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Review

Cancer Neuroscience of Kinase Inhibitors: On-Target Effects on the Nervous System

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Abstract

Cancer neuroscience has emerged as a field that explores the bidirectional interactions between tumors and the nervous system. From this perspective, we review the pharmacological and neurobiological effects of kinase inhibitors, which are widely used as anticancer therapeutics. Certain kinase inhibitors not only exert potent antitumor activity but also modulate neural function as a consequence of kinase inhibition. Representative examples include small molecules and therapeutic antibodies targeting the tropomyosin receptor kinase (Trk), rearranged during transfection (RET), vascular endothelial growth factor/ vascular endothelial growth factor receptor (VEGF/VEGFR), epidermal growth factor receptor (EGFR), and anaplastic lymphoma kinase (ALK) signaling pathways. These agents influence the nervous system through molecular mechanisms, examples of which include TrkA-mediated pain perception and growth differentiation factor 15/RET signaling-dependent appetite regulation. Elucidating these mechanistic intersections between oncogenic and neural signaling can broaden our understanding of tumor–nerve crosstalk.

Keywords: neurobiology; protein kinase inhibitors; gene amplification; pain perception; appetite regulation

1. Introduction

The emerging discipline of cancer neuroscience bridges oncology and neurobiology, as it focuses on the dynamic bidirectional communication between cancer cells and the nervous system [1]. Neural components actively influence tumor progression through neurotrophic signaling, neurotransmitters, and stress-related neuroendocrine factors. In turn, cancer and its therapies reciprocally impact neuronal function, leading to neurological manifestations such as pain, sensory dysfunction, and altered appetite regulation.

Among the most transformative advances in oncology has been the advent of targeted protein kinase inhibitors, which selectively suppress oncogenic signaling mediated by kinases and their downstream cascades [2]. To date, more than 80 kinase inhibitors have been approved for clinical use, the majority of which are anticancer drugs that have revolutionized precision oncology through selectivity and efficacy [3]. However, many of these kinases are also critical regulators of neuronal development, synaptic plasticity, and neurotrophic communication [4,5,6]. Their pharmacological inhibition can therefore result in a broad spectrum of neurological consequences, both adverse and therapeutically beneficial.

These observations highlight that kinase signaling—physiologically indispensable in neurons—is pathologically hijacked in cancer through chromosomal rearrangements, amplifications, or activating mutations. Understanding how kinase inhibitors perturb these overlapping molecular systems can provide crucial insight into both neurological adverse events and potential neuromodulatory benefits.

This review examines the neurological effects of selected kinase inhibitors—tropomyosin receptor kinases (Trk), rearranged during transfection (RET), vascular endothelial growth factor/ vascular endothelial growth factor receptor (VEGF/VEGFR), epidermal growth factor receptor (EGFR), and anaplastic lymphoma kinase (ALK) inhibitors—with a focus on their mechanistic intersections with neurotrophic pathway regulation. Rather than addressing common but non-specific neurological toxicities of anticancer therapy, such as chemotherapy-induced neuropathic pain or dysgeusia, this review emphasizes on-target neurological effects that arise directly from the inhibition of signaling pathways within the nervous system.

2. Trk Inhibitors: Withdrawal Pain, Weight Gain, and Dizziness

Trks are a family of receptor tyrosine kinases that regulate synaptic strengthening and plasticity in the mammalian nervous system. As the first neurotrophin to be studied, the nerve growth factor (NGF) was initially identified with TrkA as its receptor. Three major subtypes have since been characterized—TrkA, TrkB, and TrkC—encoded by the genes neurotrophic tyrosine receptor kinase (*NTRK)1*, *NTRK2*, and *NTRK3*, respectively. All Trk proteins are predominantly expressed in the nervous system, where they bind neurotrophin ligands and play crucial roles in neuronal

development and differentiation [7]. TrkA has a high affinity for NGF, TrkB preferentially binds the brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NT-4), while TrkC is the primary receptor for NT-3 [5].

Chromosomal rearrangements involving *NTRK* genes have been identified in various cancers. These alterations generate fusion proteins that retain Trk kinase domains, resulting in constitutively active fusion proteins that function as oncogenic drivers. To counteract this, small-molecule pan-selective inhibitors targeting the Trk kinase activity of all three Trk receptors have been developed and successfully introduced into clinical oncology. Notable first-generation inhibitors include larotrectinib, a highly selective Trk inhibitor, and entrectinib, a multi-kinase inhibitor that also targets c-ros oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK). More recently, next-generation inhibitors such as repotrectinib have been developed to overcome acquired resistance mutations [8,9,10,11].

Given the pivotal role of Trk signaling in the nervous system [12], pharmacologic inhibition can give rise to a spectrum of neurological adverse events [5]. The most frequently reported include withdrawal pain, weight gain, and dizziness [13].

2.1 Withdrawal Pain

The NGF -TrkA signaling pathway is well established as a key mediator of pain transmission [6]. This is exemplified by congenital insensitivity to pain (CIPA), a rare genetic disorder caused by loss-of-function mutations in the *NTRK1* gene, which encodes TrkA [14,15]. The mechanisms by which the NGF–TrkA axis contributes to both nociceptive and neuropathic pain have been extensively elucidated, providing a rationale for efforts to target NGF or TrkA as potential analgesics [6,16].

