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REVIEW

Understanding of Spinal Wide Dynamic Range Neurons and Their Modulation on Pathological Pain

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Abstract: The spinal dorsal horn (SDH) transmits sensory information from the periphery to the brain. Wide dynamic range (WDR) neurons within this relay site play a critical role in modulating and integrating peripheral sensory inputs, as well as the process of central sensitization during pathological pain. This group of spinal multi-receptive neurons has attracted considerable attention in pain research due to their capabilities for encoding the location and intensity of nociception. Meanwhile, transmission, processing, and modulation of incoming afferent information in WDR neurons also establish the underlying basis for investigating the integration of acupuncture and pain signals. This review aims to provide a comprehensive examination of the distinctive features of WDR neurons and their involvement in pain. Specifically, we will examine the regulation of diverse supraspinal nuclei on these neurons and analyze their potential in elucidating the mechanisms of acupuncture analgesia.

Keywords: WDR neurons, spinal dorsal horn, pain, central sensitization, receptive fields, DNIC, acupuncture analgesia

Introduction

Spinal dorsal horn (SDH) serves as the initial relay station for transmitting sensory afferents from the peripheral to the central nervous system. Neurons residing in the SDH are classified into three types based on their response to specific sensory inputs. The low-threshold mechanoreceptor (LTM) neurons are activated by innocuous stimuli, whereas the high-threshold (HT) neurons react to noxious inputs. Additionally, the wide dynamic range (WDR) neurons, also known as the convergent neurons, or multi-receptive neurons, can be activated by both light and strong stimuli.[1] WDR neurons are believed to be a class of modulatory neurons, where diverse peripheral afferents encounter and undergo modulation within this group of spinal neuron population.

The gate control theory of pain, proposed by Melzack and Wall in 1965, posits a viewpoint of central summation of somatosensory information from all kinds of primary afferents.[2] This theory holds that the large- and small-diameter afferents converge on SDH neurons to modulate pain. The capacity of WDR neurons to receive extensive types of afferent sensory signals makes them ideal platforms for the gate control. Due to their significant roles in encoding and modulating afferent information, WDR neurons have been extensively studied in examining pain processing in the central nervous system.[3–5] Previous studies analyzed the whole distribution of receptive fields (RF) of WDR neurons and suggested the significance of this neuronal population in spatial summation in nociception.[6] Additionally, a systemic review provided a general analysis on the spontaneous activities of WDR neurons in various pathological pain.[7] Despite this, the understanding and characteristics of WDR neurons, which dispersed throughout various studies, have not been systematically summarized.

This review will comprehensively analyze the properties of WDR neurons under both physiological and pathological conditions. Firstly, the characteristics of WDR neurons discharge modes will be summarized. Secondly, we will explore the influence of distinct peripheral information as well as supraspinal structures on the activities of WDR neurons. Finally, we will provide perspectives on the role of WDR neurons in the integration of acupuncture and pain signaling.

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Electrophysiological Properties of WDR Neurons

Discharge Characteristics

It has been widely known that Aβ -, Aδ- and C-fibers are three main types of afferents transmitting peripheral sensory information to the SDH. Highly myelinated Aβ-fibers are responsible for conveying non-nociceptive tactile information with the fastest conduct velocity. Aδ-fibers are thinly myelinated and respond to noxious inputs with slower-conducting velocity. C-fibers also transmit noxious stimulation information and the unmyelinated structure making them the slowest conducting types. WDR neurons receive inputs from all these types of sensory fibers via monosynaptic or polysynaptic connection (Figure 1).

