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Review Article

BDNF: The Old-New Pain Mediator and Modulator of Neuropathic Pain and Neuroinflammation

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Abstract

This manuscript will review the crucial role of BDNF as a pain mediator and modulator of neuroinflammation and neuropathic pain.

BDNF belongs to of the neurotrophin family of growth factors that is encoded by the bdnf gene. Its role as modulator was found to act on neuronal excitability and synaptic plasticity has triggered huge interest in neurobiological pain research. This pointed to renewed interest as a potential target for pharmacological agents in its long cascade of mechanism of actions.

There is no clear-cut explanation on how BDNF works. One thing we know is that BDNF mechanism of action depends on whether we are dealing with a normal nerve, after an acute injury, or following chronic state. It is considered a major tertiary mediator in the genesis of central sensitization. It mediates inflammatory and peripheral injury-induced pain and play a role by increasing dorsal horn excitability. Hence disrupting these cycles can potentially curb the genesis of chronic pain.

Some suggested mechanisms of action of BDNF in neuropathic pain is via enhanced neuronal sensitivity to painful stimuli and an enhanced co-expression of thermo-TRP channels. Another possible mechanism entails the involvement of microglia in pain. Following a peripheral injury, GABA-BDNF plays an essential role in formation of neuropathic pain. BDNF increases both the excitatory and inhibitory synaptic drives to putative excitatory interneurons while attenuating synaptic transmission to inhibitory GABAergic neurons.

In the absence of any injury and in normal states, BDNF-mediated effects contribute to pain. An increase in BDNF and TrkB expression activate MAPK/ERK and PLC-PKC kinase pathways.

In the acute stage of nerve injury, the levels of both BDNF and TrkB are decreased in the spinal cord dorsal horn. During the chronic stage of injury, pERK levels are also noted to increase. This may result from increases in both BDNF-TrkB signaling and TNFα-TNFR signaling.

BDNF may also potentially modulate spinal neuron responsiveness by potentiation of postsynaptic N-methyl-D-aspartate (NMDA) receptors.

BDNF noticeably enhanced the frequency of miniature excitatory postsynaptic currents (EPSCs) recorded in superficial dorsal horn neurons.

All these mechanisms and theories may potentially be a dream for clinicians to work on and modulate pain.

Keywords: BDNF; TrkB; Plasticity; Neuropathic Pain; Neurotrophins; Neuroinflammation; Plasticity; NMDA Receptors; IL-1β; GABA; Central Sensitization

Introduction

The last 3 decades witnessed a huge interest in the fields of pain molecular neurobiology and neuroscience. Pain practicing clinicians are faced with limited time and limited clinical treatment and management options for the chronic pain patients. The essential role of pain research, basic and clinical has elevated this filed of science to a level with higher standards of understanding of the cascades that involve pain and its complex pathways. This manuscript will review the role of BDNF in neuropathic and neuroinflammatory pain.

The traditional belief that the modulation of pain is based solely on peripheral and central pain pathways, or based on peripheral pain modulators such as bradykinin, substance P, and prostaglandin, is almost outdated and labeled as "old". Brain-derived neurotrophic factor (BDNF) is one of the most interesting neuromodulators discovered about 30 years ago. It is by far considered as the most abundant and widely distributed neurotrophin member in the central and peripheral nervous system. It is known to be involved in axonal growth, synaptic plasticity, and neuronal repair [1].

BDNF belongs to of the neurotrophin family of growth factors that is encoded by the *bdnf* gene [2]. It acts as a modulator of neuronal excitability and synaptic plasticity[2]. In this capacity, BDNF acts as neuroprotective, and promotes and modulates growth of different neuronal populations after injury. These effects are mainly concentrated around the rubrospinal, reticulospinal, and vestibulospinal tracts, in addition to proprioceptive neurons of Clarke's nucleus in the spinal grey matter of the lumbar spinal cord [3].

Histological and functional evidence has been provided, mainly from studies on acute slices and intact animals, that BDNF modulates fast excitatory (glutamatergic) and inhibitory (GABAergic/glycinergic) signals, as well as slow peptidergic neurotransmission in spinal cord. Recent studies have unraveled some of the neuronal circuitries and mechanisms involved, highlighting the key role of synaptic glomeruli in lamina II as the main sites for such a modulation [4]. BDNF was initially isolated and purified in the brain of the pig [5]. Recent evidence has shown that BDNF has a strong role in cognitive functions, notably in memory acquisition and consolidation [6].

