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Research Paper

NYX-2925, A NOVEL, NON-OPIOID, SMALL-MOLECULE MODULATOR OF THE *N*-METHYL-D-ASPARTATE RECEPTOR (NMDAR), DEMONSTRATES POTENTIAL TO TREAT CHRONIC, SUPRASPINAL CENTRALIZED PAIN CONDITIONS☆

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ABSTRACT

Pain is both a sensory and emotional experience, which serves an adaptive purpose by protecting the body from prolonged and repeated tissue damage. However, the presence of chronic pain can transition to a maladaptive state leading to life-long suffering and is currently a health care burden due to limited effective pharmacotherapies. This review aims to describe the transition to a chronic pain state and the central changes (supraspinal) that occur to prolong the unpleasant feelings of pain. In addition to alterations in the periphery and spinal cord, regions in the brain involved in pain perception as well as executive functioning undergo changes in activity that reflect painful experiences from nonpainful stimuli. These pathological changes to the nociceptive system are partly mediated by expression and activity patterns of *N*-methyl-D-aspartate receptors (NMDARs), which process and propagate excitatory transmission in response to glutamate release in the periphery, spinal cord, and brain and have an important role in learning and memory. Importantly, NMDARs have been implicated in the cellular mechanisms responsible for the maintenance of the centralized, chronic pain state within the brain. Here we present preclinical data describing the analgesic effects of NYX-2925, a novel NDMAR modulator in a variety of neuropathic pain rodent models. These data provide compelling evidence that targeting brain regions responsible for the affective and cognitive aspects of pain may alleviate chronic pain and serve as a novel mechanism to treat chronic pain conditions, including those refractory to current analgesics.

1. INTRODUCTION

Neuropathic pain is common and complex in terms of diagnosis and subsequent treatment: 7–8% of the population suffers from some form of neuropathic pain [1–3]. However, neuropathic pain itself does not define a diagnosis but rather describes a clinical syndrome with various signs and symptoms common to several diseases and lesions involving the peripheral (PNS) and central nervous systems (CNS), stemming from a variety of etiologies [4]. As a result, there are several ways in which neuropathic pain can be defined. For our purposes, we will make a clear distinction between 1) peripheral pain disorders caused by insult to the PNS; 2) central pain disorders involving damage to the brain or spinal cord; and 3) the transition to chronic, centralized supraspinal-mediated pain that originates from an initial injury or insult that ultimately also leads to long-term changes to brain circuitry. In the latter, long-term changes can result in increased sensitivity to painful stimuli (hyperalgesia), or painful responses to normally nonpainful stimuli (allodynia), along with other life-altering comorbidities, such as sleep disturbances, anxiety, and depression. It is this chronic, supraspinal, centralized neuropathic pain that is the least understood mechanistically and potentially presents the greatest unmet need for patients regarding the management of their chronic pain.

In the process of normal pain transmission, pain is perceived following injury or insult to the nervous system. Acute pain transmission involves an initial transduction of noxious stimuli via $\alpha\delta$- and C-fiber nociceptors of dorsal root ganglion neurons [5] followed by complex signaling within the dorsal horn of the spinal cord [6,7]: it is here that the primary afferent release of glutamate can lead to hyperexcitation by increasing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and *N*-methyl-D-aspartate receptor (NMDAR) activity in the dorsal horn of the spinal cord, resulting in central sensitization and thus beginning the early phases of chronic pain manifestation [8–11]. Normally, ascending projections from the dorsal horn not only relay nociceptive information to regions

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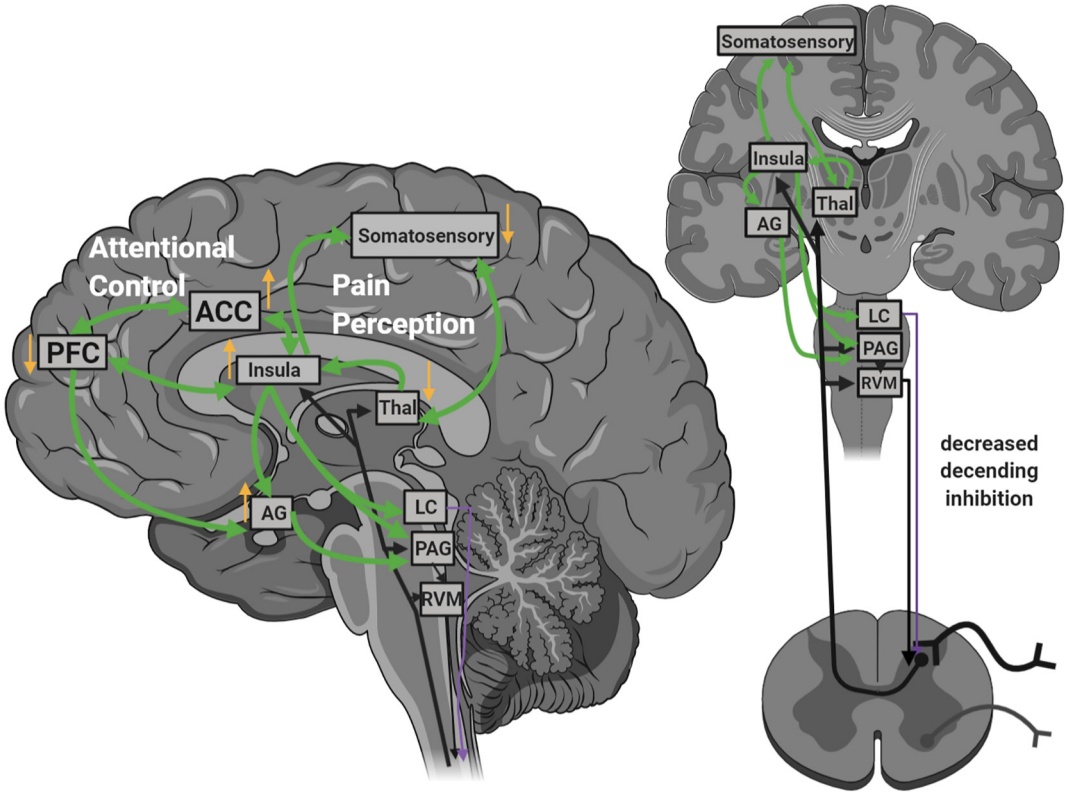