Given their role in pain signaling, Trk inhibition in oncology has been shown to associate with a unique and notable adverse event: Withdrawal pain [13,17] (Fig. 1). Upon discontinuing of Trk inhibitors, patients may experience a rebound phenomenon characterized by heightened pain sensitivity. Clinical studies have reported that pain associated with temporary or permanent discontinuation of Trk inhibitors occurs in approximately 24–35% of patients, with a higher incidence observed after longer treatment durations [13,17]. This phenomenon highlights the essential role of the Trk pathway in modulating pain perception.

2.2 Weight Gain

Weight gain represents another significant on-target adverse event of Trk inhibition, given the critical involvement of the BDNF/TrkB pathway in regulating appetite and energy expenditure [18] (Fig. 1). In addition, preclinical results using a mouse model have shown that BDNF haploinsufficiency and reduced TrkB signaling resulted in hyperphagia and obesity [19]. Conversely, pharmacologic activation of TrkB in non-human primates has been shown to enhance appetite and increase body weight, further underscoring the physiological role of this pathway in appetite and energy homeostasis [20]. In clinical practice, weight gain of at least grade 1 severity was observed in 53% of patients receiving Trk inhibitors. The frequency and severity of weight gain tend to increase with the duration of therapy [13].

Interestingly, weight gain is also a recognized side effect of some ALK inhibitors [21,22], and this is believed to be mediated, at least in part, through off-target inhibition of the TrkB receptor. While the primary target of these drugs is the ALK fusion protein found in certain non-small cell lung cancers, some ALK inhibitors also have activity against TrkB. For instance, lorlatinib, a potent ALK and ROS1 inhibitor, is also known to inhibit TrkB [23], and its use is associated with a higher incidence and severity of weight gain compared to other ALK inhibitors with less TrkB activity such as crizotinib [21,22]. This observation strengthens the link between TrkB inhibition and weight regulation. A newer generation of ALK inhibitors are being developed with greater selectivity to minimize off-target effects like TrkB inhibition and subsequent weight gain [17].

2.3 Dizziness

Dizziness has also been identified as another notable adverse event associated with Trk inhibition, as reported in approximately 40% of patients. A subset of these patients has also experienced ataxia [13]. These manifestations are closely linked to impaired TrkB and TrkC signaling. Preclinical evidence supports this association: Mice with TrkB ligand loss developed severe ataxia secondary to cerebellar insufficiency [17,24], while TrkC knockout models exhibit abnormal movements and postural instability consistent with proprioceptive insufficiency, resembling motion sickness [25].

In addition to central mechanisms, some patients developed orthostatic hypotension in the absence of overt volume depletion, suggesting that Trk inhibition may also contribute to clinically significant autonomic dysfunction [13]. Given these multiple potential etiologies, it is essential to investigate the underlying cause of dizziness in order to distinguish between central (vestibular/proprioceptive) and autonomic effects.

3. RET Inhibitors and Weight Gain

Rearranged during transfection (RET) is a receptor tyrosine kinase that plays essential roles in neural development and kidney organogenesis under physiological conditions [26]. RET activation is contingent upon co-receptor binding. The five known ligands of RET—glial cell line–derived neurotrophic factor (GDNF), neurturin, artemin, persephin, and growth differentiation factor 15 (GDF15)—have been reported to bind to GFRα1–4 and GDNF family receptor alpha like (GFRAL) co-receptors, respectively. These binding events subsequently activate RET. This