BDNF has been shown to mediate inflammatory and peripheral injury-induced pain. It should not be surprising that it also exerts deleterious effects, which are typically associated with its overexpression [7]. BDNF signaling is involved in the formation, maturation, and function of excitatory and inhibitory synapses and in synaptic plasticity [8]. This in part explains its role in causing neuroplasticity [9].

Neuropathic pain and the inflammatory cascade

To better understand the role of BDNF and where it stands in a long and busy cascade of inflammatory nerve responses, it behooves us to review the normal physiologic etiology and pathologic response to a nerve injury and development of neuropathic pain at peripheral and spinal levels. This over-simplification of the cascade is an overview with a reminder that the cellular mechanisms between males and females are very different [10].

- **Primary Mediators:** Peripheral nerve injury results in activation of primary mediators that include cytokines, neuropeptides, chemokines, Wnt ligands, and growth factors. This injury promotes a Wallerian degeneration of severed axons, neutrophils and T-lymphocytes influx, macrophages, fibroblasts, Schwann cells, and mast cells [11]. The trigger of primary mediators cause change in gene expression, enhance post-translational modification of proteins, and change ion channel status in primary afferent neurons, leading to secondary mediators release [11].
- **Secondary mediators:** Primary afferent terminals in the spinal dorsal horn release secondary mediators like colony stimulating factor 1 (CSF-1), chemokine (C-C motif) ligand 21 (CCL21), and wingless-type mammary tumor virus integration, member 5A (Wnt5a). These affect influence spinal microglial cells causing them to release tertiary mediators [11].
- **Tertiary mediators:** Derived from microglia, tertiary mediators like as BDNF, Tumor Necrosis Factor- α (TNF- α), and interleukin-1β (IL-1β) promotoe excitatory transmission and decrease inhibitory synaptic transmission in the superficial dorsal horn [11]. Tertiary mediators along with synaptic plasticity promote the movement of nociceptive information and enhance information leading to central sensitization at supra-spinal and spinal levels[11]. Persistent changes in microglial function leads to long-term changes in astrocyte function and hence chronic neuropathic pain [11].

BDNF release in spinal dorsal horn

BDNF plays its role by increasing dorsal horn excitability. It is considered a major tertiary mediator in the genesis of central sensitization [12]. CSF-1, a secondary mediator, is released from the injured primary afferents and it is activated through receptors on microglial cells. This results in up-regulation of many genes that are considered culprits in the genesis of neuropathic pain. These genes include *Ctss* (encoding cathepsin S), *Cx3cr1* (encoding the fractalkine/CX3CL1 receptor, CX3CR1), *Itgam* (encoding CD11b), and the gene *Bndf* (encoding BDNF) [11,13].

How is BDNF released?

Up-regulation of purinergic P2X4 receptors, a subtype of ionotropic ATP receptors, and because of ATP activation in spinal microglia after peripheral nerve injury, mediates BDNF release and causes neuropathic pain [14]. P2X4 opens the ion channels on cell membrane, mainly via calcium influx, activates microglia, releases some damaging factors (such as IL-1β, TNF-a, and IL-6), and induces and aggravates chronic pain [14]. And as mentioned above, activation of P2X4 on microglia and release of BDNF is seen linked to genesis of neuropathic pain in males only. It was observed that spinal microglia do not express P2X in female rodents [15]. Similarly, there is data to suggest that P2Y receptors have a role in the release of BDNF and subsequent role in microglial activation and the onset of neuropathic pain [16].

Wingless-type mammary tumor (Wnt) signaling was also implicated in the promotion of BDNF release [17]. Wnt signaling was found to provide an important bridge between enhanced neuronal activity and BDNF expression [17].

Mechanism of action of BDNF

This area of research is still in embryonic stages and clear mechanisms of actions are still scarce. There is no clear-cut explanation on how BDNF works. One thing we know, is that BDNF mechanism of action will depend on whether we are dealing with a normal nerve, after an acute injury, or following chronic state.

But amongst the suggested mechanisms of action of BDNF in neuropathic pain is via enhanced neuronal sensitivity to painful stimuli and an enhanced co-expression of thermo-TRP channels. BDNF was found to have the ability to regulate the pattern of expression and the level of activity of the transducer channel Transient Receptor Potential Vanilloid Subtype 1 (TRPV1) [18].

Another possible mechanism entails the involvement of microglia in pain. Subsequent to a peripheral nerve injury, the spinal cord activated microglia P2X (4) and their receptors (P2X (4) R) become over-expressed, and activated P2X(4)R leads to the release of BDNF from microglia [19].