Figure 1. CNS circuitry involved in the centralization of pain. As chronic pain becomes centralized, the development of maladaptive plasticity can lead to decreased glutamatergic activity within those circuits that comprise attention and pain perception networks (green arrows). Additionally, decreased descending inhibition is observed in the spinal cord with reduced levels of norepinephrine from the LC (purple arrows) and RVM, respectively. Directions of changes in glutamate levels, resulting in hyperactivation or hypoactivation, are indicated by yellow arrows next to cortical regions. Abbreviations: PFC = prefrontal cortex; ACC = anterior cingulate cortex; Thal = thalamus; AG = amygdala; LC = locus coeruleus; PAG = periaqueductal gray; RVM = retroventral medula.

of the brain involved in sensory processing but also relay the affective/attentional components of pain [12–14]. Changes in activity within these specific brain regions and circuits account for the conscious recognition of pain [15–17]. In the case of chronic, supraspinal, centralized pain, increased glutamate levels and hyperactivation persist long after the end of the initial insult or injury and are specifically seen in the anterior cingulate [18], insula [19,20], and thalamic [21] regions (Figure 1). Interestingly, in chronic pain, increased glutamatergic receptor activation is not seen within all regions involved in the attention to, and perception of, pain; rather, within specific brain regions like the medial prefrontal (mPFC) [12,13,22] and somatosensory [23] cortices, there is typically glutamatergic hypoactivation (Figure 1). Cortical regions can also modulate descending inhibition pathways originating in the locus coeruleus and retroventral medulla that allow for extensive modulation of neurons within the dorsal horn [24]: under normal conditions, those modulating signals lead to the attenuation and eventual resolution of pain. However, in some cases, chronic pain is perceived long after the initial insult, without resolution, due to increased activation of ascending pain processing networks and decreased descending inhibition (Figure 1). When pain persists for months or years after an expected healing period, it is maladaptive and no longer protective. This suggests that the body is unable to restore normal physiological functions to reinstate initial homeostatic balance but rather acquires an enhanced, persistent, and pathological state within the CNS.

Current first-line therapeutics for chronic neuropathic pain include gabapentinoids and antidepressants, and although opioids are less effective against chronic pain in animal models [25–27] and in the clinic [28–32], they are still prescribed to approximately 20% of patients presenting with chronic pain [33,34]. Binding to the mu-opioid receptor is thought to account for the analgesic effect of opioids [35]; over time, however, opioid use is associated with analgesic tolerance and the development of hyperalgesia [36]. These findings, combined with the high abuse liability of opioids [37,38], necessitates the development of treatments focused specifically on chronic pain. The most clinically prescribed treatments for neuropathic pain are the gabapentinoids, primarily gabapentin and pregabalin. Although both compounds bind the $\alpha 2\delta$-1 subunit of voltage-dependent calcium channels [39], the treatment of neuropathic pain is in part a result of decreased trafficking of NMDARs to the cell surface [40], resulting in decreased activity within hyperactivated regions of the CNS and a corresponding reduction in chronic pain. Unfortunately, more than half of patients prescribed gabapentin do not report adequate pain relief, perhaps describing cases where chronic, supraspinal, centralized pain is driven by NMDAR hypofunction [41]. Additionally, gabapentinoids have some abuse liability [42–45], particularly when taken with opioids for chronic pain [46]. The use of antidepressants, both tricyclics and serotonin and norepinephrine reuptake inhibitors (SNRIs), likely involves restoring the inhibitory balance of the descending pain inhibition pathways and increasing the levels of norepinephrine and serotonin in the dorsal horn of the spinal cord, ultimately resulting in pain relief [47–50]. For example, amitriptyline showed some efficacy in treating painful diabetic peripheral neuropathy (DPN) independent of whether the pain was accompanied by depression [51] and was later expanded for use in postherpetic neuralgia [52–54] and fibromyalgia [55–57]. Duloxetine, an SNRI, is also currently approved for use in managing DPN and fibromyalgia [58–60]. Adverse effects of SNRIs include nausea, headache, fatigue, tachycardia, and hypertension.