Discharges of WDR neurons can be distinguished to three clusters when all afferents are simultaneously activated by supra-threshold electrical stimulus.[8] First were Aβ-components of short latency that transmitted through Aβ-fibers, then appeared Aδ-components and followed by the C-components with relative long latencies, transmitted through Aδ- and

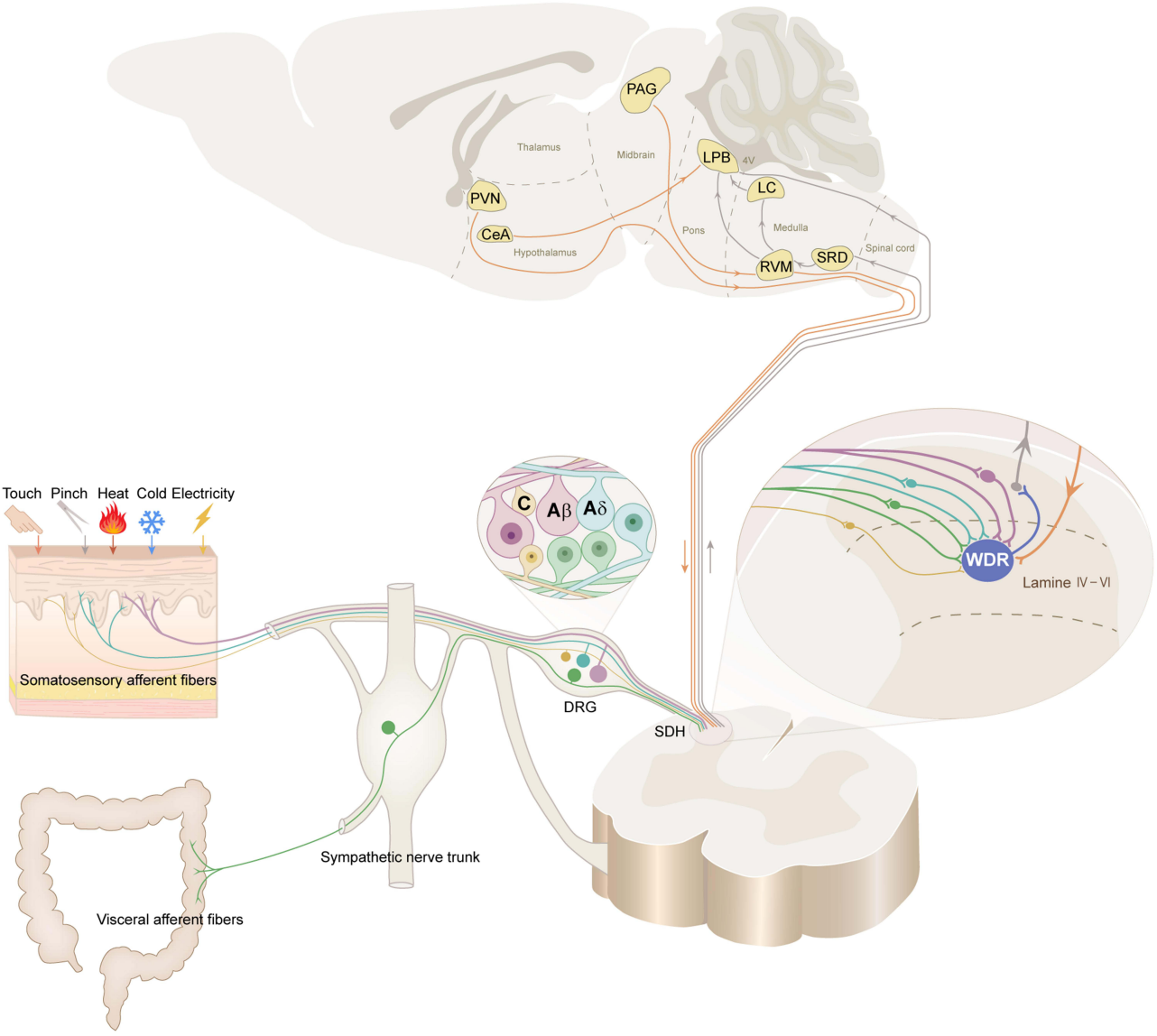

Figure 1 Spinal WDR neurons receive all types of peripheral sensory information and are modulated by the supraspinal central nerve system. They can be activated by all kinds of stimulation such as mechanical (innocuous and nociceptive pinch), temperature (heat and cold), and electrical stimulation which are transmitted by Aβ-, Aδ- and C-fibers. The peripheral information from somatosensory and visceral was transmitted through DRG and converges to the spinal dorsal horn, which are modulated by WDR neurons, located in the Lamine IV–VI. Multi-receptive properties of WDR neurons made them responsive to various kinds of innocuous and nociceptive inputs and transmitted the integrated peripheral information to the upper brain nucleus, including the subnucleus reticularis dorsalis (SRD). Meanwhile, activities of multi-receptive WDR neurons are regulated by a complex supraspinal network participated by the central nucleus (CeA), paraventricular nucleus (PVN), parabrachial nucleus (PB), periaqueductal gray (PAG), locus coeruleus (LC) and rostral ventromedial medulla (RVM).