Following a peripheral injury, GABA-BDNF plays an essential role in formation of neuropathic pain [20]. BDNF increases both the excitatory and inhibitory synaptic drives to putative excitatory interneurons while attenuating synaptic transmission to inhibitory GABAergic neurons [21].

In the absence of any injury and in normal states, BDNF-mediated effects contribute to pain. An increase in BDNF and TrkB expression activate MAPK/ERK and PLC-PKC kinase pathways. This leads to transcription of pain genes and post-translational changes such as phosphorylation of glutamate receptors [21].

In the acute stage of nerve injury, the levels of both BDNF and TrkB are decreased in the spinal cord dorsal horn [20]. MAPK/ERK pathways could be activated by BDNF-independent mechanisms, presumably an alternate pathway such as the TNFα pathway (both TNFα and TNR1 expressions are upregulated by nerve injury or spinal cord injury) [22]. A decrease in KCC2 by SCI which alters GABA-mediated chloride function is likely to contribute to pain after an injury as well [21].

During the chronic stage of injury, pERK levels are also noted to increase. This may result from increases in both BDNF-TrkB signaling and TNFα-TNFR signaling. These pathways activation could result in an increase of activity of kinase and the transition of pain genes. It is concluded that BDNF may not initiate pain-producing pathway, but potentially facilitate pain hypersensitivity during the chronic stages of injury [21].

Another plausible evidence on mechanism of action of BDNF points to the fact that it modulates spinal neuron responsiveness by potentiation of postsynaptic N-methyl-D-aspartate (NMDA) receptors. These are ionotropic glutamate receptors that play a central role in central sensitization [2,23]. Data suggest that BDNF

facilitates evoked synaptic currents in lamina II neurons via a phospholipase C (PLC) and PKC-dependent mechanisms [2,24]. In addition, electrical stimulation of primary afferent fibers leads to spinal Neurokinin-1 (NR1) phosphorylation in serine 897, an effect that is canceled by incubation with trkB-IgG in a ERK and PKC-dependent fashion [2,25].

In 2005, Matayoshi and his team out of Japan, suggested another mechanism of action of BDNF. In pointed that "BDNF may promote synaptic rearrangements in which activity in innocuous mechanoreceptors newly activates nociceptive second-order neurons" [2,26]. The following days after inflammation was induced by complete Freund's adjuvant, BDNF noticeably enhanced the frequency of miniature excitatory postsynaptic currents (EPSCs) recorded in superficial dorsal horn neurons [2,26].

Finally, another mechanism of action of BDNF, theorized that activation of spinal microglial cells is associated with BDNF enhanced expression and release from these cells [2,27]. BDNF is noted to change the excitability of superficial dorsal horn neurons by altering the anion reversal potential in these cells leading to disinhibition of these neurons. In the same study, the neutralization of microglial-derived BDNF prevented the excitability alterations in postsynaptic neurons and overturn neuropathic pain [2,27].

The ambivalent role of BDNF as pain modulator

BDNF is known to be pleomorphic in pain. It either promotes pro-nociception and/or acts as anti-nociceptive pain modulator.

1- BDNF anti-nociceptive properties

While reviewing research data related to the role of BDNF in pain, we ran into significantly more studies describing BDNF promotion of nociception rather than anti-nociception. This is a summary of the most important studies conducted in this area

Pezet., *et al.* found that BDNF antinociceptive effect was due to modulated sensory neuron synaptic activity by a facilitation of GABA transmission in the dorsal horn and spinal release of GABA [28]. This was also confirmed by Lever., *et al.* [29] that concluded that BDNF-induced release of GABA as a potential mechanism for the antinociceptive action of intrathecal BDNF in neuropathic rats [29].

Siuciak., *et al*. went even further and suggested that BDNF analgesic effect recruited both serotonin and opioid mechanisms. She reported that an infusion of BDNF was associated with by an increase in serotonergic activity within the brain and spinal cord [30].

In 2005, Dr. Tsai, an academic psychiatrist in Taiwan, pointed out that a few antidepressants work as antinociceptives for neuropathic pain by recruiting mediation of BDNF release [31]. In animal and human studies, he postulated that BDNF "modulates synaptic plasticity and neurotransmitter release across multiple neurotransmitter systems" [31].

Bardoni., *et al.* showed that at post-synaptic level, BDNF receptor TrKB enhanced the spontaneous release of GABA and glycine on lamina II neurons. By doing so, it promoted the BDNF analgesia via pain tansmission [32].

