRUG ANALGESIC MECHANISM OF ACTION

Of the millions of patients who suffer from devastating chronic pain, many are additionally diagnosed with neuropathic pain that is mediated by peripheral nerve injury[54,55]. Unlike acute pain, effective safe treatment for neuropathic pain has been elusive. Morphine derivatives are often prescribed for treatment of chronic pain conditions, including neuropathic pain. However, it has been shown that morphine repeatedly given to rats increases TNF expression in microglia, resident macrophage cells of the brain[56,57]. This finding explains morphine-induced hyperalgesia and/or tolerance that develops during chronic pain treatment, since TNF contributes to the chronic pain state[58]. Of interest, etanercept, a TNF blocker (a human TNFR2 fusion protein that blocks activity of TNF), when given intrathecally to morphine-tolerant rats decreased spinal TNF, IL-1β, IL-6 production and restored the antinociceptive effect of morphine[56]. This effect supports the contraindication of morphine as a chronic pain therapeutic.

We reported clinical benefit from perioperative clonidine use; clonidine lowered TNF levels in the cerebrospinal fluid, lowered patient VAS pain scores, and reduced postoperative morphine need[59,60]. Clonidine

manages pain mediated from elevated brain TNF, which causes neuroplasticity, that allows for transient pain relief[9,13,61]. Yet, as with most drugs, clonidine has adverse side-effects limiting its use. Despite its benefits in pain management, this drug is mostly used as an adjunct to other analgesics (opioids, nonsteroidal anti-inflammatory drugs).

Tricyclic antidepressant drugs as well as anti-convulsant drugs are first-line remedies for neuropathic pain[62-66], yet neither class of drugs effectively treats all patients. While tricyclic antidepressant drugs are employed as a treatment practice, they are only moderately effective largely due to their various additional side-effects, and these multiple, unwanted side-effects limit their use[67,68]. The tricyclic antidepressant drug analgesic mechanism of action is proposed to involve various neurotransmitter effectors (norepinephrine, serotonin, dopamine, and acetylcholine), which are dysregulated (both at their release as well as at receptor response) during neuropathic pain. Studies suggest that the tricyclic antidepressant drug analgesic mechanism involves their capacity to increase monoamines (NE, serotonin) in the synaptic cleft (at the varicosities) of neurons within the brain. Therefore, as proposed above, enhanced synaptic levels of monoamines activate the descending inhibitory pain pathway, which is compromised during neuropathic pain[64]. In fact, tricyclic antidepressants and norepinephrine reuptake inhibitors (duloxetine, milnacipran) are better for neuropathic pain than SSRIs (Prozac, fluoxetine)[69,70]. This may occur because, although each monoamine can activate both descending pain inhibitory and facilitatory pathways[71,72], brain norepinephrine preferentially activates descending pain inhibitory pathways[73], whereas serotonin promotes descending pain facilitation[74]. At the same time, tricyclic antidepressant drug-mediated increase of peripheral-monoamines would enhance afferent pain signal transmission; therefore, tricyclic antidepressant drug analgesic action must occur specifically within the brain to be the most efficacious. In support, during chronic constriction injury (CCI)-induced neuropathic pain, increases in TNF levels occur in the periphery (injured sciatic nerve) as well as in the brain; yet, treatment with amitriptyline (tricyclic antidepressant drug, intraperitoneal injection) only decreased TNF production in the brain (hippocampus) and not in the spinal cord concomitant with alleviation of pain[10]. Thus, the reduction of peripheral TNF production can be an unwarranted side-effect, where inflammatory responses may be necessary for healing or to combat associated infections. Specifically, we found that chronic treatment with amitriptyline, when initiated early after peripheral injury, reduced brain TNF and alleviated CCI-induced peripheral hypersensitivity[10]. In contrast, we showed that acute amitriptyline treatment, at peak hyperalgesia, only briefly blocked CCI-induced hyperalgesia, but enhanced total brain TNF level[48]. Thus, increased brain norepinephrine release is required for antinociception. Amitriptyline increases brain norepinephrine release (through reuptake inhibition and, as an additional effect, adjusting TNF production), which may be antinociceptive by increasing the activity of the descending inhibitory bulbospinal pathway (inactive during neuropathic pain)[75]. This acute, transient antinociceptive effect of amitriptyline is most likely explained by norepinephrine activation of presynaptic-α_2-adrenergic autoreceptor-coupled-Gα proteins that inhibit norepinephrine release. Of particular interest, their sensitivity to inhibit norepinephrine release is enhanced by TNF, thereby maintaining a chronic pain state due to preventing engagement of the descending inhibitory pain pathway[10]. While the α_2-adrenergic agonist clonidine normally inhibits TNF production[61], the transient analgesic effect by clonidine in the CCI model of neuropathic pain occurs at the time when we have established that the presynaptic-α_2-adrenergic receptor response to TNF actually switches from inhibiting to facilitating norepinephrine release[61]. We propose that while this plays a role in the natural dissipation of CCI-induced thermal hyperalgesia, it can be provoked by blocking TNF production and can be involved in resolving neuropathic pain in humans[48,61].