Importantly, current therapeutics do not adequately treat all chronic neuropathic pain patients [61] and do not seek to directly address a significant component of chronic, centralized pain—what Apkarian and colleagues describe as the inability to extinguish pain memory induced by an initial inciting injury [62]. This memory-induced supraspinal-mediated centralized pain is hypothesized to occur largely because of pain-induced NMDAR hypofunction, particularly in brain regions like the mPFC. In the present review, we will summarize how the preclinical development of

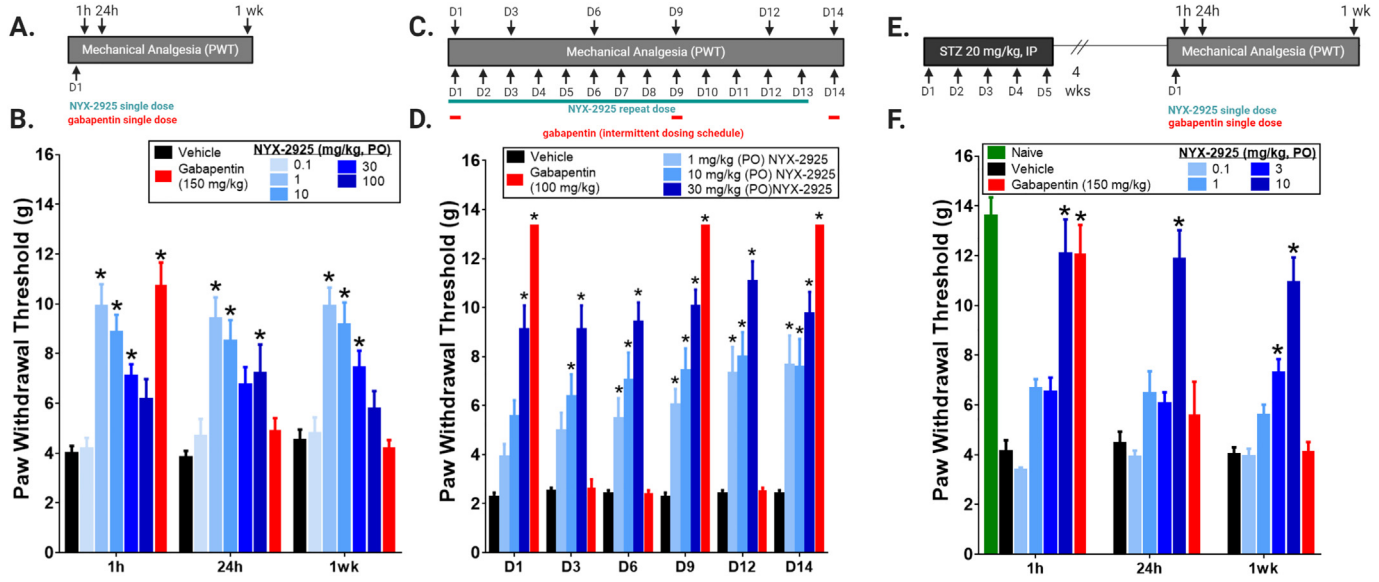

Figure 2. Acute and repeated dosing of NYX-2925 treats CCI-induced neuropathic pain, and acute dosing treats STZ-induced neuropathic pain. (A) Rats were dosed once with NYX-2925 or gabapentin (D1), and (B) a single dose of NYX-2925 alleviated neuropathic pain for up to 1 week. (C) Rats were dosed daily with NYX-2925 or intermittently with gabapentin, and (D) repeated dosing of NYX-2925 had sustained analgesic effects, whereas gabapentin only produced an analgesic effect at 1 h postdosing. (E) Rats were administered STZ to allow for the development of diabetes-mediated neuropathy, followed by a single dose of NYX-2925 or gabapentin. (F) A single dose of NYX-2925 produced analgesic effects for up to 1 week, whereas a single dose of gabapentin was only effective at 1 h. Figure adapted with permission [82].

NYX-2925, a glutamate co-ligand of the NMDAR, has led to the identification of a potential novel therapeutic target for the alleviation of chronic, supraspinal, centralized pain conditions.

1.1. The Preclinical Development of NYX-2925

NYX-2925 was developed from a platform of spiro-β-lactam compounds based on the dipyrrolidine structural features of rapastinel (GLYX-13) with a unique pharmacological profile. NYX-2925 acts as a glutamate co-ligand to positively modulate the NMDAR that binds all 4 NMDAR2A-D subtypes and preferentially binds NMDAR2B [63]. Importantly, NYX-2925 facilitates NMDAR channel opening in the absence of glycine, suggesting that it is not a canonical partial agonist or a positive allosteric modulator of the glycine site [63]. NMDARs have been a target for the treatment of chronic neuropathic pain for more than 2 decades; more specifically, NMDAR2B is thought to have an important role in the development and treatment of neuropathic pain. In the dorsal horn of the spinal cord, where NMDAR hyperactivation is thought to be essential for central sensitization in chronic pain conditions, NMDAR2B antagonists are effective in treating mechanical allodynia following spinal cord injury [7,64]. In contrast to the role of NMDAR in centralized pain at the level of the spinal cord, direct injection of the NMDAR partial agonist D-cycloserine into the mPFC, where NMDAR2B levels were actually decreased with chronic pain, reversed mechanical allodynia following spinal nerve injury [65]. These findings indicated that NMDAR positive modulation could alleviate pain and led to the selection of chronic, supraspinal-mediated centralized pain as a potential therapeutic area for NYX-2925.