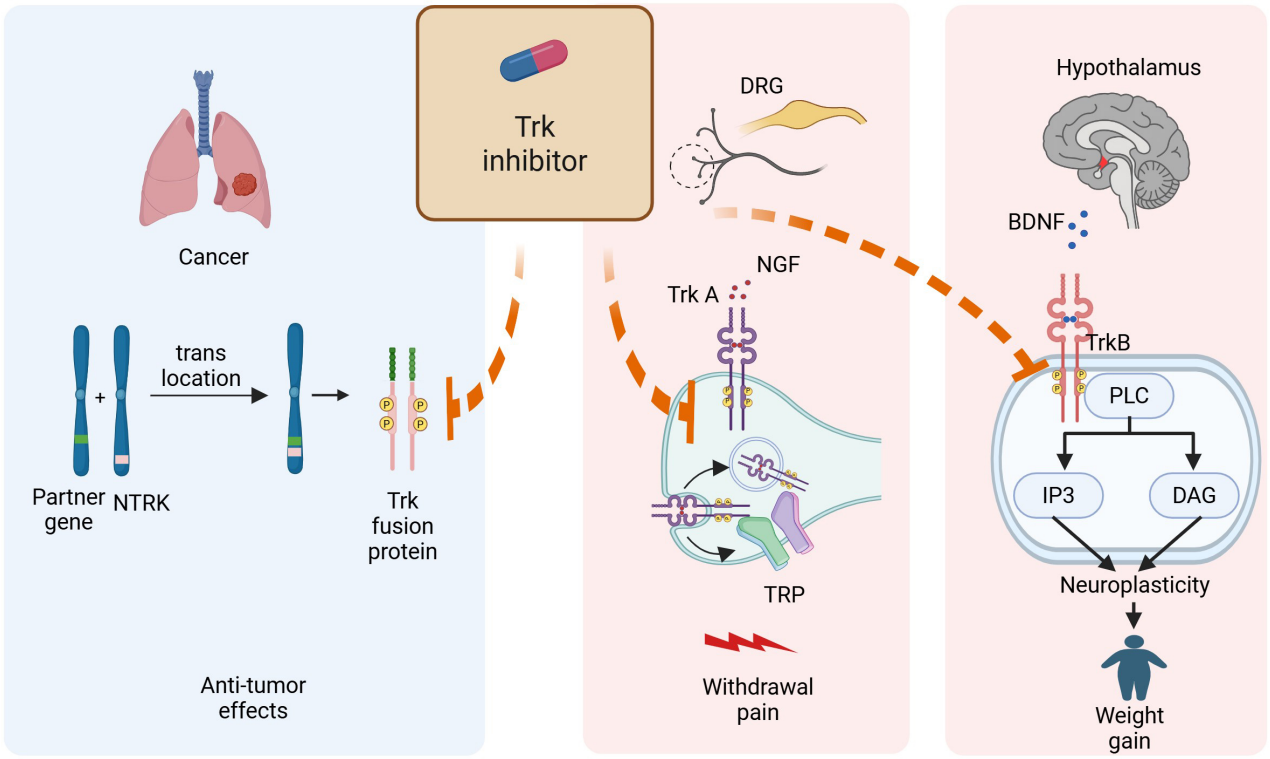

Fig. 1. Effects of Trk inhibitors on withdrawal pain and weight gain. Trk fusion proteins generated by *NTRK* gene translocations can cause ligand-independent Trk activation and tumorigenesis. Trk inhibitors suppress this aberrant signaling to exert antitumor effects. In neurons, NGF binding to TrkA induces TRP channel activation and pain signaling. Discontinuation of the TrkA inhibitors may trigger withdrawal pain through reactivating the NGF/TrkA-TRP pathway. Trk inhibitors are also associated with weight gain, likely through interference with hypothalamic appetite regulation. Inhibition of BDNF/TrkB signaling disrupts the hypothalamic control of energy balance, leading to hyperphagia, obesity and dizziness. Trk, tropomyosin receptor kinases; NGF, nerve growth factor; TRP, transient receptor potential; BDNF, brain-derived neurotrophic factor; DRG, dorsal root ganglion; PLC, phospholipase C; IP3, inositol 1,4,5-triphosphate; DAG, diacylglycerol. The figure was created with BioRender.com.

multi-ligand, co-receptor architecture allows tissue-specific RET signaling in both the central and peripheral nervous systems [4,27].

Aberrant activation of RET—through chromosomal rearrangements or activating point mutations—can lead to constitutive RET kinase signaling, driving oncogenesis in several tumor types, most notably non–small cell lung cancer (NSCLC) and medullary thyroid carcinoma (MTC) [28]. RET fusions and mutations activate downstream pathways, thereby promoting tumor cell proliferation, survival, and metastasis [26,29]

To therapeutically target aberrant RET activation, several small-molecule inhibitors have been developed. Early efforts employed nonselective multikinase inhibitors (e.g., cabozantinib, vandetanib). However, their broad target profiles resulted in significant off-target toxicities, highlighting the need for more selective agents. The first-generation selective RET inhibitors, i.e., selpercatinib and pralsetinib, have since demonstrated strong clinical efficacy and relatively favorable safety profiles in patients with RET fusion–positive NSCLC and RET-mutant thyroid cancers [26].

A particularly interesting on-target manifestation of RET inhibition is weight gain, which is linked to the disruption of the GDF15–GFRAL–RET axis (Fig. 2). Under normal conditions, GDF15 functions as a stress-induced cytokine that suppresses appetite by activating GFRAL and RET signaling in the hindbrain appetite centers [27]. RET inhibition interrupts this anorectic pathway, which may consequently lead to an increase in food intake and body weight. Recent clinical observations have suggested that weight gain is a relatively common and potentially on-target adverse event associated with selective RET inhibition, particularly in agents with central nervous system (CNS) penetration abilities [30]. In a retrospective analysis, among 116 patients treated with CNS-penetrant RET inhibitors (e.g., selpercatinib, pralsetinib), approximately 73.3% developed weight gain of at least grade 1 during therapy [30].

Interestingly, while weight gain is regarded as an adverse event in many patients receiving RET inhibitors, it may represent a beneficial effect in others. In oncology, cancer cachexia—a syndrome characterized by progressive weight and muscle loss—is a major cause of morbidity and

