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REVIEW ARTICLE

Interplay of BDNF and GDNF in the Mature Spinal Somatosensory System and Its Potential Therapeutic Relevance

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Abstract: The growth factors BDNF and GDNF are gaining more and more attention as modulators of synaptic transmission in the mature central nervous system (CNS). The two molecules undergo a regulated secretion in neurons and may be anterogradely transported to terminals where they can positively or negatively modulate fast synaptic transmission. There is today a wide consensus on the role of BDNF as a pro-nociceptive modulator, as the neurotrophin has an important part in the initiation and maintenance of inflammatory, chronic, and/or neuropathic pain at the peripheral and central level. At the spinal level, BDNF intervenes in the regulation of chloride equilibrium potential, decreases the excitatory synaptic drive to inhibitory neurons, with complex changes in GABAergic/glycinergic synaptic transmission, and increases excitatory transmission in the superficial dorsal horn. Differently from BDNF, the role of GDNF still remains to be unraveled in full. This review resumes the current literature on the interplay between BDNF and GDNF in the regulation of nociceptive neurotransmission in the superficial dorsal horn of the spinal cord. We will first discuss the circuitries involved in such a regulation, as well as the reciprocal interactions between the two factors in nociceptive pathways. The development of small molecules specifically targeting BDNF, GDNF and/or downstream effectors is opening new perspectives for investigating these neurotrophic factors as modulators of nociceptive transmission and chronic pain. Therefore, we will finally consider the molecules of (potential) pharmacological relevance for tackling normal and pathological pain.

Keywords: BDNF, GDNF, nociception, spinal dorsal horn, chronic pain, neuropathic pain.

1. INTRODUCTION

Neurotrophic factors (NFs) are a large and heterogeneous group of molecules supporting the growth, survival, and differentiation of developing and mature neurons. However, besides their "classical" trophic activity, NFs also act as neuronal modulators, affecting synaptic plasticity and neuronal endeavor [1]. Several NFs have received particular attention as modulators of nociception and players in the maladaptive changes leading to chronic pain under pathological conditions [2, 3]. Initial studies on the intervention of NFs in the modulation of the nerve pathways that convey pain-related information to the brain have mainly focused on the role of nerve growth factor (NGF) in nociception and led to the development of novel pharmacological approaches to treat certain altered pain conditions [4]. More recently, the brain-derived neurotrophic factor (BDNF) [5] and the glial cell line-derived neurotrophic factor (GDNF) [6] have gained increasing attention as pain modulators. The reasons for such an interest are that the two factors and their receptors are expressed by the nociceptors, and the former likely play a role in the sensitization processes leading to chronic pain. However, the anatomical localization and the effects on neuronal activity induced by BDNF and GDNF are different, thus suggesting a dissimilar contribution to the processing of nociceptive stimuli.

In this review, we will reconsider the state of art roles played by BDNF and GDNF in the control of nociceptive transmission and in the maladaptive changes that occur in pain pathological conditions. We will pay particular attention to the putative interactions and complementarities between the two molecules and, eventually, to the pharmacological strategies that may derive from this knowledge.

2. NEUROTROPHIC FACTOR FAMILIES AND THEIR RECEPTORS: AN OVERVIEW

NFs belong to three main families: the neurotrophin (NT) family, the GDNF ligand (GFL) family and the ciliary neurotrophic factor (CNTF) family. Here, we will focus on the NT and GFL families, which include BDNF and GDNF, respectively. There are two reasons for this choice. First, during development, NTs and GFLs promote the differentiation and survival of the primary sensory neurons [7-11]. Second, in adulthood, they intervene in the regulation of the functional properties of these neurons, particularly in the modulation of their synaptic activity [5, 6, 12, 13].

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2.1. The Neurotrophin Family

NGF, BDNF, neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) compose the NT family. NTs share numerous commonalities: first, they all express extensive structural homologies in both genes and proteins [14]; second, the encoding genes contain a signal sequence and a prodomain; hence NTs are synthesized as pro-NTs, which need to be subsequently proteolyzed to obtain the functionally active mature molecules; third, NT molecules are typically released as homodimers, which is the required configuration for binding to their respective receptors.

NTs activate two different families of membrane receptors: a pan-NT receptor, known as $p75^{NTR}$, and a group of tyrosine kinase receptors, collectively known as Trk receptors [15, 16].

$p75^{NTR}$ is a member of the tumor necrosis factor superfamily. It consists of an extracellular domain with four cysteine-rich motifs and an intracellular domain (including a "death domain") acting on a pool of cytoplasmatic proteins. The receptor expression level in the peripheral and central nervous system decreases with the progression of development, but typically increases following injury [17]. $p75^{NTR}$ lacks an intrinsic catalytic activity, however, it can interact with other NT receptors (*i.e.,* the Trk receptors), as well as with sortilin and Nogo, to produce a broad spectrum of downstream effects [17].

Both NT and pro-NT dimers activate $p75^{NTR}$, although with opposing effects [18]. Specifically, pro-NTs bind $p75^{NTR}$ with high affinity and, in combination with the co-receptor sortilin, induce apoptosis or inhibit axonal growth [19]. This "death pathway" is intracellularly mediated by JNK kinases, which, in turn, cause cell death *via* the p53 and Bax pro-apoptotic pathways [18]. Unlike pro-NTs, mature NTs exhibit a low affinity for $p75^{NTR}$ and promote neuronal survival and differentiation [14, 20]. This "life pathway" seems largely mediated *via* the interaction between $p75^{NTR}$ and the Trk receptors, *i.e.* by increasing the affinity of the mature NTs for the Trks [21].

Each mature member of the NT family binds with high affinity to a specific Trk receptor: NGF preferentially activates TrkA, BDNF and NT4/5 bind TrkB, and NT3 is associated with TrkC, but it is also a low-affinity agonist for TrkA and TrkB [22]. Trk receptors have an extracellular domain consisting of a cysteine-rich cluster, three leucine-rich repeats, another cysteine-rich cluster, two immunoglobulin-like domains, and an intracellular domain that possesses tyrosine kinase activity [14]. NTs binding induces Trk receptor dimerization, followed by phosphorylation of the cytoplasmic tyrosine residues, which, in turn, initiates the activation of downstream effectors [22]. Interestingly, Trk receptors are also active in the absence of NTs. Namely, they can be trans-activated *via* a signaling pathway triggered by several G protein-coupled receptors (GPCRs [14, 23]). The adenosine receptor $A2_A$ was firstly proposed to trans-activate TrkB receptors *via* G protein-dependent activation of Src kinases [24]. Subsequently, other GPCR neuromodulators were shown to induce Trk transactivation, such as the pituitary adenylate cyclase-activating polypeptide receptor (PACAP [23],), the angiotensin receptor type 2 [25], and the low-density lipoprotein receptor-related protein-1 [26]. Tyrosine kinase activity can also be induced by mechanisms other than those mediated by GPCRs, for instance, by the epidermal growth factor receptor [27], or zinc, which is co-released with glutamate at excitatory synapses [28].