Chronic, supraspinal, centralized pain induces plastic changes that lead to alterations in pain circuits, rewiring of resting-state networks, and maladaptive structural and neuroplastic reorganization of the cortex [62,66–72]. In fact, those changes can be used as a predictive tool for the transition to centralized pain from acute to chronic [66]. Importantly, changes within networks do not lead to all brain regions within those circuits being hyperactivated; for example, the mPFC is clearly hypoactivated [12,13], with reduced functional connectivity to other regions like the hippocampus [73], periaqueductal gray [74], and thalamus, and changes in connectivity to those regions are highly correlated with perceived pain intensity [75]. Importantly, in naive rats, NYX-2925 facilitates NMDAR-mediated current and NMDAR-dependent long term potentiation (LTP) while decreasing long-term depression at Schaffer collateral synapses in CA1 of the hippocampus and also facilitates NMDAR-dependent LTP in layer V of the mPFC [63]. The ability to facilitate NMDAR-dependent LTP in those regions further supports the development of NYX-2925 for the treatment of chronic, supraspinal, centralized neuropathic pain.

NMDARs in the mPFC are specifically implicated in the etiology of chronic pain, in particular, the affective and cognitive components [15–17,65,66]. Morphological, structural, and functional reorganization occurs in the mPFC with the centralization of chronic pain [12–15,76,77]. NYX-2925 enhances positive emotional learning (PEL) [63], a measure of improved positive affect in rodents that is regulated by NMDAR2B receptors in the mPFC [78]. Additionally, chronic pain patients can have cognitive deficits [79–81], and unfortunately, gabapentinoids exacerbate these deficits [41]. The nootropic properties of NYX-2925 [63] and the enhancement of PEL in the chronic constriction injury (CCI) rodent model specifically [82,83], make it attractive as a potential therapeutic for the treatment of chronic, supraspinal, centralized neuropathic pain. Based on the above findings, the efficacy of NYX-2925 was specifically evaluated in multiple rodent models of chronic, supraspinal, centralized neuropathic pain.

1.2. NYX-2925 Alleviates Neuropathic Pain in the Chronic Constriction Injury Rodent Model

The potential therapeutic effect of NYX-2925 was first evaluated in the rat CCI model, where the sciatic nerve is loosely constricted with a ligature resulting in chronic, centralized neuropathic pain [82]. Thermal and mechanical hyperalgesia was assessed 2–3 weeks post-CCI when chronic pain is thought to be centralized, including changes to the brain [84]. Oral administration of NYX-2925 (10 mg/kg, PO) attenuates thermal hyperalgesia measured by the Hargreaves plantar test at 1 h postdosing, as revealed by significantly higher paw withdrawal latencies compared to CCI vehicle-treated rats. Sciatic nerve injury can result in variations in hind paw temperature [85], and heat applied to the injured paw can elicit a pain response [86]. Thermal hypersensitivity is observed in humans with chronic neuropathic pain, including some DPN patients [87] and frequently in those with fibromyalgia [88,89].

More extensive studies focused on the effect of NYX-2925 on mechanical allodynia where CCI rats were orally dosed with a single dose of vehicle