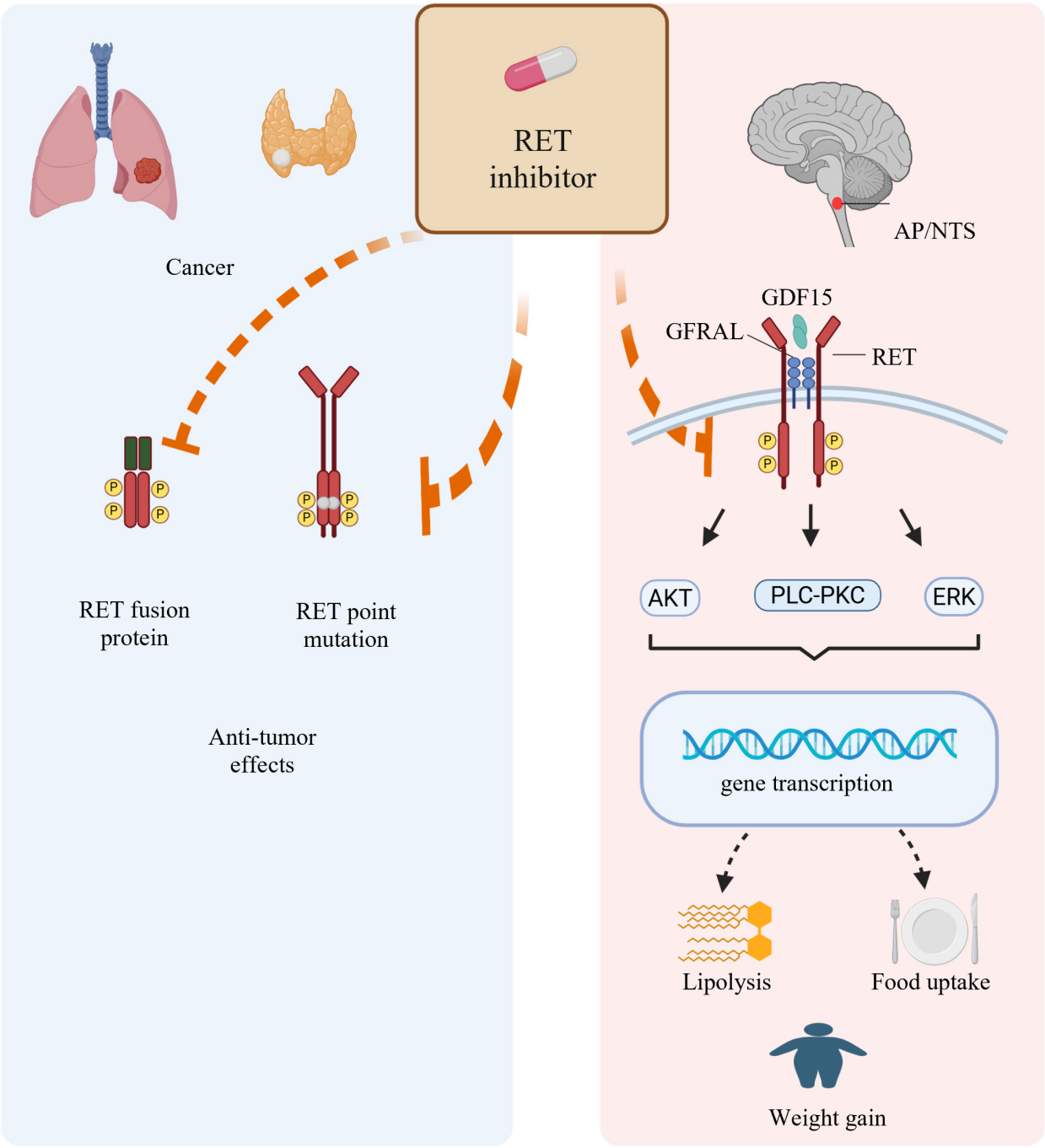

Fig. 2. Effects of RET inhibitors on weight gain. Activating mutations in RET, including gene fusions and point mutations, can result in constitutive signaling and tumorigenesis. RET inhibitors suppress RET activity and are clinically used as targeted anticancer agents. Weight gain observed in patients treated with RET inhibitors is likely mediated by effects on the area postrema/nucleus tractus solitarius (AP/NTS) region of the brain. Under normal conditions, GDF15 binding to GFRAL/RET receptor complexes activates downstream signaling that reduces food intake and body weight. RET inhibition blocks this pathway, leading to increased food intake and weight gain. RET, rearranged during transfection; GDF 15, growth differentiation factor 15; GFRAL, glial cell line–derived neurotrophic factor family receptor alpha like; PKC, protein kinase C; ERK, extracellular signal-regulated kinase. The figure was created with BioRender.com.

mortality. By attenuating GDF15–GFRAL–RET signaling, RET inhibition may partially counteract cachexia in vulnerable patients. In fact, the pharmacologic inhibition of GDF15 signaling is currently being explored as a therapeutic strategy for cancer-related cachexia [31,32]. In a phase II randomized, double-blind clinical trial, ponsegromab (a humanized monoclonal antibody targeting GDF15) produced significant weight gain, improved appetite, and in-

creased physical activity in cancer patients with elevated GDF15 levels [33]. Preclinical studies have further supported this mechanism, showing that blocking the GDF15–GFRAL–RET axis reversed tumor-induced weight loss and prevented cachexia in murine models [34,35].

4. VEGF Antibody Bevacizumab and Analgesic Effects

Bevacizumab, a monoclonal antibody that neutralizes vascular endothelial growth factor A (VEGF-A), was originally developed as an antiangiogenic agent for cancer therapy [36]. By inhibiting VEGF–VEGFR signaling, bevacizumab suppresses tumor vascularization, endothelial proliferation, and metastasis. Clinically, it has become a cornerstone of therapy across multiple malignancies, including colorectal, lung, and renal cancers, as well as glioblastoma [36].

Interestingly, accumulating preclinical evidence in the mouse model indicated that bevacizumab exerts direct analgesic effects, independent of its antitumor activity [37]. This phenomenon has been most clearly documented in patients with nerve-sheath tumors, such as vestibular schwannomas and plexiform neurofibromas associated with neurofibromatosis types 1 and 2 [38]. In these cases, pain relief often occurs before measurable tumor regression, suggesting a pharmacologic neuromodulator mechanism rather than a secondary effect of tumor shrinkage [39].