Trk receptor activation is associated with three major signaling pathways: the Ras/mitogen-activated protein kinase (MAPK) pathway; the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, and the phospholipase C-γ (PLCγ)/diacylglycerol (DAG)/protein kinase C (PKC) pathway [14, 29]. All these pathways are involved in cell survival and differentiation, but also in the modulation of neuronal activity (*i.e.,* acting on ion channels and ion transporters) and in the regulation of neuronal plasticity [14, 16, 22]. PLCγ is then thought to play a major role in synaptic plasticity through inositol-3-phosphate release and Ca^{2+} mobilization from intracellular stores.

To add another level of complexity, different splicing variants exist in each group of Trk receptors. Besides the "classical" full-length forms, splicing generates TrkB and TrkC isoforms that miss the tyrosine kinase domain and are often referred to as truncated receptor variants [30]. Although the role of these isoforms is still poorly understood, yet different studies have demonstrated that they are not inactive, as originally thought, but can evoke Ca^{2+} transients and trigger intracellular signals. Interestingly, a growing number of evidence indicates that signals from truncated Trk isoforms typically counteract the function of the respective full-length receptors, for instance, by inhibiting dimerization or by disrupting intracellular responses [31-35].

2.2. The GDNF Ligand Family

The members of the GFL family, GDNF, neurturin, artemin and persephin, are structurally related to the transforming growth factor β (TGF-β) superfamily [36, 37]. Each member of the family is translated as a pre-pro-precursor protein, which is subsequently cleaved to generate an active form [38, 39]. GFLs signal through a multi-competent receptor complex comprising the tyrosine kinase transmembrane receptor Ret and a high-affinity ligand-binding glycosylphosphatidylinositol (GPI)-anchored co-receptor referred to as GFRα [37]. Ret is a tyrosine kinase receptor constituted by an extracellular domain containing several cadherin-like repeats, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain [40]. For the ligand to activate RET, it must bind first to the appropriate GFRα co-receptor. Each member of the GFL family matches with a specific GFRα isoform characterized by a distinct structure of the cysteine-rich repeats in the ligand-binding domains [37]. Namely, GDNF preferentially binds to GFRα1, neurturin to GFRα2, artemin to GFRα3 and persephin to GFRα4 [36]. Like NTs, also GFLs are released as homodimers, each binding two GFRα receptors that, in turn, induce Ret dimerization, thus conserving a 2:2:2 stoichiometry [41]. Ret dimers

activate downstream intracellular pathways through their cytosolic tyrosine kinase domain. The interaction between GFLs, GFRα and Ret is favored by glycosaminoglycans, such as heparan sulphate, as the lack of these molecules is sufficient to abolish the survival and axonal growth effects of GDNF [42, 43]. Moreover, receptor/co-receptor interaction mainly occurs within sphingolipid- and cholesterol-rich membrane microdomains, known as *lipid rafts*, in which GFRsα are confined [44]. Therefore, the disruption of Ret localization in lipid rafts significantly weakens the associated intracellular signals [44]. GFRα-Ret activation mainly signals through Ras/MAPK, phosphatidylinositol-3 kinase (PI3K)/Akt and PLCγ, which play a key role in neurite outgrowth and cell survival in the nervous system [45-47].

Consistently with a broader expression of GFRα than Ret in neurons, GFLs can also transduce through GFRα in a Ret-independent pathway [47, 48]. This was clearly demonstrated in Ret-deficient cell lines, in which GFRα-mediated signals activate the Src-like kinase that phosphorylates the cAMP response element-binding protein (CREB) and induces c-fos expression and cell survival [48]. A special role in the activation of the Ret-independent pathway is played by the neural cell adhesion molecule (NCAM). Actually, NCAM acts as an alternative signaling pathway for GFLs, at the point that GFRα-NCAM, GDNF-NCAM and GDNF-GFRα-NCAM may differentially transduce various intracellular pathways (vertical signaling) or engage other molecules at the cell membrane (horizontal signaling) [46, 47, 49].

3. LOCALIZATION OF BDNF AND GDNF AND THEIR RECEPTORS IN NOCICEPTIVE PATHWAYS

Spinal nociceptive pathways, in their most simple configuration, consist of a chain of three neurons: a primary sensory neuron, or nociceptor, located in dorsal root ganglia (DRGs), a secondary neuron in the spinal cord dorsal horn, and a third neuron in the ventroposterolateral nucleus of the thalamus, which eventually transmits the nociceptive information to the somatosensory cortex. An analogue chain of neurons conveys nociceptive stimuli from the head and the initial part of the neck along the trigeminal pathway.

BDNF, GDNF and their receptors have been consistently described in these pathways, and particularly in DRGs and in spinal dorsal horn neurons (see for review [5, 6] and Fig. **1**). Understanding the anatomical distribution of these molecules into labeled nociceptive lines is the necessary premise to get insight into their role in pain processing.

3.1. Localization of BDNF and its Preferred Receptor TrkB in DRGs and Dorsal Horn of the Spinal Cord

Early *in situ* hybridisation and immunohistochemical studies demonstrated the expression of BDNF mRNA and protein by a subpopulation of sensory neurons in DRGs, both in rodent and human tissues [50-52]. In mice and rats, BDNF positive DRG neurons are mainly small-to-medium-sized [53-55]. BDNF is localized in a population of peptidergic neurons expressing the calcitonin gene-related peptide (CGRP), which typically characterizes the nociceptors encoding thermal pain [56, 57]. Conversely, the neurotrophin is not expressed by non-peptidergic sensory neurons, that are identified by isolectin B4 (IB4), and represent a group of nociceptors principally involved in the transduction of mechanical pain [56, 57]. Accordingly, BDNF-positive fibres in the superficial dorsal horn overlap the localization of CGRP-expressing fibres in lamina I and lamina II outer [55, 58]. Interestingly, BDNF has also been observed in sensory neurons that express neither CGRP nor IB4 [55]. Consistently, by using a *BDNF-LAcZ* reporter transgenic mouse, Basbaum's group has recently demonstrated a broader expression of BDNF than previously described [59]. In particular, these authors observed expression in large myelinated primary afferents, suggesting a still poorly understood role in the processing of non-nociceptive sensory information from the periphery [59].

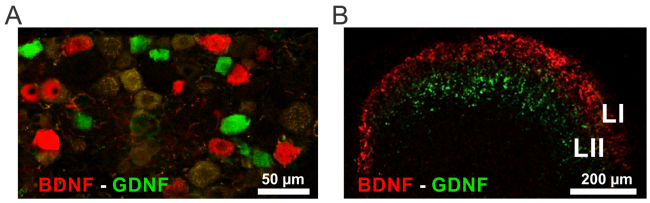

Fig. (1). Localization of BDNF and GDNF in the mouse DRGs and spinal dorsal horn. (**A**) Distribution of the two NFs in DRGs. Both BDNF (red) and GDNF (green) are expressed in small-to-medium primary sensory neurons, yet in distinct populations. (**B**) Distribution of BDNF (*red*) and GDNF (*green*) in the superficial dorsal horn. BDNF immunoreactive fibers are mainly localized in laminae I-II outer, while GDNF immunoreactive fibers mainly end in lamina II. Abbreviations: LI = lamina I, LII = lamina II. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The TrkB protein and mRNA are also expressed by DRG neurons of variable size in both rodents and humans [51, 52, 54, 60], with a majority of medium-to-large-sized neurons [60]. By using transgenic $TrkB^{tauEGFP}$, Li and colleagues [61] demonstrated a foremost expression of the BDNF receptor in Aδ low threshold mechanoreceptors, which heavily terminate in lamina III of the dorsal horn. On the other hand, we have previously shown that a subset of CGRP-positive nociceptors also co-express BDNF and TrkB, which suggests the existence of an autocrine activation loop at their peptidergic terminals [54].