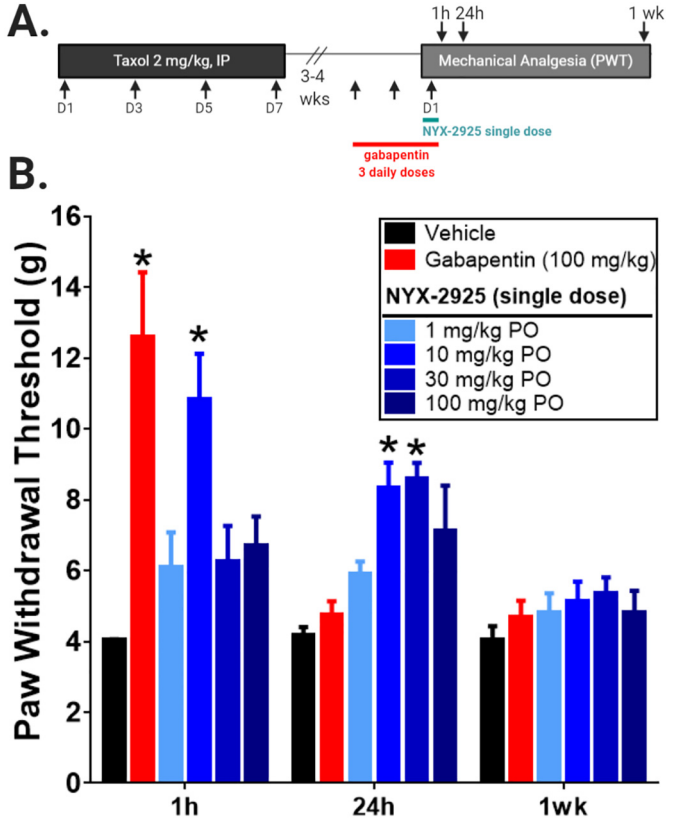

Figure 3. An acute dose of 10 mg/kg (PO) NYX-2925 treats paclitaxel-induced neuropathic pain for 24 h. (A) Rats were dosed with paclitaxel (2 mg/kg in a volume of 1 mL/kg IP, QAD, for an 8-mg/kg cumulative dose) prior to a 3-week waiting period to allow for paclitaxel-induced neuropathic pain to manifest (based on observed mechanical hypersensitivity as measured by von Frey filaments [82]). (B) Three daily doses of gabapentin (100 mg/kg, PO) only relieved the neuropathic pain for 1 h after the last dose, and a single dose of NYX-2925 (10 mg/kg, PO) alleviated neuropathic pain for at least 24 h (compounds were given in volumes of 2 mL/kg, PO in 0.5% CMC/water).

or NYX-2925 (0.1–100 mg/kg), and paw withdrawal thresholds were measured using Von Frey filaments at 1 h, 24 h, and 1 week post oral administration [82]. NYX-2925 has robust, rapid, and long-lasting analgesic effects at dose levels of 1, 10, and 30 mg/kg. Interestingly, 100 mg/kg (PO) NYX-2925 does not have analgesic effects at 1 and 24 h, which is suggestive of an inverted-U dose response, where higher doses have reduced effects (Figure 2). Although not fully understood, it may be that NYX-2925 at higher doses activates adaptive responses through complex cellular signaling and negative feedback mechanisms that ultimately limits NMDAR activation and trafficking, which is fairly common in biological systems with complex feedback mechanisms, such as receptor dynamics at the synapse. Although some areas of the CNS have increased glutamate release and are hyperactivated in chronic, centralized neuropathic pain (Figure 1), NYX-2925 does not cause hyperalgesia. Known negative feedback mechanisms that control NMDAR function have not been specifically evaluated with NYX-2925 in rodent models, but the initiation of signaling pathways that restore homeostatic balance might explain the lack of either analgesic or hyperalgesic effects at the highest doses of NYX-2925.

It has been suggested that NMDAR2B activation contributes to analgesic tolerance with morphine [90]. Given that NYX-2925 binds NMDAR2B [63], repeated dosing of NYX-2925 was evaluated to specifically look for tachyphylaxis [82]. The analgesic effect of NYX-2925 is maintained with daily administration of NYX-2925 (1, 10, and 30 mg/kg, PO) for 13 days and suggests that repeated dosing of NYX-2925 does not result in diminished analgesic efficacy of a therapeutic dose in the rodent (Figure 2). The maintenance of an effect with repeated dosing in rodent models suggests that NYX-2925 may be suitable for long-term use in the treatment of chronic, supraspinal, centralized neuropathic pain in patients.

1.3. NYX-2925 Alleviates Neuropathic Pain in the Streptozotocin-Induced Rodent Model of DPN

To date, the streptozotocin (STZ)-induced DPN rodent model is the most commonly used preclinical model to evaluate potential novel therapeutics: STZ is administered systemically to induce diabetes, and left untreated, the rats develop chronic neuropathy in as little as 2–4 weeks [91,92]. In humans, 15–20% of diabetic patients develop chronic neuropathy [92]. Patients with painful DPN are likely a heterogenous population, and a better understanding of the patient population is required to select the right treatment for the right patient. For example, pregabalin can reduce pain by at least 50% in only 40% of DPN patients, and it has proved difficult to identify those likely to benefit from treatment [93].

NYX-2925 was evaluated in the STZ-induced diabetic neuropathy rodent model after the establishment of mechanical hypersensitivity, as measured by paw withdrawal threshold [82,91]. NYX-2925 significantly reversed mechanical allodynia at the 1-h, 24-h, and 1-week time points [82]. After a single dose, NYX-2925 (10 mg/kg, PO) produced significant analgesia at 1 h, 24 h, and 1 week as compared to the vehicle control group. A lower dose of NYX-2925 (3 mg/kg) also produced significant analgesia at the 1-week time point; however, NYX-2925 at the lowest dose (0.1 mg/kg) tested was not analgesic at any time point. Like the duration