Mechanistically, VEGF contributes to nociceptive sensitization via the activation of VEGFR1 and VEGFR2 and interactions with neuropilin-1 in peripheral sensory neurons, which can enhance excitability through downstream protein kinase C (PKC) and mitogen-activated protein kinase (MAPK) signaling cascades through cross-talk with transient receptor potential (TRP) channels [40,41]. A preclinical study using the mouse model indicated that Bevacizumab's inhibition of VEGF effectively reduces this neuronal hyperexcitability, attenuating hyperalgesia, allodynia, and peritumoral inflammation [42]. Clinical reports have further demonstrated that bevacizumab administration leads to durable reductions in pain intensity and decreased opioid use, with pain recurrence frequently observed upon treatment discontinuation [39]. Despite its limited penetration across an intact BBB due to its large molecular size (~150 kDa), clinical studies have shown that bevacizumab significantly reduces circulating VEGF-A121 plasma level in patients with recurrent glioblastoma following systemic intravenous administration [43]. This systemic inhibition of VEGF signaling can attenuate nociceptive sensitization by modulating VEGFR1 activity in peripheral sensory neurons, particularly through transient receptor potential vanilloid 1 (TRPV1)/transient receptor potential ankyrin 1 (TRPA1)-associated pathways, thereby contributing to analgesic effects independent of direct BBB penetration [37,44].

Preclinical models have consistently shown rapid pain relief with VEGF/VEGFR2 inhibitors——frequently preceding measurable tumor regression—which strongly supports an on-target analgesic effect of VEGF inhibition. However, clinical evidence has remained limited to retrospective analyses, small prospective cohorts, and case reports, precluding definitive attribution to target engagement over indirect anti-tumor effects. Further mechanistic and clinical investigations are warranted to elucidate the precise neurobiological pathways linking VEGF blockade to pain modulation in neurofibromatosis-associated tumors.

5. EGFR Inhibitors and Neuropathic Pain

The EGFR belongs to the erythroblastic oncogene B (ErbB) family of receptor tyrosine kinases and plays a critical role in regulating cell proliferation, differentiation, and survival through activation of downstream signaling cascades [45,46]. Aberrant EGFR signaling—via overexpression, amplification, or activating mutations—drives oncogenesis in multiple tumor types, including NSCLC, glioblastoma, and colorectal cancer. The development of EGFR inhibitors such as gefitinib, erlotinib, afatinib, osimertinib, and the monoclonal antibody cetuximab has revolutionized targeted therapy for EGFR-driven malignancies [47].

While EGFR inhibitors are primarily used for their antitumor efficacy, emerging evidence indicates that they also modulate nociceptive processing. Several preclinical and clinical studies have shown that EGFR inhibition can reduce neuropathic pain intensity, even in patients without tumor regression [48,49]. For instance, cetuximab, a monoclonal antibody targeting EGFR, has demonstrated analgesic effects in refractory neuropathic pain syndromes and cancer-related neuropathic pain. The analgesic response is often rapid—within hours to days—and reversible upon drug discontinuation, suggesting a direct pharmacological mechanism rather than a delayed antitumor effect [49,50].

Mechanistically, EGFR signaling contributes to pain sensitization through crosstalk with VEGF and inflammatory mediators [51,52]. Activation of EGFR in nociceptive neurons and satellite glial cells enhances excitability via the MAPK and PKC pathways, possibly potentiating transient receptor potential channels [48]. EGFR inhibition disrupts this feed-forward loop, reducing neuronal hyperexcitability and attenuating peripheral and central sensitization [48,52,53].

6. ALK Inhibitors: Weight Gain and Pain Relief

Anaplastic lymphoma kinase (ALK) is a transmembrane tyrosine kinase receptor that belongs to the leukocyte tyrosine kinase (LTK) receptor subfamily, which is comprised of two members: ALK and LTK. Like the other receptor tyrosine kinases, the ALK contains an extracellular domain (ECD), a transmembrane domain, and an intracel-