The reduction in levels of TNF in the brain elicited by tricyclic antidepressant drugs appears to be the likely mechanism of action directing their off-label analgesic drug use. Since the perception of pain is a product of the brain, and brain synthesized TNF is a key factor in neuropathic pain development, the elevated amounts of TNF in the brain of neuropathic pain patients could profoundly influence various neurotransmitter effectors. It follows therefore, that brain-TNF production when selectively targeted would create a potent and efficacious therapy. As previously stated, while TNF is increased in the brain during animal neuropathic pain models[9,10,13,14], TNF regulates norepinephrine release from noradrenergic nerve terminals, and norepinephrine release in the brain is decreased at the same time[13,14,48], which supports a role for TNF in the neuroplasticity associated with the development and maintenance of neuropathic pain. Not only does TNF directly inhibit norepinephrine release, but TNF also modifies the response of the presynaptic α_2-adrenergic autoinhibitory receptor, a principal inhibitor of norepinephrine release[3,4]. The presynaptic α_2-adrenergic autoinhibitory receptor is activated by the release of norepinephrine in the synaptic cleft, as an inhibitory feedback mechanism having a primary effect on norepinephrine release. When activated, the presynaptic α_2-adrenergic autoinhibitory receptor decreases further release of norepinephrine upon depolarization. Of particular interest, not only do tricyclic antidepressant drugs decrease TNF production, but they are also known to down regulate and desensitize the presynaptic α_2-adrenergic autoinhibitory receptor[76,77]. This simultaneous double-hit response by tricyclic antidepressant drugs on TNF production and on the presynaptic α_2-adrenergic autoinhibitory receptor would have a profound response on depolarized release of norepinephrine culminating with analgesic functioning. It follows that the analgesic mechanism of tricyclic antidepressant drugs is likely the

result of their effect on TNF levels. Thus, the increased expression and levels of brain-TNF that are mediated by peripheral nerve injury is a viable therapeutic target[3,10].

Founded on the fact that TNF regulates (inhibits) norepinephrine release in the brain both directly as well as indirectly by its effect on presynaptic α_2-adrenergic autoinhibitory receptors, a pathologic increased level of TNF in the brain, and in particular, in the hippocampus, would be a key nociceptive target affecting norepinephrine bioavailability in the brain. Therefore, it follows that utilizing the inhibition of TNF activity as an antidepressant mechanism supports the monoamine theory of depression as well as the role of norepinephrine in the etiology of chronic pain. This current and comprehensive knowledge of inflammatory mediators such as TNF in chronic pain etiology will allow for the ushering in of new therapeutics that apply these mechanisms to direct the efficacy of new tricyclic antidepressant drug formulations or any other new therapies. Medicine that specifically reduces TNF levels in the brain are effective in animal models of neuropathic pain[29,30,78]. Unfortunately, FDA-approved anti-TNF drugs are designed to target peripheral TNF and not brain TNF (*i.e.*, Infliximab) and, therefore, have very limited access to the brain; this could explain conflicting clinical reports[11,79-81]. For instance, not all patients with sciatica receive benefit with peripherally administered TNF blockers[80,81]. Meanwhile, tricyclic antidepressant drugs that can alleviate pain do in fact decrease the production of TNF in the brain[10]; however, due to their mode of delivery, they produce significant side-effects that confound their efficacy[67,68]. Therefore, targeting the pathophysiologic levels of TNF that are specifically found within the brain, and in particular within the hippocampus, may be required to efficaciously alleviate pain. This premise is often incorrectly challenged by researchers/clinicians who administer anti-inflammatory drugs peripherally instead of through means that adequately target CNS-TNF alone. This is because when administered peripherally, a drug must distribute throughout the entire body where it is accessible and undergo metabolism through the liver, leaving significantly less unmetabolized drug to reach vital brain targets. Since very little drug reaches the brain when it is delivered peripherally, the (drug) effect on this organ would be minimal[82]. Even drug delivery *via* intrathecal injection, which delivers more drug to the brain than intravenous injection, is quite limited. Non-invasive drug administration that targets brain effectors would be a pioneering discovery with wide ranging potential for numerous brain disorders.