Finally, an interesting study by Huang., *et al.* [33], demonstrated a dual behavior of BDNF in the same setting, where it acted as pronociceptive and anti-nociceptive. This behavior depended on the activation of certain intracellular cascades and different cell types. Huang and colleagues showed that intrathecal administration of BDNF into the spinal cord of uninjured rats decreased the potassium–chloride cotransporter 2 (KCC2). By doing so, it enhanced the disinhibition and hypersensitivity, after spinal cord injury, and the same BDNF treatment increased KCC2 and restored synaptic inhibition [33]. This finding translates into the fact spinal cord injury transforms how BDNF affects GABA function and means that the clinical benefit of BDNF will depend on fiber sparing extent [33].

2- BDNF nociceptive properties

This section will address the possible relationship of BDNF and pain (pro-nociception). For the sake of simplicity, this section will be divided into the following sub-sections: the role of BDNF in central sensitization, role of BDNF in inflammatory pain, the role of BDNF in neuropathic pain, BDNF role in transition of acute to chronic pain, and finally the role of BDNF in other forms of pain such as trigeminal neuralgia, spinal cord injury, hyperalgesia, migraine, diabetic neuropathies, and cancer pain.

2A- BDNF and central sensitization

This subsection alone will need a dedicated manuscript of its own, as the data is voluminous, and many studies delineated this relationship. In this synopsis, we will choose the most direct, simplest, and plausible correlation.

BDNF acts at multiple levels of the CNS. In response to ATP, and mediated by purinergic receptor P2X4, BDNF is produced by target tissues such as synovial fibroblasts and become expressed in sensory neurons [34].

Through anterograde axonal transport, BDNF is transported to the spinal dorsal horn. By increasing spinal hyperexcitability, it contributes to central sensitization [1].

Growth., *et al.* demonstrated that thermal hyperalgesia was induced by intrathecal injection of BDNF in healthy mice. If intrathecal injection of TrkB antisense oligonucleotides takes place, it caused inhibition of TrkB expression, and this blocks BDNF-induced hyperalgesia [35].

In a monumental paper displaying the relationship of BDNF to central sensitization, Melemedjian and his colleagues [36] showed that although different kinases may be responsible for the sparking of persistent nociceptive sensitization, they do not participate in the maintenance of chronic pain. He pointed to possibility that a ZIP-reversible process is responsible for the maintenance of persistent sensitization. He also demonstrated that BDNF played an essential role in triggering and maintaining chronic nociceptive sensitization through a ZIP-reversible process. His research concluded that BDNF controlled PKMζ and PKCλ nascent synthesis via mTORC1 and that BDNF increased PKMζ phosphorylation at spinal synapses. He demonstrated that molecular association between pain and memory mechanisms, BDNF signaling to PKMζ, and PKCλ is preserved in CNS synapses [36].

Kerr., *et al*. [37] demonstrated that BDNF induces c-fos expression in dorsal horn neurons. In this experiment, exogenous BDNF significantly enhanced NMDA receptor-mediated responses, known to result in central sensitization. It then showed systemic Nerve Growth Factor treatment raised BDNF levels in sensory neurons and enhanced nociceptive spinal reflex excitability that caused reduction of trkB-IgG, a known BDNF antagonist [37]. The study concluded that BDNF is "localized and regulated in inflammatory states and is sufficient and necessary for the expression of central sensitization" [37].

In laboratory rats with induced bone cancer, Bao., *et al.* [38] showed that activation of proteinase-activated receptor (PAR2) set off the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. This markedly upregulated the BDNF function. The ultimate result was increased glutamatergic transmission in spinal dorsal horn and thermal and mechanical hypersensitivity [38].

2B- BDNF and inflammatory pain

Research studies have suggested a role of BDNF in inflammatory pain. As we were reviewing data related to this matter, it is noted the majority is about 2-3 decades old.

A study suggested that altered gene transcription and protein synthesis in DRG neurons can be the result of peripheral inflammation and nerve injury [39].

Lalisse., *et al.* [40], suggested that the ATP-gated purinergic receptors P2RX4, which are expressed by sensory neurons, controls neuronal BDNF release. This leads to hyper-excitability during chronic inflammatory pain and establish P2RX4 in sensory neurons as a therapeutic target to fight chronic inflammatory pain [40].