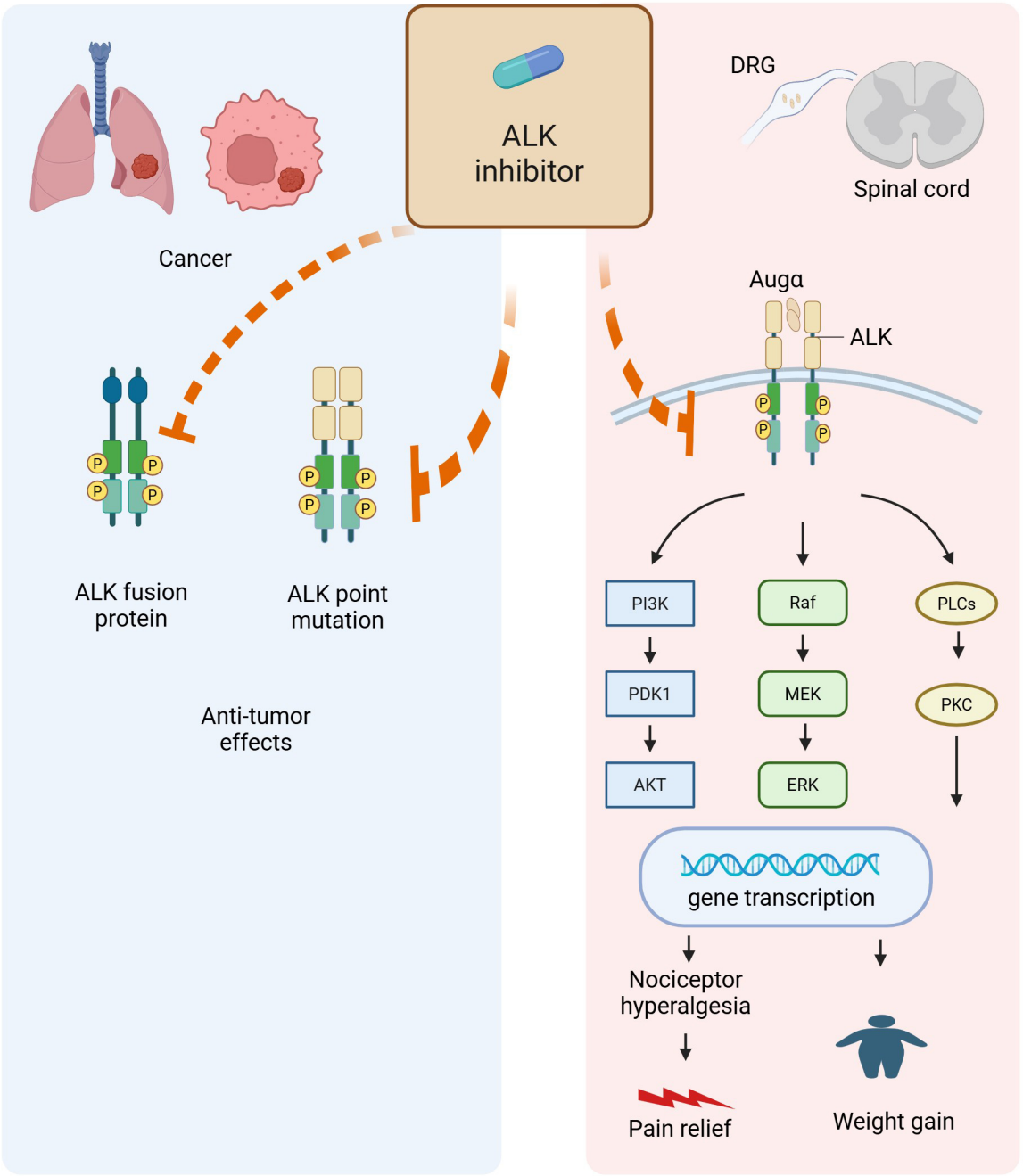

Fig. 3. Effects of ALK inhibitors on pain relief and weight gain. The oncogenic activation of ALK receptor signaling can be initiated by activating point mutations in the full-length receptor, gene amplification, or chromosomal rearrangements. ALK inhibitors effectively block abnormal ALK activity. Binding of ALK extracellular domains with Augα or Augβ hyperactivation of ALK downstream signaling via the JAK/STAT, RAS/MAPK, and PI3K/AKT/mTOR pathways may contribute to hyperalgesia and weight gain. ALK, anaplastic lymphoma kinase; JAK, Janus kinase; STAT, signal transducers and activators of transcription; RAS, rat sarcoma; MAPK, mitogen-activated protein kinases; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin. The figure was created with BioRender.com.

lular domain (ICD) [54]. Interestingly, ALK is a unique receptor tyrosine kinase (RTK) with an extracellular region comprised of two MAM (meprin, A5 protein, and protein phosphatase μ) domains and a low-density lipoprotein (LDL) domain that differs from the other RTKs [55]. Nevertheless, the functional significance of this architecture remains to be fully elucidated.

ALK expression is predominantly confined to nervous system development. In mice, extensive *ALK* mRNA expression has been observed in the brain and peripheral ner-

Table 1. Effects of selected kinase inhibitors on nervous system.

Target kinase	Representative drugs	Primary neurological effect	Proposed mechanistic basis
Trk	Larotrectinib, Entrectinib	Withdrawal pain, weight gain, dizziness [13]	Inhibition of NGF–TrkA signaling (nociception) [6], BDNF–TrkB (appetite) [18], TrkC (proprioception) [25]
RET	Selpercatinib, Pralsetinib	Weight gain [30]	Disruption of GDF15–GFRAL–RET anorectic pathway [30]
VEGF/VEGFR	Bevacizumab	Analgesic effect in neurofibroma-related pain [39]	Inhibition of VEGF–VEGFR–TRP nociceptive signaling
EGFR	Cetuximab, Erlotinib, Gefitinib	Analgesic effect in neuropathic pain [48]	Suppression of EGFR–MAPK–PKC signaling and TRP sensitization
ALK	Crizotinib, Alectinib, Lorlatinib	Weight gain, analgesic effect in neuropathic pain [22,63,68]	Disruption of hypothalamic ALK–Augα/Augβ signaling and suppression of MAPK signaling [63,67]

VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; EGFR, epidermal growth factor receptor.

vous system of developing embryos, but there is a rapid postnatal decline and maintenance of low levels in adults [56]. Furthermore, during the development of chicks, ALK expression was found in the developing central and peripheral nervous system, including spinal cord motoneurons, sympathetic ganglia, and dorsal root ganglia [57]. In the adult human, the physiological expression of ALK is mainly limited to the central and peripheral nervous systems, with undetectable or very low levels in other tissues. From these extensive expression profiles, ALK has been postulated to play an important role in the physiological development and function of the nervous system, but the direct biological role of ALK remains to be fully elucidated [56,58].