BDNF and TrkB are also expressed by sparse propriospinal neurons. *In situ* hybridization studies showed the expression of the BDNF mRNA in the deep dorsal horn of adult rats [52, 58]. Conversely, the receptor is expressed by the majority of neurons in the spinal cord [52, 62], including most ascending projection neurons in lamina I and in the deep dorsal horn laminae [62].

The expression of BDNF and TrkB in pain-related supraspinal centres has received less attention. However, few studies have demonstrated the involvement of the neurotrophin in different key areas for pain encoding, including

the thalamus [63] and the parabrachial-amygdaloid pathways [64]. Previously, our group, in collaboration with Priestley's group, demonstrated that BDNF is costored in individual dense-core vesicles (DCVs) with CGRP in the parabrachial projection to the amygdala [65].

3.2. Localization of GDNF and Its Preferred Receptor GFRα1/Ret in DRGs and the Dorsal Horn of the Spinal Cord

As BDNF, GDNF is mainly expressed by small-to-medium-sized neurons in DRGs [55, 66, 67], although in a distinct and smaller population [55]. In mouse DRGs, GDNF is localized in a specific subgroup of peptidergic neurons containing CGRP and somatostatin [55]. The neurotrophic factor is anterogradely transported to the spinal dorsal horn, as suggested by immunohistochemical studies that localized the protein in the peptidergic afferent fibres within lamina I and lamina II outer [55, 68-70].

The mRNA of the GFL family receptor Ret is expressed by more than half of the lumbar DRG neurons in both the rat [66, 71-73] and mouse [74]. Most of the RET-expressing neurons also express the GDNF specific co-receptor GFRα1: 66% in adult rats [73] and 89% in adult mice [75]. A similar expression pattern is also detected in the thoracic DRGs from adult humans, albeit in a sensibly lower percentage [51]. Interestingly, while GDNF is mainly expressed by the peptidergic neurons, the GFRα1/Ret receptor complex is typically found in the non-peptidergic IB4-positive neurons, as well as in a small subset of non-peptidergic IB4-negative neurons [75, 76]. During development, Ret is up-regulated in non-peptidergic neurons, while TrkA is depleted; thus these neurons pass from NGF- to GDNF-dependence [75]. Ret expression in these sensory neurons is critical for their differentiation and for the expression of several important molecules that are necessary for the detection of noxious stimuli [76, 77].

Consistently with the expression of GFRα1/Ret in non-peptidergic primary sensory neurons, GDNF receptors have been detected in primary afferent fibres in the dorsal horn, and, particularly, in the inner aspect of lamina II [70, 78]. Moreover, at the ultrastructural level, GFRα1 receptors are specifically expressed by IB4-positive terminals in the mouse spinal dorsal horn and are mainly localized ventrally to GDNF-expressing peptidergic terminals in lamina II [55, 70].

There is not compelling evidence of a propriospinal source of GDNF. Conversely, GFRα1/Ret are also expressed by some neurons in the dorsal horn, including putative projection neurons in lamina I that also express the substance P preferred receptor NK1 [78].

4. ROLE OF BDNF AND GDNF IN NOCICEPTION

Although the localization of BDNF and GDNF and their receptors in primary sensory neurons strongly suggests an intervention in nociception, yet their significance in pain physiology remains elusive. The lack of specific pharmacological tools targeting the two molecules together with the difficulty to generate classical knockout animals due to the requirement of both factors for neuronal survival have for long hampered the investigation of the role of BDNF and GDNF in nociception. In recent times, however, the development and availability of conditional mutant mice in which the expression of specific molecules can be selectively depleted in mature neurons has opened new avenues to interrogate the contribution of the two NFs to pain transmission.

Initial studies on the conditional blockade of a mutant TrkB receptor in mice led to conclude that BDNF does not contribute to acute heat, mechanical or chemical pain sensitivity [79]. More recently, Dembo and colleagues [59] have investigated the contribution of BDNF to nociceptive transmission by using a conditional transgenic mouse model in which BDNF can be selectively deleted in virtually all primary sensory neurons by tamoxifen injection. The ablation of BDNF produced only minor effects, including a slight increase in the heat threshold of male mice, but not females, to the tail immersion test and no effects on mechanical or cold sensitivity [59]. Consistently, it seems reasonable to infer that ongoing TrkB signaling facilitates the development of synaptic plasticity in the outer aspect of the superficial dorsal horn, where thermal input is mainly processed, while it has a minor impact deeper, where mechanical input is conveyed, thus making the system more prone to thermal sensitization [80].

A different scenario has been described when the GDNF receptor Ret was ablated from sensory neurons. By the conditional deletion of Ret in Nav1.8 expressing nociceptors in mice, Golden and colleagues [77] have demonstrated that the mutants express increased sensitivity to cold and increased formalin-induced pain, thus demonstrating a constitutive inhibitory role of Ret signaling in modulating nociception. These data are consistent with our findings *ex vivo* [70], demonstrating that GDNF, acting on the GFRα1 receptor complex, constitutively constrains the excitatory drive induced by afferent fiber activation upon spinal dorsal horn neurons (Fig. **2**).

While the role of BDNF and GNDF in the physiology of pain transmission is still debated, it is, on the other hand, well established that both NFs significantly contribute to the maladaptive changes occurring in pathological conditions, as it will be described in the following paragraphs.

5. ROLE OF BDNF IN PATHOLOGICAL PAIN

Several lines of evidence converge to indicate that BDNF principally acts as a pro-nociceptive modulator in sensory pathways, with a central role in the initiation and maintenance of inflammatory, chronic and/or neuropathic pain [81]. Nevertheless, a BDNF anti-nociceptive modulation has also been occasionally described, suggesting heterogeneity of BDNF actions that depend on the molecular pathways involved, the cells affected and the type of pathological conditions (for review [5, 82-85]). In this section, we review the role of BDNF as a pain modulator emerging from different preclinical models of pathological pain.