Using immunohistochemistry, Cho., *et al*. [41] studied the alterations of BDNF immunoreactivity in the DRG and spinal cord following peripheral inflammation. There was marked elevation of BDNF-immunoreactive (IR) neuron profiles in the L5 DRG and significant increase in the expression of BDNF-IR terminals in the spinal dorsal horn were after following peripheral tissue inflammation. This inflammation was induced by an intraplantar injection of Freund's adjuvant into the rat paws. The result pointed that inflammation caused elevated BDNF synthesis in the DRG and an increase in anterograde transport of BDNF to the spinal dorsal horn [41].

Mannion, and colleagues, including Dr. Woolf, concluded that BDNF as a highly specialized growth factor during development, it contributes to synaptic plasticity at multiple sites in the brain. In the DRG neurons, with its upregulation, and in collaboration with

Nerve Growth Factor, after being transported to the spinal cord, and upon its release, and after acting on TrkB-expressing cells in the dorsal horn, BDNF contributes to stimulus-induced hypersensitivity after inflammation [42].

2C- BDNF and neuropathic pain

In 2005, published in the journal Nature, Jeffrey Coull [27] and his team deciphered the biophysical mechanism by which microglia, once stimulated by ATP, cause hyperexcitability of spinal neurons. In this case, microglia releases BDNF, which changed chloride ion distribution across the plasma membrane of neurons in lamina I of the spinal cord. This caused activation of in GABA triggering neuropathic pain [27].

In a recent 2020 publication, Cao., *et al.* [43] theorized that BDNF and its primary "non-truncated" receptor TrkB are essential for CNS development, neuroprotection in adulthood and contribution to neuronal survival and its recovery phase. But they noted that BDNF upregulated truncated receptor TrkB.T1 has deleterious effects in response to injury and inflammation. This leads to activation of cell cycle proteins, inhibiting axonal repair and facilitating the development of neuropathic pain. To confirm, experimentally, a deletion of the TrkB.T1 receptor has fortunately curbed the untoward effects while improving recovery from injury and tweaked pain [43].

In an experimental study on male rats, to detect the role of local BDNF on transected sciatic nerves, Marcol., *et al.* [44] divided the study into 3 subgroups, with connective tissue chambers with fibrin, with fibrin and BDNF, and with fibrin and antibody against BDNF. This was compared to control rats with no chambers. Seven weeks post-procedure, counting of surviving and regenerating neurons in DRG were assessed. The team concluded that local BDNF played a role in the formation of neuropathic pain after sciatic nerve injury [44].

In a study by Ulman and colleagues [19], as a result of a peripheral nerve injury, the spinal cord activated microglia purinergic P2X (4) and their receptors (P2X (4) R) become over-expressed, and these activated P2X (4) R lead to the release of BDNF from microglia [19]. This research also emphasized the role of ATP as a known mediator of inflammatory and neuropathic pain and concluded that $P2X_4R$ contribute to chronic pain through a central inflammatory pathway [19].

Related to neuropathic pain, peripheral diabetic neuropathies (PDN) were also found to be related to BDNF [45]. In these diabetic rats, "increased BDNF expression in the lumbar DRG [45] was linked with decreased expression of voltage-gated potassium (K_v) channels in the lumbar DRGs and primary sensory neuron hyperexcitability" [45-47].

Following findings in diabetic rats, Sobue., *et al.* [48] found that mRNA levels for the neurotrophins NGF, BDNF and NT-3 and their receptors were upregulated in peripheral nerves with axonal pathologies in patients with PDN. These increased BDNF and NT-3 mRNA levels in the affected sections of peripheral nerves matched the extent of nerve affectation by T-cells and macrophages rather than axonal abnormalities or demyelination [48]. It is concluded that neuroinflammation was a landmark finding in PDN [47].

Regarding chemotherapy-induced peripheral neuropathy (CIPN), in a clinical observation based on experience of the authors, Azoulay and his co-author opined that low blood circulating BDNF levels in blood can be used as a potential biomarker for susceptibility to CIPN [49]. He also added that higher levels of BDNF can reflect prognosis and potential response to treatment [49].

BDNF, one of the serum protein biomarkers was associated with CIPN. As such, it can be used as a reflective measurement tool for detection and profiling of risk stratus in certain oncological clinical practice [50].

2D- BDNF role in the transition of pain from acute to chronic

In a published article in 2021, we elucidated multiple theories behind the unfortunate transition of acute to chronic pain [51]. Ling., *et al*. [52] demonstrated that spinal dorsal horn neurons might carry an engram representing a molecular mechanism of central sensitization that may promote pain [52]. His research concluded that active form of an atypical protein kinase C (PKC) isozyme, "protein kinase M zeta (PKMζ)", is essential for this LTP maintenance [52].