Blockade of TNF activity specifically in the brain is difficult due to the large size and structure of anti-TNF biologics such that they do not easily cross the blood-brain barrier. Therefore, a new pioneering breakthrough is underway. Perispinal injection is a subcutaneous, peri-venous route for delivery to the brain that is less invasive than epidural or intrathecal routes[83]. Drugs injected outside and posterior to the spine (ligamentum flavum and spinal canal) are absorbed by the external vertebral venous plexus, part of the cerebrospinal venous system, which is a direct pathway to the brain[84]. Perispinal etanercept injection immediately followed with head-down positioning (Trendelenburg positioning) delivers the TNF fusion protein into the choroid plexus and cerebral ventricles in minutes, as shown by PET scan[85]. In fact, discogenic back pain patients that received perispinal etanercept delivery reported substantial, sustained recovery that was verified by reduction in Oswestry scores[11]. Also, patients reduced significantly or completely discontinued analgesic medication after perispinal etanercept. This included 11 of 20 patients requiring chronic opioids[11]. More recently, we reported a case study whereby perispinal injection of etanercept was performed to treat neurological dysfunction, including pain, induced by a traumatic brain injury suffered several years prior[86]. The results from this case indicate that even years after an acute brain injury, the pathologic levels of TNF induced by the injury may provide a feasible therapeutic target. Taken together, these case reports provide compelling evidence that the specific targeting of brain-TNF is superior and thus an effective analgesic.

ROLES FOR TNF IN NEUROPATHIC PAIN ETIOLOGY

There are multiple roles for TNF in the development and maintenance of neuropathic pain. While many animal model studies show that systemic levels of TNF increase during neuropathic pain and contribute to its pathology[19,87,88], increased TNF levels specifically in select brain regions alone enhance or initiate peripheral hyperalgesia (increased noxious sensitivity), which is a typical neuropathic pain response[26]. The increased levels of TNF within the brain direct neuropathic pain onset[9,13,14,48], as shown in the sciatic nerve CCI model[9,61,89]. Likewise, the neuropathic pain that develops during diabetes, diabetic neuropathy, is accompanied by high serum TNF levels[90-92]. High peripheral TNF levels in diabetes are associated with and possibly trigger peripheral nerve dysfunction and death[93,94]. Interestingly, TNF directs neuron responsiveness, similar to the immune effector cell, the macrophages, and thus TNF stimulates neurons to produce more TNF[4,61,95,96]. This creates a perpetuating feed-forward cycle, whereby inflammatory mediators released from damaged neurons stimulate cells and result in further production of TNF[97]. This perpetual cycle may ultimately result in neuronal death, causing atrophy, which is an effect of TNF that may contribute to the decrease in brain gray matter experienced by chronic pain patients[98]. This atrophy effect may be due to increased glutamate release by TNF, since excessive glutamate is neurotoxic[39]. However, this effect, one of the many pleiotropic responses to TNF, may reflect the originally defined function of TNF as a TNF or

agent of cachexia or wasting syndrome. Moreover, the blockade of TNF activity by peripherally administered infliximab in rodent diabetes models restores glucose homeostasis[99], but only reduces diabetic neuropathy[30]. This inefficient effect by peripheral TNF blockade is in contrast to the complete alleviation of neuropathic pain observed in the CCI model, when TNF was specifically blocked in the brain[9,12]. Mice deficient in TNF production ($TNF\alpha^{-/-}$ mice) do not develop diabetic neuropathic pain following injection of streptozotocin (STZ), an antibiotic toxic to pancreatic β-islet cells and used to induce diabetes[30]. Thus, it is apparent that TNF has a pivotal role in neuropathic pain, and therapies that decrease systemic, but more importantly, brain levels of TNF will provide greater efficacious neuropathic pain treatment, and most importantly, with fewer side effects.

CONCLUSION

In order to design novel therapies to treat neuropathic pain, it is necessary to use our current and comprehensive knowledge of biochemical mechanisms occurring specifically within the brain that elicit the development as well as the maintenance of neuropathic pain. An increased hippocampal TNF level plays a key role in the propagation and perception of neuropathic pain[9,13,14,26,48,61,89]. Since brain synthesized TNF modifies adrenergic neuron activity, it follows that sympathetic output is altered, and consequently, has profound effects on descending inhibitory pain pathways that normally provide endogenous analgesia. The limited success in treating neuropathic pain with current agents stems from lack of specific and selective targeting of a fundamental mechanism associated with pain perception such as the pathologically overexpressed TNF in the brain and in particular in the hippocampus[10,12,21,37]. In conclusion, elevated brain TNF levels drive the pathogenesis of neuropathic pain, and therapies that specifically lower this pathologic level of brain TNF may provide more efficacious chronic pain treatment, with fewer side effects and negligible abuse potential.

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P- Reviewer: Afzal M, Ajmal M, Chen C, Mentes O
S- Editor: Cui LJ **L- Editor**: A **E- Editor**: Huang Y

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