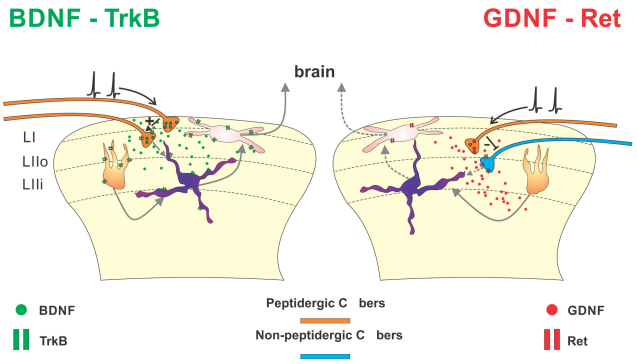

Fig. (2). Effects of BDNF and GDNF on nociceptive transmission. The cartoon schematically illustrates the localization of BDNF (left) and GDNF (right) in spinal nociceptive pathways and their putative role in modulating nociceptive transmission. Left: BDNF (green dots) is synthesized by peptidergic primary sensory neurons in dorsal root ganglia and anterogradely transported to lamina I (LI) and outer lamina II (LII_o) of the dorsal horn *via* primary afferent C fibers (orange). BDNF acts both pre- and post-synaptically through its preferred receptor TrkB. Notably, BDNF+ peptidergic afferent fibers express pre-synaptic TrkB receptors, suggesting an autocrine function. BDNF/TrkB activation in superficial dorsal horn plays a major pro-nociceptive role by increasing local network excitability. Right: Another sub-population of peptidergic fibers (orange), distinct from that expressing BDNF, ends in lamina II_o and contains GDNF (red dots). Once released, GDNF activates the Ret/GFRα1 complex (in the diagram, only Ret is shown for simplicity), which is mainly expressed by non-peptidergic afferent terminals (blue) ending in inner lamina II (LIIi). GDNF, acting on pre-synaptic Ret/GFRα1, reduces the glutamate release associated with the activation of non-peptidergic fibers, thus limiting their associated excitatory drive. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.1. BDNF as Pro-nociceptive Neuromodulator in Inflammatory Pain

BDNF expressed by the sensory neurons and released by their primary afferent fibers is necessary for the development of both formalin and carrageenan-induced inflammatory pain [86]. The pro-nociceptive effect of BDNF in inflammatory pain has been typically associated with a pre- and post-synaptic potentiation of the glutamatergic neurotransmission in the spinal dorsal horn *via* NMDA receptor plasticity. In carrageenan-treated rats, BDNF potentiates nociceptive spinal reflex activity and induces c-fos expression in dorsal horn neurons in NMDA receptor-dependent manner [87]. The BDNF-sequestering molecule trkB-IgG has also been observed to rescue hyperalgesic behavior and functional alterations [87]. Similarly, the co-administration of BDNF with the NMDA receptor antagonist D(-)-2-amino-5-phosphonovaleric acid (D-APV) prevents the BDNF-induced hyperalgesia in mice [88]. NMDA potentiation is mediated through the activation of PKC and PLC-dependent pathways [89, 90].

BDNF may act pre-synaptically to induce hyperalgesic behavior. A pre-synaptic mechanism has been described in a rat model of inflammation based on subcutaneous injections of complete Freund's adjuvant (CFA) [91]. The authors showed that BDNF increases the presynaptic release of glutamate upon lamina II neurons. The effect was associated with an increased synaptic input from large myelinated Aβ afferent fibers in lamina II, which typically encode light touch stimuli and thus may underlie allodynia in CFA rats [91].

More recently, the contribution of peripheral BDNF to inflammatory pain has been reconsidered in a conditional Advilin-CreERT2 knock-out mouse model, which lacks BDNF specifically in sensory neurons [59, 81]. Both studies observed a reduced nocifensive response in the second phase of the formalin test, which indicates a reduced central sensitization [59, 81], although the effect was observed only in males [59]. Surprisingly, however, Dembo and colleagues [59] did not detect any difference in the development of pain hypersensitivity in the CFA model of chronic inflammatory pain. On the other hand, Sikandar and colleagues [81] observed that BDNF deletion critically affects hyperalgesic priming, *i.e.* a neuroplastic mechanism producing a latent state of hyperresponsiveness in sensory neurons, which is thought to favor the transition from acute to chronic pain [81]. Hyperalgesic priming was induced by intraplantar injection of carrageenan and the effect was uncovered by prostaglandin E2 (PGE2) injection after six days. While primed control mice expressed long-lasting hyperalgesia following PGE2 injection, mice lacking BDNF in sensory neurons only exhibit a transient decrease of nociceptive thresholds [81].

5.2. BDNF as Pro-nociceptive Neuromodulator in Neuropathic Pain

BDNF also underlies the maladaptive plasticity occurring in neuropathic pain. Early studies in rats and mice with partial sciatic nerve lesion demonstrated that spinal BDNF contributes to the alterations resulting from the nerve damage in nociceptive pathways [92-95]. Systemic administration of either anti-BDNF or anti-TrkB neutralizing antibodies, Trk inhibitors or the BDNF scavenger TrkB/Fc abolishes behavioral pain hypersensitivity [92-94]. Up-regulation of BDNF in sensory neurons and its central release upon spinal dorsal horn neurons have been observed in different nerve-injury models, including sciatic nerve transection, chronic constriction injury and nerve ligation [96-102].

A significant leap forward in understanding the role of BDNF in neuropathic pain was achieved with the study by Coull and colleagues [103]. The authors identified the spinal microglia as the main source of BDNF in nerve-injured rats. In this model, the purinergic P2X4 receptors activate spinal microglia to trigger the release of BDNF, which, in turn, decreases KCC2 function, the main Cl^- extruder in lamina I projection neurons. The subsequent accumulation of Cl^- in these neurons reduces the strength of GABA/glycine ionotropic transmission, hence leading to hyperexcitability and pain hypersensitivity. These effects are recapitulated by intrathecal transfer of ATP-stimulated microglia or by BDNF administration [103, 104], and are prevented by either depleting BDNF in microglia [103, 105], blocking TrkB [103, 105], or knocking out P2X4 expression [105, 106].

BDNF also causes hyperexcitability of spinal neurons by increasing the NMDA receptor function, as reported in inflammatory pain. Indeed, in rats with spinal nerve ligation, intrathecal injection of BDNF induces mechanical allodynia and long-term potentiation (LTP) *via* a mechanism involving the activation of NR2B-containing NMDA receptors [96, 107].

The concomitant alterations of inhibitory and excitatory transmission likely interact to sensitize central sensory neurons. Recent studies have specifically addressed this question. In particular, Hildebrand and colleagues [108] have reported that the downregulation of KCC2 induced by BDNF is both sufficient and necessary to promote NR2B-NMDA phosphorylation and LTP induction in lamina I neurons of nerve-injured rats. A key role in the signaling between BDNF-dependent Cl^- dysregulation and NMDA phosphorylation is played by STEP61 phosphatase, whose down-regulation is coupled with KCC2 depletion and is sufficient to drive the potentiation of excitation [109]. Importantly, these mechanisms were also recapitulated in an *ex-vivo* spinal cord preparation obtained from human tissue, thus shortening the distance to clinical interventions [109].

Although the above-described mechanisms are based on post-synaptic alterations, pre-synaptic effects have also been reported. In mice with chronic constriction injury, BDNF increased the expression of the Cl^- transporter NKCC1 in DRGs, thus causing an increase of intracellular Cl^-, leading to transient presynaptic disinhibition and hypersensitivity [110]. The presynaptic effects are also likely mediated by microglial BDNF, which has been shown to act on afferent terminals for potentiating the NMDA-mediated responses [111]. Altogether, these data confirm the existence of coupling mechanisms involving Cl^- dysregulation and NMDA potentiation at both pre- and post-synaptic levels, which may be affected by BDNF.