Melemedjian and colleagues [36] suggested that there may be other PKCs kinases that initiate chronic pain, but do not participate in maintaining it. He postulated that a ZIP-reversible process may be responsible for the maintenance of persistent sensitization, and that BDNF has a role in initiating and maintaining persistent nociceptive sensitization. He added that BDNF not only regulates the control of PKMzeta by enhancing its phosphorylation but also has control effect on other PKCs. Melemedjian., *et al.* [36] concluded that BDNF, through its receptor tyrosine receptor kinase type B (trkB), acts as a key regulator in PKC synthesis and phosphorylation and plays a vital role in maintenance of persistent and chronic pain. This landmark finding is the first to directly demonstrate that neurotransmitter-neurotrophin relationship is related to initiation and maintenance of central chronic pain state [36].

Nijs and his team [53] emphasized BDNF is a driving force behind neuroplasticity with sensitizing capacity at every level of the pain pathways including the peripheral nociceptors, dorsal root ganglia, spinal dorsal horn neurons, and brain descending inhibitory and facilitatory pathways. He added that blocking the signaling pathways of proteinase-activated receptors 2–NK-κβ, and administration of phencyclidine for antagonizing NMDA receptors, or blockade of the adenosine A2A receptor may possibly block neuroplasticity and chronic pain [53].

Sikandar et al[54] deleted the bdnf gene from adult peripheral sensory neurons. This is aimed to determine its role in acute and chronic pain processing. His result was that BDNF didn't contribute to acute pain but found it is necessary for the "transition from acute to chronic inflammatory pain and some neuropathic pain states" [54].

Conclusion

Chronic pain is difficult to treat. As enumerated in this manuscript, potentially, there are tens of potential target points, at BDNF and other levels of the pain cascade.

Hopefully many preclinical and clinical research therapeutic trials are now conducted or in the process, based on the advances in pain molecular neurobiology and neuroscience.

We owe it to our patient to improve the therapeutic armamentarium we have in our pockets, and elevate their quality of life, improve their functionality, and decrease their pain and suffering.

Conflicts of Interest

Authors equally declare no financial or scientific.

Bibliography

1. Nijs J., *et al*. "Brain-derived neurotrophic factor as a driving force behind neuroplasticity in neuropathic and central sensitization pain: a new therapeutic target?" *Expert Opinion on Therapeutic Targets* 19.4 (2015): 565-576.

2. Pezet S and McMahon SB. "Neurotrophins: mediators and modulators of pain". *Annual Review of Neuroscience* 29 (2006): 507-538.

3. Keefe KM., *et al*. "Targeting Neurotrophins to Specific Populations of Neurons: NGF, BDNF, and NT-3 and Their Relevance for Treatment of Spinal Cord Injury". *International Journal of Molecular Sciences* 18.3 (2017): 548.

4. Merighi A., *et al*. "BDNF as a pain modulator". *Progress in Neurobiology* 85.3 (2008): 297-317.

5. Yamamoto H and Gurney ME. "Human platelets contain brain-derived neurotrophic factor". *Journal of Neuroscience* 10.11 (1990): 3469-3478.

6. Miranda M., *et al.* "Brain-derived neurotrophic factor: a key molecule for memory in the healthy and the pathological brain". *Frontiers in Cellular Neuroscience* 13 (2019): 363.

7. Garraway SM and Huie JR. "Spinal plasticity and behavior: BDNF-induced neuromodulation in uninjured and injured spinal cord". *Neural Plasticity* (2016).

8. Levine ES., *et al.* "Brain-derived neurotrophic factor rapidly enhances synaptic transmission in hippocampal neurons via postsynaptic tyrosine kinase receptors". *Proceedings of the National Academy of Sciences of the United States of America* 92.17 (1995): 8074-8077.

9. Gottmann K., *et al.* "BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses". *Experimental Brain Research* 199.3-4 (2009): 203-234.

10. Halievski K., *et al.* "Sex-dependent mechanisms of chronic pain: a focus on microglia and P2X4R". *Journal of Pharmacology and Experimental Therapeutics* 375 (2020): 202-209.

11. Boakye PA., *et al.* "Mediators of Neuropathic Pain; Focus on Spinal Microglia, CSF-1, BDNF, CCL21, TNF-α, Wnt Ligands, and Interleukin 1β". *Frontiers in Pain Research (Lausanne)* 2 (2021): 698157.