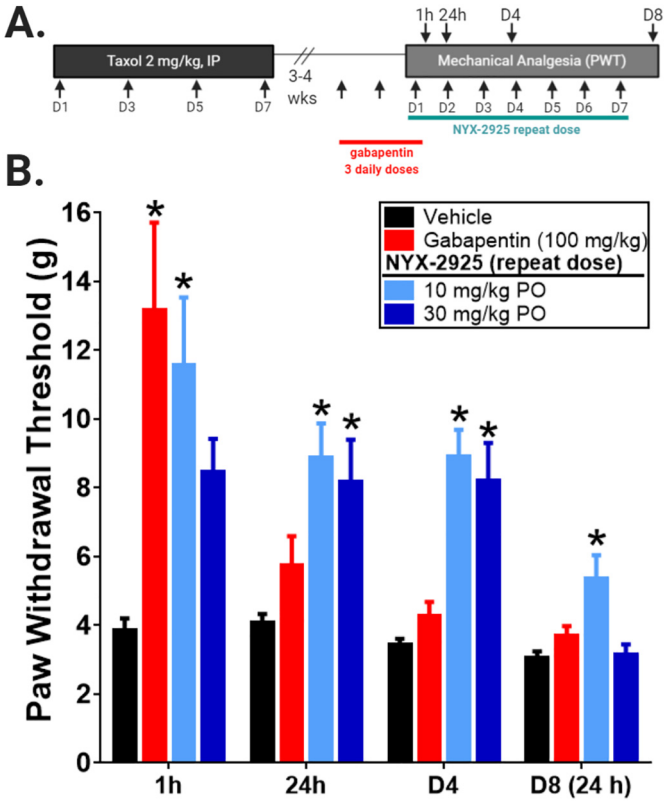

Figure 4. Repeat dosing of 10 mg/kg (PO) NYX-2925 treats paclitaxel-induced neuropathic pain for at least a week. (A) Rats were dosed with paclitaxel (2 mg/kg in a volume of 1 mL/kg IP, QAD, for an 8-mg/kg cumulative dose) prior to a 3-week waiting period to allow for paclitaxel-induced neuropathic pain to manifest (based on observed mechanical hypersensitivity, as measured by von Frey filaments [82]). (B) Three daily doses of gabapentin (100 mg/kg, PO) only relieved the neuropathic pain for 1 h after the last dose, and repeat dosing of NYX-2925 (1 mg/kg, PO, XD) alleviated neuropathic pain for a week, even 24 h after the last dose on day 8 (compounds were given in volumes of 2 mL/kg, PO, in 0.5% CMC/water).

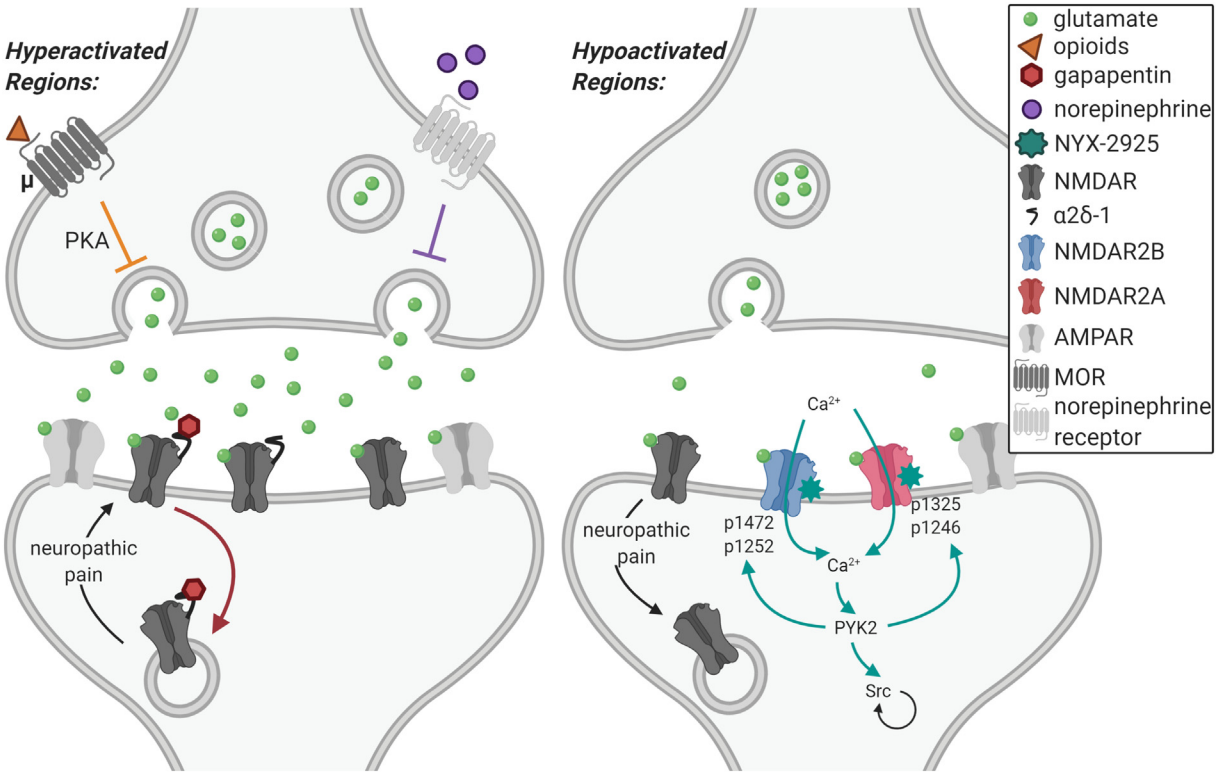

Figure 5. Proposed mechanism of action for NYX-2925 in the alleviation of neuropathic pain. Opioids and gabapentinoids are thought to work by reducing glutamate release and NMDAR surface expression in hyperactivated regions, whereas NYX-2925 is thought to increase NMDAR activation and surface levels in hypoactivated regions without increasing activity in hyperactivated regions.

of efficacy in the CCI model, a single dose of gabapentin (150 mg/kg, PO) produced analgesic activity only at 1 h (Figure 2).