5.3. BDNF Involvement in other Forms of Chronic Pain

Besides inflammatory and neuropathic pain, BDNF is involved in several other forms of chronic pain, including pain following spinal cord injury [34], trigeminal pain and migraine [112-114], opioid-and nicotine-induced hyperalgesia [105, 115], painful diabetic neuropathy [116, 117] and cancer pain [118-122]. Although these different models of pathological pain are based on distinct etiological grounds, yet pain hypersensitivity gated by BDNF is associated with the recurrent involvement of a restricted number of molecular actors, including P2X4 receptors, KCC2/NKCC1 transporters and NMDA receptors. Such commonality of mechanisms has important implications in conceiving new treatments for future therapeutic approaches, as later discussed in this review.

5.4. BDNF as an Anti-nociceptive Neuromodulator

While most published data indicate BDNF as a pain amplifier, yet other lines of evidence suggest that it may also exert anti-nociceptive effects. Early studies in the field showed that the central administration of BDNF may produce analgesic behavior. For instance, injections of BDNF into the rat midbrain caused thermal analgesia, likely acting on endogenous opioidergic/serotoninergic system [123]. Similarly, intracerebroventricular injections of BDNF in rats increased the latency of hind paw licking in the hot-plate test [124].

BDNF has also been reported to reverse established allodynic/hyperalgesic behaviors in animals with neuropathic pain clinical signs. Indeed, the administration of BDNF intrathecally [125] or through viral vectors [126] reverses thermal and/or mechanical hypersensitivity following nerve injury. These anti-nociceptive effects of BDNF consistently rely on specific interactions between the trophic factor and synaptic inhibition mechanisms at both pre-and post-synaptic level. Pre-synaptically, TrkB activation stimulates the release of GABA from dorsal horn neurons upon primary afferent terminals [125, 127], while post-synaptically, it enhances the spontaneous release of GABA and glycine upon lamina II neurons [128]. However, it should be stressed out that the comprehension of the mechanisms of action of BDNF (and other modulators) in the superficial dorsal horn is made difficult by the still disguised circuitry of this area of CNS. As an example, the observations by Bardoni and colleagues [128] regarding the enhancement of inhibitory neurotransmission in lamina II have been recently correlated with a polysynaptic chain consisting of a C peptidergic nociceptor, two islet cells in sequence, a central cell, a large vertical cell, and, eventually, a lamina I excitatory projection neuron [129]. As the first islet cell inhibits the second islet cell that, in sequence, is inhibitory to the central cell, the circuit is excitatory onto the large vertical cell. Thus, this type of configuration can explain why BDNF was shown to produce *ex vivo* a depression of the evoked IPSCs as well as an increase of mIPSCs at synapses in the superficial dorsal horn [128].

Yet, the apparently contradictory co-existence of pro-nociceptive and anti-nociceptive effects is not surprising, as it belongs to the pleomorphic nature of BDNF. Recently, in fact, Huang and colleagues demonstrated that while the intrathecal administration of BDNF to the spinal cord of uninjured rats decreases KCC2, thus promoting disinhibition and hypersensitivity, nonetheless after spinal cord injury, the same BDNF treatment increases KCC2 and restores synaptic inhibition [130]. Such dual behavior likely depends on the activation of specific intracellular pathways, as well as on the involvement of different cell types, thus highlighting that it is not possible to achieve efficacious BDNF-targeted pharmacological solutions without an accurate understanding of the cellular and molecular actors and circuitries involved.

6. ROLE OF GDNF IN PATHOLOGICAL PAIN

GDNF displays both pro-nociceptive and anti-nociceptive functions in the sensory system, depending on the site of action and on the type of pain. While GDNF principally acts as an anti-nociceptive modulator in neuropathic pain, pro-nociceptive effects are often reported at the peripheral level and in experimental models of inflammatory pain (see for review [6, 12]).

6.1. GDNF as an Anti-nociceptive Neuromodulator

GDNF anti-nociceptive effects have been well established in different models of neuropathic pain, including nerve-injury and diabetic neuropathy [131, 132].

In rats with sciatic nerve partial ligation or L5 spinal nerve ligation, intrathecal infusion of GDNF reverses mechanical and thermal hyperalgesia and GDNF pre-treatment avoids the insurgence of these neuropathic pain signs by preventing the alterations induced by nerve-injury on peripheral sodium channel subunits [12, 131]. Similarly, injections of viral vectors inducing the expression of GNDF [133-135] or of mesenchymal stem cells over-expressing the trophic factor [136] alleviate the allodynic and hyperalgesic signs associated with a nerve injury in rodents. Specifically, intraspinal delivery of GDNF-expressing lentiviral vectors in rats prevented the up-regulation of the activating transcription factor 3 (ATF-3), a marker of nerve injury, as well as the down-regulation of the phenotypic marker of non-peptidergic nociceptors IB4 [134]. Injection of adenovirus vectors encoding GDNF attenuated allodynia and thermal hyperalgesia, reduced chronic constriction injury-induced neuronal apoptosis, inhibited microglia activation and cytokine production, indicating a neuroprotective action of the NF [133]. Similar effects have also been reported in mice [135]. Importantly, also human patients with neuropathic pain symptoms exhibit decreased levels of GDNF in their cerebrospinal fluid, thus reinforcing the clinical significance of the observations in animal models [137].

Different mechanisms have been proposed to underlie the anti-hyperalgesic effects of GDNF. GDNF released from peptidergic nociceptors may exert an inhibitory control on the glutamate excitatory drive from non-peptidergic fibres, with a subsequent reduction in neuronal activity [70]. Alternatively, GDNF may act on other targets, such as NCAM and other adhesion molecules, which concur to GDNF analgesic effects at the spinal level in a Ret-independent manner [138-140]. In addition, GDNF and its receptors may alter pre-synaptically the neuronal excitability by directly acting on voltage-dependent channels. Indeed, a potentiation of the Kv4.1 potassium channel in the sensory neurons of nerve-injured animals has been recently described [141]. These interactions may also require the modulation of other transmitters activating GPCRs that, in turn, reduce neuronal excitability and promote analgesia. In particular, intrathecal application of GDNF enhances the expression and the central release of the analgesic peptide somatostatin, suggesting a GDNF anti-allodynic effect *via* somatostatinergic mechanisms [142, 143].

Monoamines are another group of analgesic transmitters that have been associated with the GDNF analgesic effects. Indeed, injection of GDNF into the locus coeruleus of nerve-injured rats exerted prolonged analgesia by enhancing the descending noradrenergic inhibition to spinal dorsal horn neurons *via* α2-adrenoceptor [144].

Little is known, however, regarding the signaling pathways through which GDNF and its receptors produce analgesia. In spinal dorsal horn neurons, GDNF administration to nerve-injured rodents leads to the down-regulation of different intracellular pathways associated with pain hypersensitivity, such as nectin-1/c-Src [138] and integrin β1/FAK [145], or the up-regulation of anti-nociceptive pathways, such as E-cadherin/p120 catenin [146].