12. Alles SRA and Smith PA. "The etiology and pharmacology of neuropathic pain". *Pharmacological Reviews* 70 (2018): 315-347.

13. Guan Z., *et al.* "Injured sensory neuron-derived CSF1 induces microglial proliferation and DAP12- dependent pain". *Nature Neuroscience* 19 (2016): 94-101.

14. Ulmann L., *et al.* "Up-regulation of P2X4 receptors in spinal microglia after peripheral nerve injury mediates BDNF release and neuropathic pain". *Journal of Neuroscience* 28 (2008): 11263-11268.

15. Mapplebeck JCS., *et al.* "Microglial P2X4R-evoked pain hypersensitivity is sexually dimorphic in rats". *Pain* 159 (2018): 1752-1763.

16. Zhang X and Li G. "P2Y receptors in neuropathic pain". *Pharmacology Biochemistry and Behavior* 186 (2019): 172788.

17. Zhang W., *et al.* "Neuron activity-induced Wnt signaling upregulates expression of brain-derived neurotrophic factor in the pain neural circuit". *Journal of Biological Chemistry* 293 (2018): 15641-15651.

18. Ciobanu C., *et al.* "Acute and chronic effects of neurotrophic factors BDNF and GDNF on responses mediated by thermosensitive TRP channels in cultured rat dorsal root ganglion neurons". *Brain Research* 1284 (2009): 54-67.

19. Ulmann L., *et al.* "Up-regulation of P2X4 receptors in spinal microglia after peripheral nerve injury mediates BDNF release and neuropathic pain". *Journal of Neuroscience* 28.44 (2008): 11263-11268.

20. Garraway SM., *et al.* "Intermittent noxious stimulation following spinal cord contusion injury impairs locomotor recovery and reduces spinal brain-derived neurotrophic factor-tropomyosin-receptor kinase signaling in adult rats". *Neuroscience* 199 (2011): 86-102.

21. Garraway SM and Huie JR. "Spinal plasticity and behavior: BDNF-induced neuromodulation in uninjured and injured spinal cord". *Neural Plasticity* (2016).

22. Garraway SM., *et al.* "Peripheral noxious stimulation reduces withdrawal threshold to mechanical stimuli after spinal cord injury: role of tumor necrosis factor alpha and apoptosis". *Pain*155.11 (2014): 2344-2359.

23. South SM., *et al.* "A conditional deletion of the NR1 subunit of the NMDA receptor in adult spinal cord dorsal horn reduces NMDA currents and injury-induced pain". *Journal of Neuroscience* 23.12 (2003): 5031-5040.

24. Garraway SM., *et al.* "BDNF sensitizes the response of lamina II neurons to high threshold primary afferent inputs". *European Journal of Neuroscience* 18.9 (2003): 2467-2476.

25. Slack SE., *et al.* "Brain-derived neurotrophic factor induces NMDA receptor subunit one phosphorylation via ERK and PKC in the rat spinal cord". *European Journal of Neuroscience* 20.7 (2004): 1769-1778.

26. Matayoshi S., *et al.* "Actions of brain-derived neurotrophic factor on spinal nociceptive transmission during inflammation in the rat". *The Journal of Physiology* 569. Pt.2 (2005): 685-695.

27. Coull JA., *et al.* "BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain". *Nature* 438.7070 (2005): 1017-1021.

28. Pezet S., *et al.* "BDNF modulates sensory neuron synaptic activity by a facilitation of GABA transmission in the dorsal horn". *Molecular and Cellular Neuroscience* 21.1 (2002a): 51-62.

29. Lever I., *et al.* "Release of BDNF and GABA in the dorsal horn of neuropathic rats". *European Journal of Neuroscience* 18.5 (2003): 1169-1174.

30. Siuciak JA., *et al.* "Antinociceptive effect of brain-derived neurotrophic factor and neurotrophin-3". *Brain Research* 633.1-2 (1994): 326-330.

31. Shih-Jen Tsai. "Possible involvement of brain-derived neurotrophic factor in the antinociceptive effect of antidepressants in neuropathic pain". *Medical Hypotheses* 65.3 (2005): 530-533.

32. Bardoni R., *et al.* "BDNF-mediated modulation of GABA and glycine release in dorsal horn lamina II from postnatal rats". *Developmental Neurobiology* 67.7 (2007): 960-975.

33. Huang YJ., *et al.* "Complete spinal cord injury (SCI) transforms how brain derived neurotrophic factor (BDNF) affects nociceptive sensitization". *Experimental Neurology* 288 (2017): 38-50.