Although the exact mechanism by which diabetic patients go on to develop neuropathic pain is unknown, it does involve changes in the periphery, dorsal horn of the spinal cord, and cortical regions. NMDAR hyperfunction in the dorsal horn of the spinal cord [94,95] and hypofunction in some cortical regions, like the hippocampus [96] and mPFC [97], are associated with mechanical hyperalgesia in diabetes. NMDAR agonists also improve STZ-induced learning impairments [98] and may therefore be capable of improving neuropathic pain scores through learned pain tolerance [97].

1.4. NYX-2925 Alleviates Neuropathic Pain in the Paclitaxel-Induced Rodent Model of CIPN

Anticancer therapeutics significantly prolong the lives of cancer patients, but some of these drugs have detrimental adverse effect profiles which serve to both encourage early discontinuation, thus limiting their efficacy, as well as negatively impact a patient's quality of life once the therapy has ceased (either due to a cancer-free diagnosis or voluntary withdrawal). A major dose-limiting adverse effect of several first-line chemotherapeutic agents is termed *chemotherapy-induced painful neuropathy* (CIPN) [99–102]. CIPN patients present with a sensory dominant neuropathy and experience paresthesias, dysesthesias, numbness, and loss of dexterity primarily in the fingers and toes, which is directly linked to the treatment schedule [99,102–104]. The neurotoxic effects to the PNS can appear during, or after concluding, the administration of cancer therapeutics and can either resolve or, unfortunately, progress to chronic neuropathy [105–107].

Although CIPN is common among the various classes of neoplastic agents, the incidence of CIPN from cancer treatment with taxanes (including paclitaxel, docetaxel, and cabazitaxel) can range from 11% to 87%, with the highest rates following the use of paclitaxel [103,108,109]. There are limited treatments for CIPN: most prescribed therapeutics are those used to treat chronic, noncancer pain [110]. Gabapentin is ineffective [111], and other studies on concomitant use of gabapentin and opioids only evaluated improvements in pain within weeks of final chemotherapeutic treatment [112], a time point when some patients naturally recover from CIPN [113]. A recent placebo-controlled study of duloxetine indicated that those who developed CIPN from the platinating agents received greater benefit than those who were treated with taxanes [114], suggesting some heterogeneity of pain treatment even within the CIPN population. NYX-2925 was evaluated in a rat model of CIPN using the taxane paclitaxel.

In rodent models, it is standard to deliver paclitaxel systemically via intravenous or intraperitoneal routes [100,115,116], and similar to the CCI and DPN models, the development of chronic pain is monitored using evoked pain measures. In rodent models, as in the clinic, the cumulative dose influences the degree of damage observed in the PNS [117–119]. In rats, we observed mechanical allodynia 3–4 weeks following a low dose of paclitaxel (8 mg/kg cumulative dose) [116], which is typical for most rodent models where neuropathy develops and persists for months after treatment [116,117,120,121]. Unlike gabapentin, a single, acute dose of 10 mg/kg NYX-2925 (PO) was able to reverse the mechanical allodynia as measured with von Frey filaments for up to 24 h following dosing (Figure 3). Gabapentin was dosed for 3 consecutive days [122] and did not have a sustained effect in this model and, importantly, has also not shown efficacy in the clinical setting [111]. Additionally, rats that were dosed with 30 mg/kg NYX-2925 (PO), although not analgesic at the 1-h time point, demonstrated significant analgesia as measured by decreased tactile sensitivity to von Frey filaments 24 h after dosing when gabapentin was no longer effective. The long-lasting analgesic effects after a single dose of NYX-2925 (up to 24 h) in a rat CIPN model may translate to meaningful improvements in patients' overall pain scores and quality of life.

In a repeat dosing paradigm, the long-lasting analgesic effects of NYX-2925 became apparent when the 2 most efficacious doses in the acute paclitaxel study were evaluated (Figure 4). NYX-2925 at a dose of 10 mg/kg (PO) resulted in significant analgesia as measured by von Frey filaments

for up to 24 h following the last of 7 daily doses. Daily treatment of rats with CIPN with 30 mg/kg NYX-2925 (PO) for 7 days was not as immediately effective or as long-lasting when compared to the maximally efficacious dose of 10 mg/kg (PO) NYX-2925, which was both rapid-acting and long-lasting in the treatment of neuropathic pain symptoms as a result of paclitaxel exposure in a rodent model. NYX-2925 may be a potential therapeutic candidate for the treatment of CIPN, demonstrating both rapid and long-lasting analgesic effects in a preclinical model.

1.5. NYX-2925 Alleviates Chronic, Centralized Neuropathic Pain via an NMDAR-Dependent Mechanism

The mechanisms by which current first-line therapeutics are thought to alleviate neuropathic pain are largely mediated through the spinal cord. In the process of normal pain transmission, norepinephrine and serotonin are inhibitory neurotransmitters within the descending pain pathway that suppress pain at the level of the spinal cord [123]. Following central synaptic changes associated with chronic pain, the descending pain pathway becomes less inhibitory (less analgesic) due to the diminished actions of serotonin and norepinephrine (spinal and supraspinal), further exacerbating the cumulative effects of persistent stimulation of sensory afferents resulting from damage to the PNS [124]. Increasing the levels of norepinephrine and serotonin in the synaptic clefts within these pathways as a result of tricyclic antidepressants and SNRI exposure restores the inhibitory balance of the descending pain pathway, resulting in pain relief at the level of the spinal cord (Figure 5). Gabapentin, by binding to the $\alpha 2\delta$-1 subunit of voltage-dependent calcium channels, inhibits trafficking of $\alpha 2\delta$-1 subunit-bound NMDARs in the rat dorsal horn to reduce the high NMDAR levels and ultimately alleviate chronic pain [39,125], likely by limiting NMDAR-mediated PKC and ERK1/2 activation [126,127] (Figure 5). Intrathecal injection of gabapentin is sufficient to produce analgesia [41]; however, whether gabapentinoids also act within altered brain circuits to alleviate neuropathic pain is unclear [41,128].