6.2. GDNF as a Pro-nociceptive Neuromodulator

While GDNF is frankly anti-nociceptive in neuropathic pain, it has more prominent pro-nociceptive functions in inflammatory pain. Ogun-Muyiwa and colleagues [147] observed that exogenous GDNF up-regulates pro-nociceptive mediators, such as substance P, in adult rat DRG cultures. The pronociceptive role was subsequently confirmed by direct intraplantar injection of GDNF, which enhances both thermal sensitivity mediated by the thermal transducer TRPV1 [148] and mechanical sensitivity associated with IB4-positive nociceptors [149, 150]. As IB4-positive neurons are known to express GFRα/Ret receptor complex, these sensory neurons are the more obvious target for GDNF-dependent sensitization. Indeed, ablating IB4-positive nociceptors prevent GDNF-induced mechanical hyperalgesia [149]. In the same study, Bogen and colleagues were able to reverse the GDNF-dependent hyperalgesia by interfering with several kinases downstream to GFRα/Ret, including PLCγ, MAPK/ERK, PI3K, CDK5 and Src family kinase.

The effect of GDNF on IB4-positive neurons is not only limited to nociceptor sensitization but also extends to hyperalgesic priming [151, 152]. GDNF induces priming in IB4-positive neurons *via* PKCε signaling pathway [151] and priming is directly associated with a reduction in the levels of the GPCR kinase 2 (GRK2) [152].

The involvement of GDNF in the development of inflammatory pain has been described in different chronic pain models, such as CFA-induced inflammation [153, 154]. In rats with CFA-induced arthritis, GDNF stored in DRGs is depleted and the intrathecal injection of a function-blocking antibody against GDNF decreases the inflammatory hyperalgesia [153]. GDNF, as well as other related GFLs (in particular artemin), have also been involved in several other models of inflammatory pain, including bone inflammation [155] and cystitis [156, 157].

7. INTERPLAY BETWEEN GDNF AND BDNF IN NOCICEPTIVE PATHWAYS

In the previous sections, we have explored in-depth the current knowledge on the role of BDNF and GDNF in the control of nociceptive neurotransmission under normal and pathological conditions. Interestingly, several distinctive and somehow complementary features characterized the localization of these two NFs in nociceptive pathways (Fig. **2**). Specifically: 1- BDNF and GDNF are basically expressed by two distinct populations of peptidergic nociceptors [55]; 2- in DRGs, BDNF is mainly expressed by the same neurons expressing its cognate receptor TrkB, suggesting an autocrine function [5, 54], while the GDNF receptor complex (GFRα-Ret) is expressed by the non-peptidergic sensory ne-

Table 1. BDNF and GDNF levels in neurological disorders.

Disease	Model	BDNF	GDNF
Spinal cord ischemia	Rat model of transient ischemia [158]	↑ in spinal neurons	↑in spinal neurons and astrocytes
Parkinson's disease	Lesion of the rat nigrostriatal pathway by 6-hydroxy-dopamine [159]	↑ in striatum and midbrain of young rats ↓ in striatum and ↑ in midbrain of old rats	↑ in striatum and ↔ in midbrain of young rats ↔ in striatum and midbrain of old rats
Alzheimer's disease	B6C3-Tg transgenic mouse [160]	↓in cortex	↑in cortex
Learning and memory impairment	Pneumococcal meningitis in rat [161]	↓in hippocampus	↓in hippocampus
Alcohol spectrum disorder	Ethanol administration to postnatal rats [162]	↑ in amygdala and ↔ in pyriform cortex in P7 rats ↓ in amygdala and ↓in pyriform cortex in P15 rats	↑in amygdala and ↑ in pyriform cortex in P7 rats ↑ amygdala and ↓pyriform cortex in P15 rats
Hyperoxia	Exposure of P7-12 rats to the hyperoxic condition [163]	↓mRNA in prefrontal cortex and ↑ in isocortex	↑ mRNA in prefrontal cortex and ↑ in isocortex

urons [66, 70]; 3- while clearly, pro-nociceptive and anti-nociceptive effects cannot be univocally associated to one trophic factor or the other, yet a general consensus supports the concept that in neuropathic pain, BDNF is pro-nociceptive, while GDNF is anti-nociceptive [5, 6, 129].

Several works in the last years have explored how pathological conditions affect BDNF and GDNF expression in CNS, thus demonstrating the implications of both factors in the shift from normality to an altered neurological situation Table (**1**). In several cases, the levels of the two NFs are regulated in an opposing direction, reinforcing the hypothesis that they play alternative/complementary roles.

However, only a few studies have properly addressed whether BDNF and GDNF directly interact in modulating the function of central neurons. For instance, Giehl and colleagues [164] showed that GDNF prevents the degeneration of lesioned corticospinal neurons *via* BDNF signaling. Similarly, combined administration of GDNF and BDNF, but not each factor individually, favors motor neuron differentiation *in vitro* [165] and improves motor dysfunction in a rat model of spinal cord injury [166]. An interaction between GDNF and BDNF was also observed in the hippocampus in 3xTg-AD mice that modeled Alzheimer's disease [167]. Here, the over-expression of GDNF improved cognition performances and increased BDNF expression.

Importantly, imbalances in the expression of BDNF and GDNF are associated with several neurological alterations in humans. Aged subjects exhibiting cognitive decline or with mild Alzheimer's disease display decreased BDNF and GDNF serum levels when compared with healthy subjects [168]. A significant decrease in both NFs has also been reported in patients with schizophrenia [169]. Conversely, in patients diagnosed with bipolar disorder where only BDNF was decreased, lithium-based therapy inverted the ratio of circulating BDNF/GDNF, suggesting that the reciprocal levels determine the overall effect on the nervous system [170].

8. THERAPEUTIC PERSPECTIVES

Given the part played by BDNF and GDNF in pain modulation preclinically, the two molecules certainly represent an attractive target for the development of novel therapeutic strategies. Several approaches have been proposed in animal studies, particularly for the treatment of neuropathic pain in which, as highlighted above, BDNF and GDNF have opposite effects.

8.1. Targeting BDNF/TrkB

The main approaches derived from preclinical studies to treat pain by blocking BDNF/TrkB signaling can be distinct in: i) scavenging BDNF, ii) targeting the extracellular TrkB domain, iii) interfering with the intracellular kinase domain.

8.1.1. Scavenging BDNF

Scavenging BDNF can be achieved *in vivo* by delivering a TrkB-Fc fusion protein, obtained from the extracellular domain of TrkB and the Fc domain of human IgGs [171]. This approach has been extensively used to probe the role of endogenous BDNF in pain models, including nerve injury [103], diabetic neuropathy [172], and pain incision model [173]. Although highly specific, the method is poorly translatable in clinical settings since the scavenger needs to be applied intrathecally or locally at the central sites where BDNF is released.