34. Klein K., *et al.* "ATP induced brain-derived neurotrophic factor expression and release from osteoarthritis synovial fibroblasts is mediated by purinergic receptor P2X4". *PLoS One* 7.5 (2012): e36693.

35. Groth R and Aanonsen L. "Spinal brain-derived neurotrophic factor (BDNF) produces hyperalgesia in normal mice while antisense directed against either BDNF or trkB, prevent inflammation-induced hyperalgesia". *Pain* 100.1-2 (2002): 171-181.

36. Melemedjian OK., *et al.* "BDNF regulates atypical PKC at spinal synapses to initiate and maintain a centralized chronic pain state". *Molecular Pain* 9 (2013): 12.

37. Kerr BJ., *et al.* "Brain-derived neurotrophic factor modulates nociceptive sensory inputs and NMDA-evoked responses in the rat spinal cord". *Journal of Neuroscience* 19.12 (1999): 5138-5148.

38. Bao Y., *et al.* "PAR2-mediated upregulation of BDNF contributes to central sensitization in bone cancer pain". *Molecular Pain* 10 (2014): 1744-8069.

39. Hökfelt T., *et al.* "Messenger plasticity in primary sensory neurons following axotomy and its functional implications". *Trends in Neurosciences* 17.1 (1994): 22-30.

40. Lalisse S., *et al.* "Sensory neuronal P2RX4 receptors controls BDNF signaling in inflammatory pain". *Scientific Reports* 8.1 (2018), 1-12.

41. Cho HJ., *et al.* "Increased brain-derived neurotrophic factor immunoreactivity in rat dorsal root ganglia and spinal cord following peripheral inflammation". *Brain Research* 764.1-2 (1997): 269-272.

42. Mannion RJ., *et al.* "Neurotrophins: peripherally and centrally acting modulators of tactile stimulus-induced inflammatory pain hypersensitivity". *Proceedings of the National Academy of Sciences of the United States of America* 96.16 (1999): 9385-9390.

43. Cao T., *et al.* "Function and mechanisms of truncated BDNF receptor TrkB. T1 in neuropathic pain". *Cells* 9.5 (2020): 1194.

44. Marcol W., *et al.* "BDNF contributes to animal model neuropathic pain after peripheral nerve transection". *Neurosurgical Review* 30 (2007): 235-243.

45. Fernyhough P., *et al.* "Altered neurotrophin mRNA levels in peripheral nerve and skeletal muscle of experimentally diabetic rats". *Journal of Neurochemistry* 64 (1995): 1231-1237.

46. Cao XH., *et al.* "Reduction in voltage-gated $K^{(+)}$ channel activity in primary sensory neurons in painful diabetic neuropathy: Role of brain-derived neurotrophic factor". *Journal of Neurochemistry* 114 (2010): 1460-1475.

47. Khan N and Smith MT. "Neurotrophins and neuropathic pain: role in pathobiology". *Molecules* 20.6 (2015): 10657-10688.

48. Sobue G., *et al.* "Expression of mRNAs for neurotrophins (NGF, BDNF and NT-3) and their receptors (p75NGFR, Trk, TrkB, and TrkC) in human peripheral neuropathies". *Neurochemical Research* 23 (1998): 821-829.

49. Azoulay D and Horowitz NA. "Brain-derived neurotrophic factor as a potential biomarker of chemotherapy-induced peripheral neuropathy and prognosis in hematological malignancies; what we have learned, the challenges and a need for global standardization". *British Journal of Haematology* 191 (2020): 17-18.

50. Apfel SC and Kessler JA. "Neurotrophic factors in the therapy of peripheral neuropathy". *Bailliere's Clinical Neurology* 4 (1995): 593-606.

51. Shanti BF., *et al.* "Metamorphosis of Acute to Chronic Pain: A Novel Era of Discoveries in the Field of Pain Medicine". *Acta Scientific Neurology* 4.12 (2021): 07-11.

52. Ling DS., *et al*. "Protein kinase Mzeta is necessary and sufficient for LTP maintenance". *Nature Neuroscience* 5 (2002): 295-296.

53. Jo Nijs., *et al.* "Brain-derived neurotrophic factor as a driving force behind neuroplasticity in neuropathic and central sensitization pain: a new therapeutic target?" *Expert Opinion on Therapeutic Targets* 19.4 (2015): 565-576.

54. Sikandar S., *et al.* "Brain-derived neurotrophic factor derived from sensory neurons plays a critical role in chronic pain". *Brain* 141.4 (2018): 1028-1039.