The oncogenic activation of ALK receptor signaling can be initiated by activating point mutations in the full-length receptor, gene amplification, or chromosomal rearrangements. Notably, *ALK* fusion is more prevalent than *ALK* mutation in cancer. In particular, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK)* is well-characterized in NSCLC and activating ALK point mutations are the most prominently associated with neuroblastoma among them. Aberrant ALK variants have been demonstrated to induce malignant transformation by means of hyperactivating ALK downstream signaling via the Janus kinase (JAK)/signal transducers and activators of transcription (STAT), rat sarcoma (RAS)/MAPK, and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathways, promoting cell survival and proliferation [59,60].

The abnormal ALK protein can be effectively blocked by ALK inhibitors. To date, a total of three generations of these inhibitors have been developed, with the new generation being proposed as more efficient at penetrating the blood-brain barrier and reducing brain metastasis: First generation (crizotinib), second generation (ceritinib, alectinib, brigatinib, ensartinib) and third generation (lorlatinib) [61,62]. However, these inhibitors are, albeit tentatively, associated with hypothalamic toxicity [63].

6.1 Weight Gain

Weight gain is purportedly an on-target effect of ALK inhibition (Fig. 3). Research has shown that ALK and its ligand, augmentor α/β (Augα/Augβ) were co-opted from a neuronal pathway in body weight regulation to drive several human cancers through the aberrant expression of constitutively active ALK mutants [22,63]. The specific binding of ALK extracellular domains with Augα and Augβ has been demonstrated to activate multiple intracellular signaling pathways that may operate within the hypothalamus, arcuate nucleus (ARC), and paraventricular nucleus (PVN) neurons region [63]. Preclinical models using Drosophila and mice during the investigation of the endogenous role of ALK in the CNS showed that a knockout of *Alk* leads to decreased triglyceride levels or thinness via hypothalamic ALK expression controlling energy expenditure through sympathetic-mediated adipose lipolysis [64]. In addition, mice deficient in Augα and Augβ individually or mice deficient in both molecules displayed a similar thinness phenotype and resistance to diet-induced obesity [63]. In a recent meta-analysis of data from clinical trials, BBB penetration of ALK inhibitors increases across generations and correlates with weight gain incidence. Lorlatinib revealed the highest risk of treatment-induced weight gain (36%), followed by alectinib (15%) and crizotinib (5%) [22,65,66].

6.2 Pain Signaling

MAPKs play essential roles in intracellular signal transduction, neural plasticity, and inflammatory responses, positioning them as promising molecular targets for therapeutic intervention in pathological pain conditions [67]. MAPKs have been reported to be involved in nociceptive pathway to pain hypersensitivity via phosphorylation or

Table 2. Kinase inhibitors with the nervous system on-target effects: indication and CNS penetration.

Target	Drug	Generation	Approved year	Indication	CNS penetration	References
Trk	Larotrectinib	1st selective	2018	NTRK fusion-positive solid tumors	Yes	[72,73]
	Entrectinib	1st	2019	NTRK fusion-positive solid tumors; ROS1 fusion-positive NSCLC	Yes	[73,74]
	Repotrectinib	3rd	2024	NTRK fusion-positive solid tumors; ROS1 fusion-positive NSCLC	Yes	[75]
RET	Cabozantinib	Multikinase	2012	MTC, RCC	Yes	[76]
	Vandetanib	Multikinase	2011	MTC	Yes	[77]
	Selpercatinib	1st selective	2020	RET fusion-positive NSCLC, RET-mutant thyroid cancers	Yes	[78]
	Pralsetinib	1st selective	2020	RET fusion-positive NSCLC, RET-mutant thyroid cancers	Yes	[79]
VEGF	Bevacizumab	mAb	2004	Colorectal cancer, NSCLC, RCC, GBM	Poor	[80]
EGFR	Cetuximab	mAb	2004	Colorectal cancer, HNSCC	Poor	[81]
	Erlotinib	1st	2004	EGFR-mutant NSCLC, pancreatic cancer	Moderate	[82,83]
	Gefitinib	1st	2003	EGFR-mutant NSCLC	Moderate	[83,84]
ALK	Crizotinib	1st	2011	ALK fusion-positive NSCLC	Low	[83,85,86,87]
	Ceritinib	2nd	2014	ALK fusion-positive NSCLC	Moderate/high	[83,85,86,87]
	Alectinib	2nd	2015	ALK fusion-positive NSCLC	High	[83,85,86,87]
	Brigatinib	2nd	2017	ALK fusion-positive NSCLC	Low/Moderate	[85,86,87]
	Ensartinib	2nd	2024	ALK fusion-positive NSCLC	Low/Moderate	[87]
	Lorlatinib	3rd	2018	ALK fusion-positive NSCLC, ROS1 fusion-positive NSCLC	Very high	[83,85,86,87]

mAb, monoclonal antibody; NSCLC, non–small cell lung cancer; ROS1, c-ros oncogene 1; NTRK, neurotrophic tyrosine receptor kinase; MTC, medullary thyroid carcinoma; RCC, renal cell carcinoma; GBM, glioblastoma multiforme; HNSCC, head and neck squamous cell carcinoma; CNS, central nervous system.