The mechanism by which NYX-2925 alleviates chronic, supraspinal, centralized neuropathic pain is clearly a result of modulating NMDAR-mediated activity in the mPFC [82]. Unlike gabapentin and duloxetine, intrathecal injection of NYX-2925 across a wide concentration range (0.01–1000 μg) does not alleviate mechanical allodynia [82]; only the direct injection of NYX-2925 into the mPFC alleviates chronic, supraspinal, centralized neuropathic pain. An important limitation of these studies is the potential for still even higher doses of NYX-2925 to produce hyperalgesia after direct spinal administration; however, the wide concentration range tested based on the levels of NYX-2925 that reach the spinal cord after oral administration [82], and the known role of NMDAR modulation in homeostatic balance support the idea that NYX-2925 did not cause further hyperactivation of the NMDAR in the dorsal horn. As a glutamate co-agonist of the NMDAR, NYX-2925 likely increases activity in the mPFC, thereby restoring the hypoactive region to normal levels of activity to alleviate a cortical-driven centralized chronic pain response [12,82], and, importantly, may not indiscriminately increase NMDAR-mediated activity, causing further hyperactivation of the NMDAR in the dorsal horn. Thus, NYX-2925 may be capable of selectively increasing NMDAR activity in hypoactive regions.

To further understand the molecular basis for the analgesic actions of NYX-2925 in the mPFC using the CCI model, we evaluated the molecular signaling changes underlying the NMDAR-dependent plasticity in the mPFC of CCI rats and the capability of NYX-2925 administration to reverse those changes [129]. Oral administration of NYX-2925 reversed CCI-induced decreases in 2 Src phosphorylation sites on both GluN2A (Tyr1246 and Tyr1325) and GluN2B (Tyr1472 and Tyr1252) in the mPFC. Moreover, phosphorylated Src levels (Tyr416) were also reduced at the synapse with CCI and recovered to sham levels with NYX-2925 treatment [129]. To demonstrate the reliance of the analgesic effect of NYX-2925 on the restoration of Src activation in the mPFC, a nonselective Src family kinase activation inhibitor (PP2) and a specific Src activation inhibitor (Compound 4, KB SRC 4) were directly injected into the mPFC: both PP2 and Compound 4 inhibited the analgesic effect of orally dosed NYX-2925 for up to 1 week in CCI rats. Direct injection of the more specific inhibitor (Compound 4) in the mPFC also prevented the NYX-2925–driven recovery of Src phosphorylation in CCI rats [129], further supporting the hypothesis that NYX-2925 administration restores NMDAR-mediated signaling via Src activation in the mPFC to ultimately produce analgesia and treat chronic, supraspinal, centralized neuropathic pain (Figure 5).

2. CONCLUSIONS

The development of more effective therapeutics to treat chronic, centralized neuropathic pain is limited by the poor phenotypic profiling of the patient population. In addition, the underlying mechanisms of neuroplasticity in the CNS responsible for the development of chronic pain are complex, and multiple mechanisms are likely involved. The NMDAR clearly plays a key role in the development of chronic, centralized neuropathic pain based on the ability of NYX-2925, an NMDAR modulator, to reverse allodynia associated with nerve injury, diabetes, and cancer therapeutics. Although additional studies examining the NYX-2925 mechanism of action are still needed, including the specific examination of downstream effects on other glutamatergic receptors like AMPAR, the data reviewed here suggest that NYX-2925 is likely to have the greatest therapeutic potential when a constant barrage of painful signals originating in the dorsal horn causes significant and long-lasting changes to brain function via synaptic plasticity processes that ultimately result in hypofunction of the mPFC.

Importantly, in Phase I studies, NYX-2925 was shown to be orally bioavailable and CNS penetrant, with dose-proportionate PK and minimal accumulation after 7 daily doses [130]. It also had high safety and tolerability even at doses 5–10 times the anticipated therapeutic dose, with no serious or severe adverse events, with no safety or tolerability issues, and, importantly, without the dissociative or ECG adverse effect characteristic of other NMDAR modulators [130]. NYX-2925 is currently in Phase II clinical development for painful DPN and fibromyalgia. The potential for a novel therapeutic to target abnormal NMDAR activity with minimal impact on normal physiological function could ultimately lead to better pain management without serious adverse effects.

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Conflict of Interest

J.M. Gajda, M. Asiedu, and A.L. Barth are current employees and have stock/ownership in Aptinyx, Inc.

G. Morrison, J.A. Dunning, and N. Ghoreishi-Haack are former employees and may retain stock/ownership in Aptinyx, Inc.

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