8.1.2. Targeting the Extracellular TrkB Domain

Targeting the extracellular domain, thus reducing the probability of ligand binding, can be achieved either through TrkB blocking antibodies [174] or by developing new receptor antagonists [175]. Monoclonal function-blocking antibodies against TrkB receptors have been successfully employed in preclinical investigations (*i.e.*, mouse clone 47 [176]), and proved to be effective in blocking the effects of BDNF on neuronal activity in acute spinal cord slices [177], as well as in reversing neuropathic [103] and other forms of pathological [105] pain in rodents. Similarly to TrkB-Fc, systemically administered anti-trkB blocking antibodies do not reach the CNS, which, together with the relatively low sensitivity [176], makes them poor candidates for clinical treatments. In the last decade, the identification of novel small molecules acting as negative allosteric modulators of TrkB receptors has brought important advances in pharmacokinet-

ics and drug bioavailability. By using a peptidomimetic approach, Cazorla and colleagues identified a small BDNF fragment, cyclotraxin-B, which allosterically alters the conformation of TrkB [178]. Cyclotraxin-B was thereafter proved to have clear antinociceptive effects in different pain models, including post-stroke pain [63], nerve ligation injury [113], and inflammatory pain [179]. On the other hand, cyclotraxin-B does not only act on the BDNF dependent mechanisms but also ont the BDNF independent forms of TrkB activation, which raises the issue of the specificity of the effect. Moreover, the peptide is effective if delivered intravenously, but not orally. These limitations have been overcome by the same group through the identification of ANA-12, a non-peptidic small molecule [175]. ANA-12 allosterically prevents BDNF from binding TrkB with nanomolar potency [175] and, unlike cyclotraxin-B, can be delivered orally, thus representing a promising and specific approach for clinical trials. Very promising, an increasing number of preclinical studies have confirmed the antinociceptive efficacy of ANA-12 in different pain models, including nerve injury [111], inflammatory pain [180], trigeminal pain [114] and migraine [112, 181]. Recently, ANA-12 has also been documented to counteract chronic hypersensitivity due to visceral pain in cyclophosphamide-induced cystitis [182] and in a model of irritable bowel syndrome induced by maternal separation in rats [183].

8.1.3. Interfering with the Itracellular Kinase Domain

The main approach to intracellularly block tyrosine kinases activity is to interfere with the ATP binding site of the enzymes [184, 185]. The indolocarbazole K252a is one of the first used compounds acting as a competitive inhibitor of the ATP site, thus blocking Trk catalytic activity [186, 187]. K252a administration effectively blocks the rise of intracellular Ca^{2+} promoted by BDNF in acute slices of the rat superficial dorsal horn [177] and, *in vivo*, it reduces hypersensitivity in visceral [188, 189], neuropathic [103, 190], inflammatory [191], and skeletal pain [192].

Encouraged by preclinical studies, different pharmaceutical companies have invested considerable resources in improving kinases inhibitors, some of which are currently under clinical trials or investigations for a broad range of diseases, including oncological disorders and pain (for review [184, 193-196]). Although most of them exhibit high potency *in vitro*, yet the development of a TrkB inhibitor as a marketed product has not been successful at present. Unfortunately, developing tyrosine kinase antagonists for specific Trk receptors is challenging since ATP competitive Trk inhibitors are at best Trk specific (pan-Trk inhibitors) but can hardly discriminate between Trk subtypes [184]. Therefore, a major limitation concerning the use of these molecules is the risk to develop central side effects. To limit adverse effects, several attempts have been made to develop molecules that do not cross the blood-brain barrier (BBB) but mainly act at the periphery. Some of these molecules, *e.g.*, ARRY-470 [197] or PF-06273340A [198], exhibit antinociceptive effects in animal models of chronic pain. In a recent randomized, double-blinded clinical trial, the pan-Trk inhibitor ONO-4474 was proved to be analgesic in patients with moderate to severe osteoarthritis [199]. Yet, it is likely that all these molecules also target peripheral Trk receptors other than TrkB (*e.g.,* TrkA).

8.2. Alternative Targets to Counteract BDNF Pronociceptive Effects

Due to the above-described limitations, to date, there are no effective pain treatments based on BDNF/TrkB. The critical role played by BDNF and TrkB receptors in the survival of central neurons further limits the use of TrkB antagonists as a safe therapeutic approach. Moreover, the complexity and plurality of the intracellular signaling pathways activated by tyrosine kinase receptors make it difficult to develop selective pharmacological treatments. Targeting BDNF/TrkB can lead to both on-target side effects, due to the inactivation of BDNF-dependent pathways important for the normal functioning of the healthy nervous system, and off-target side effects, due to the lack of specificity and the interaction with relevant non-BDNF pathways [200].

Other viable therapeutic options to counteract TrkB-dependent pathological alterations can be achieved by targeting upstream or downstream effectors.

Upstream targeting of microglia can effectively reduce the BDNF-dependent alterations in neuropathic pain [201]. In this respect, microglial P2X4 receptors, whose activation is necessary for the subsequent release of BDNF, are viable targets for clinical interventions [202]. Alternatively, several GPCR receptors, such as dopamine receptor 1 (D1R [203]), PACAP receptor [23], adenosine A2 receptor [204] and the cannabinoid receptor 1 [205], can transactivate TrkB, thus representing alternative targets to reduce TrkB signaling.

Among downstream signaling pathways, a key mechanism underlying TrkB-dependent pain hypersensitivity, acts through the downregulation of KCC2, which causes an imbalance between excitatory and inhibitory neurotransmission [103]. KCC2 itself represents a putative pharmacological target [206]. Therefore, the development of KCC2 enhancers is a promising therapeutic avenue to restore inhibition and counteract the symptoms associated with the BDNF-TrkB-KCC2 cascade [207].

8.3. Targeting GDNF/GFRα1/Ret

Although GDNF and its receptor, as well as other GFLs, have been shown to either increase or decrease sensitivity in different preclinical models of pain, the antinociceptive role of GDNF in neuropathic pain has been consistently reported (for review, see [6]). Thus, potentiating the GDNF system is, theoretically, a viable strategy to counteract neuropathic pain symptoms. To achieve this goal, the following strategies have been explored: i) direct administration of GDNF; ii) synthesis and delivery of small molecule agonists; iii) alternative druggable targets to potentiate GDNF/GFRα1/Ret pathways.

8.3.1.)- Administration of GDNF

In different experimental neuropathic pain models, the antinociceptive effects of GDNF have been demonstrated by the direct administration of GDNF, mostly intrathecally [131, 142, 143, 208]. In terms of translatability into clinical settings, however, intrathecal administration of GDNF is hampered by the invasiveness of the procedure and potential side effects [209]. On the other hand, the poor CNS bioavailability of proteinaceous molecules with high molecular weight, such as the NFs, strongly limits the use of systemic administration in clinical interventions [210, 211]. Many efforts have been made to overcome the BBB obstacle and improve GDNF availability to the nervous tissue, for instance, by intranasal administration using cationic liposomes [212, 213] or by encapsulating GDNF in microspheres, allowing a slower release when centrally injected [214-216].

Gene-transfer approaches represent a more effective way to deliver GDNF in the CNS. These approaches can be either implemented by trojan horses, such as liposomes, that carry GDNF-encoding plasmids across the BBB to the central neurons [217], or by gene transfer with recombinant viral vectors locally infecting the target neurons [210]. A number of viral vectors carrying the *gdnf* gene have been developed, in particular, for rescuing motor performance in animal models of Parkinson's disease [210]. These include the herpes simplex virus (HSV [218]), lentiviruses [219], adenoviruses [220] and adeno-associated viruses (AVV [221-223]). Vector-mediated GDNF delivery has also been proposed to reverse neuropathic pain symptoms after nerve injury, either by spinal injection of lentiviral vectors [134, 135], intracutaneous inoculation of engineered herpes simplex virus [224] or intramuscular injection of recombinant adenovirus [133, 225].