non-transcriptional mechanism [53,67]. According to the currently proposed mechanism, aberration in ALK, which is known to drive MAPKs signaling pathways, may contribute to the generation of neuropathic pain (Fig. 3). Improved pain outcomes are therefore considered as on-target manifestation of ALK inhibitors. Preclinical studies have shown that injecting Augα for targeting dorsal root ganglion (DRG) and spinal cord neurons induce ALK activation, which leads to hyperalgesia in mice. Pharmacological inhibition of the Augα-ALK signaling axis crizotinib or lorlatinib in the preclinical mouse model effectively prevents nociceptor hyperexcitability and suppressed persistent pain associated with inflammation or nerve injury [68]. Meta-analysis of clinical trials has revealed that crizotinib and ceritinib significantly improve pain symptoms in adult patients with ALK-positive NSCLC receiving ALK inhibitors [69].

7. Conclusion

The integration of oncology and neuroscience has revealed that targeted kinase inhibitors, though originally developed to suppress oncogenic signaling, also in-

fluence neural physiology in profound and sometimes unexpected ways. Many of the kinases targeted in cancer—such as Trk, RET, VEGF/VEGFR, EGFR, and ALK—play indispensable roles in neuronal development, synaptic signaling, and neurotrophic communication under physiological conditions [4,12,16,40] (Table 1, Ref. [6,13,18,22,25,30,39,48,63,67,68]).

In malignancy, these same pathways are pathologically hijacked through chromosomal rearrangements, gene amplifications, or activating mutations, which transform normal signaling into oncogenic drivers. Pharmacologic inhibition of such pathways therefore carries dual consequences: Tumor suppression on and neural perturbation.

While several factors influence drug concentrations within the CNS, the BBB plays a dominant role in controlling the entry of most therapeutic agents into the CNS. BBB is a highly selective and semipermeable barrier that allow the passage of essential nutrient and gases and protect the brain from toxins and pathogens in blood. Sufficient drug delivery to the brain is therefore believed to be associated with higher therapeutic efficacy as well as increasing the on-target effectiveness to the CNS. Therefore, there was an effort to develop various emerging strategies that can increase the permeability regulation and BBB crossing of the small molecule inhibitors [70,71]. The CNS penetration ability of the kinase inhibitors discussed in this paper is shown in Table 2 (Ref. [72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87]).

Among the neurological manifestations of kinase inhibition, pain modulation has emerged as a particularly illustrative example. Trk inhibitors demonstrate how blocking neurotrophin signaling can disrupt pain homeostasis, leading to withdrawal pain upon treatment cessation [17,88]. Preclinical investigations suggest that the pharmacological inhibition of the Augα/ALK signaling can reduce nociceptor hyperexcitability and attenuate neuropathic pain, although the precise downstream signaling pathways remain incompletely defined [68]. VEGF inhibition, exemplified by bevacizumab, has provided consistent pain-relieving benefits in patients with nerve-sheath tumors, including neurofibromas and schwannomas [38,39]. EGFR inhibitors have shown analgesic effects, particularly in neuropathic and cancer-related pain, likely through suppressing aberrant neurotrophic and inflammatory signaling [49,50].

Another example of neural involvement is seen in kinase inhibitor–induced weight gain, which, in certain cases such as TrkB, ALK or RET inhibition, arises from interference with distinct neurotrophic circuits governing appetite and energy balance. TrkB inhibition disrupts hypothalamic BDNF-TrkB signaling, a pathway critical for regulating satiety and energy expenditure, leading to hyperphagia and weight gain [13]. It appears that ALK inhibition exerts its effect on the Augα–ALK pathway, which plays a pivotal role in regulating metabolic processes within the hypothalamus and, consequently, the control of body weight [63]. Nevertheless, the precise mechanism by which ALK inhibitors induce weight gain remains to be fully elucidated. One clinical study has indicated that weight gain may be a consequence of the off-target effect of other RTKs, particularly TrkB, in certain agents, including alectinib and lorlatinib [22]. In contrast, RET inhibition interferes with the GDF15–GFRAL–RET axis in the hindbrain, which normally mediates appetite suppression during metabolic stress [30]. Together, these mechanisms suggest that what has conventionally been regarded as a metabolic adverse effect may instead represent a neurologically mediated manifestation of kinase pathway inhibition.

The field of cancer neuroscience continues to evolve, emphasizing that neurological outcomes should not be regarded solely as side effects but as integral biological consequences of pathway modulation. Comprehensive characterization of kinase-dependent neuronal processes will allow oncologists and neuroscientists to jointly exploit these mechanisms—mitigating neurologic toxicity while identifying novel therapeutic strategies for pain, cancer cachexia, and neurodegeneration.

Author Contributions

SYH conceived and wrote the manuscript, performed the literature search, and integrated molecular and clinical findings. TLT designed and created the figures illustrating kinase–neural interactions. Both contributed to editorial changes in the manuscript. Both authors reviewed and approved the final manuscript. Both have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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