Eventually, cell therapy represents another putative strategy to deliver GDNF to central neurons. Administration of astrocytes, macrophages and neural stem cells engineered to express GDNF, or carotid bulb cells, an endogenous source of GDNF, have been successfully employed to prevent cell loss in certain neurodegenerative diseases [226-228]. The use of GDNF-based cell therapy has also been successfully adopted for the treatment of pain hypersensitivity in nerve-injured rats [229].

Clinical trials to test the effectiveness of GDNF-based therapies in humans have so far largely failed, and more importantly, have unveiled the main limitations of this approach: first, the onset of unwanted side effects, such as nausea, weight loss, anorexia; second, the inadequate concentration reached by GDNF in target tissues; and third, the production of neutralizing anti-GDNF antibodies in a number of patients [230, 231]. Gene therapy may represent an improvement as compared to the direct administration of the NF, as demonstrated in preclinical investigations. A large clinical trial is currently ongoing to address the effectiveness of AAV-*gdnf* administration in the putamen of patients with Parkinson's disease [232], which may subsequently open the avenue for similar approaches for the treatment of neuropathic pain. Indeed, GDNF has not yet been employed to treat neuropathic pain in humans. Artemin, instead, has already been tested in two clinical studies in patients with sciatica, with the main purpose to verify the safety, tolerability, and pharmacokinetics of the NF [233, 234].

8.3.2. Small Molecule Agonists

To overcome the BBB, another viable strategy is the synthesis of non-peptidyl small molecule agonists activating GDNF receptors complex GFRα1/Ret. The first described agonist of GFRα1 was XIB4035 [235]. Local XIB4035 administration was shown to alleviate the symptoms of diabetic neuropathy [132]. More recently, Sidorova and colleagues [236] identified by high-throughput screening, a novel Ret agonist, named BT13. This molecule directly modulates RET and its downstream intracellular signaling cascades. BT13 systemic administration reverses nerve injury-induced alterations in sensory neurons [236].

8.3.3. Alternative Druggable Targets to Potentiate GDNF/GFRα1/Ret Pathways

Emerging evidence suggests that the activation of the intracellular Ret signaling cascade is the endpoint of a complex and multifaceted ensemble of interacting factors, among which GFLs and GFRs likely represent a necessary but not sufficient component. Understanding the specific relevance and involvement of these interacting factors may provide novel approaches to restore pharmacologically Ret signaling in pathological settings.

The molecular composition of the membrane microdomains (lipid rafts) in which the GFRs are anchored represents a key factor influencing intracellular Ret signaling pathways [44]. Indeed, GDNF-mediated activation of GFRα1 fosters the recruitment of Ret to lipid rafts, thus favoring Ret/Src kinases coupling [44]. The interaction of GFRα1 and Ret outside lipid rafts microdomains does not preclude Ret activation but attenuates downstream functional effects [237]. GM1 ganglioside is an important component of lipid rafts and displays neurotrophic actions *in vitro* and *in vivo* [238, 239]. A recent study showed that the administration of GM1 promotes Ret phosphorylation by enhancing the interaction between GDNF and GFRα1 [239]. Interestingly, the administration of GM1 to patients with post-herpetic neuralgia or spinal cord injury was found to sensibly reduce pain severity [240].

Transcription factors represent other alternative targets for indirectly manipulating the Ret function. Specifically, the transcription factor nurr1 has been shown to stimulate Ret tyrosine kinase activity in animal models of Parkinson's disease [241, 242]. Pharmacologically, nurr1 can be targeted by delivering bexarotene, an agonist of retinoic X receptors, which in turn forms heterodimers with the transcription factor [242]. Interestingly, bexarotene also exerts antinociceptive effects in neuropathic pain by counteracting certain spinal neuroinflammatory processes [243], thus leaving open the possibility that nurr1-Ret pathways may also be targeted in the spinal cord.

Eventually, as reported earlier, GDNF may exert antinociceptive effects, also acting upon receptors other than Ret.

In particular, adhesion molecules such as NCAM, E-cadherin and nectin-1 have been implicated in GDNF antinociceptive signaling pathways [49, 138, 140]. Importantly, C3D, a NCAM mimetic peptide, recapitulates the analgesic effects of GDNF in the model of nerve injury [49], thus representing another alternative strategy for pain treatment.

CONCLUSION

While pre-clinical studies in the last 20 years have consistently reported that BDNF and GDNF play a significant role in the development of pain hypersensitivity, no novel pharmacological strategies have been successfully developed based on this knowledge. The reasons are multiple (see for review [244, 245]), and include the difficulty to correctly dose and deliver the treatments, as well as the necessity to deal with advanced stages of the pathology in humans. On the mechanistic side, however, one major obstacle is the tremendous fluidity of NFs activity. As discussed in this review, the same NFs can generate opposite effects by activating different intracellular pathways or different receptors; not to say that the same molecules have short- and medium-term effects on neuronal function, but also long term trophic effects on neuronal survival and differentiation. Therefore, the identification of specific downstream targets in Ret- and TrkB- dependent pathways involved in the onset of pain symptoms (or in their reduction) is probably a more viable and safer strategy rather than directly tackling NFs receptors. In this respect, defining the mechanistic ground through which NFs promote sensitization in pathological pain is necessary to refine pharmacological interventions, reduce side effects and increase effectiveness. Additionally, more efforts are needed to be made not only in the analysis of the effects of individual relevant factors but also in their reciprocal interactions. In this review, we showed that BDNF and GDNF exert distinct complementary effects in pain processing. Their reciprocal contribution appears particularly evident in neuropathic pain, where BDNF/TrkB signaling plays a dominant pro-nociceptive role, while GDNF/GFRα1/Ret signaling mainly exerts anti-nociceptive effects. Any imbalance in their contribution to the modulation of pain processing may concur with the development of pathological conditions. Although we are still far from understanding properly the circuitry that triggers the opposing effects of BDNF and GDNF in the initial process of nociceptive stimuli [129], this dual mechanism of action provides, at least theoretically, the possibility to pharmacologically modulate its final outcome by the combinatory use of agonist (mimetic) and antagonist (lytic) drugs to each NF in a fashion similar to that currently in use in the pharmacological control of sympathetic and parasympathetic visceral neurotransmission. It is at present difficult to foresee which could be the advantages or disadvantages of such an approach. If indeed, it will be possible to develop adequate pharmacological tools that overcome the limitations described in the previous section of this paper, however, one has to keep in mind that any drug acting on either of the two NFs will influence their relative functional balance. Thus, it might be speculated that, for *e.g.,* the development of a GDNF agonist would be equally effective than that of a BDNF antagonist in the control of pathological pain. In the transition from preclinical studies to therapeutic intervention, the interactions between the two NFs should be taken into consideration. Most of the clinical trials in the past were focused on single targets, with the idea that a single molecule or receptor can effectively restore a pathological condition. The interactions of BDNF and GDNF in nociceptive pathways impose a change of approach toward combinational therapies [246], including the delivery of both trophic factors and/or small molecules acting on downstream targets, aiming to restore an altered balance. On the other hand, the successful development of combinational therapies based on a homeostatic approach implies the availability of diagnostic tools to non-invasively explore the neurotrophic content at both central and peripheral levels in different types of painful neuropathies [247-249].

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