C-fibers, respectively. Usually, when WDR neurons were recorded at the rat spinal enlargement, response evoked by Aβ-inputs was about 0–20 ms post-stimulus, Aδ- was 20–90 ms and C- was 90–500 ms approximately.[9–11] In the mice, WDR neuronal responses to single intracutaneous electrical stimulus could be separated as 0–40 ms of A- and 40–250 ms of C-components.[12] Latencies of diverse components can be calculated through dividing the distance between electrical stimulus and recording site by the conduction velocities (CV) of different afferent fibers. However, in most cases, C-components appeared later than estimated time and there exists a silent period between A- and C- discharges. One possible explanation for this phenomenon was the polysynaptic connection between WDR neurons and C-fibers. Additionally, inhibitory effects of A-inputs on nociceptive information may also lead to this delay.[3]

Despite the convergence of A- and C-inputs on same WDR neurons, neuronal discharges induced by different fibers are found not always synchronously. In most cases, Aδ- and C-fiber-evoked activities of WDR neurons significantly increased in neuropathic and inflammatory pain, along with decreased activating thresholds, while no or just slight alteration was found in Aβ-evoked responses.[9,13,14] Electrophysiological combined pharmacological studies reported that spinal application of CB2-selective cannabinoid agonist or capsazepine also reduced Aδ- and C-components of WDR neurons while Aβ-components remains unchanged.[15,16] Similarly, electrical stimulation of dorsal root only attenuated C-components of the WDR neurons as well.[17] Moreover, although all primary afferents release glutamate as a kind of fast transmitter and play excitatory effects on their postsynaptic targets, blockade of NMDA-subtype glutamate receptors suppressed C-fiber response while leaving A-fiber response unaffected.[18,19] Furthermore, activation of T-type Ca^{2+} channels was necessary for excitability of WDR neurons induced by both nociceptive and non-nociceptive mechanical stimulation.[20] However, Aβ-fiber transmission to WDR neurons may be less dependent on calcium than C-fiber mediated response.[21] A reasonable inference is that an increase in nociceptive discharges of WDR neurons may result from activation of spinal nociceptive circuits by low-threshold mechanosensory afferents.

Different from electrical stimulation, precise onset time of application of mechanical stimulus is difficult to specify to the millisecond level, making it hard to distinguish the different components of WDR neurons according to the latency. So as chemical and thermal stimulation. One of the most important characteristics of WDR neurons is their increased firing rate in response to enhanced stimulating intensity. Consequently, the frequency and duration of WDR neurons discharge to graded intensity of stimulus were compared in most studies.[22–24] In consistent with unaltered A-components evoked by electrical stimulation mentioned above, discharge of WDR neurons caused by non-noxious mechanical stimulation also remained unchanged though in pathological pain conditions.

In addition to the evoked discharges, many studies reported that WDR neurons also showed hyperexcitability without peripheral stimulation.[25–27] Increased spontaneous firing of WDR neurons in pain conditions is presumed to underlie the development of allodynia and hyperalgesia. Besides, post-discharges of WDR neurons, which are usually defined as 300–800 ms after the stimulation, are considered a regular index of nociception.[28–30] Mechanisms of post-discharge are merely figured out. As there is no stimulation during the discharge, this phenomenon seems like another form of spontaneous discharge. It should be noted that unprompted regular firing activities may also be induced by A-inputs. Therefore, the spontaneous activities of WDR neurons and the spontaneous pain are not completely synchronized. Results from several experiments observed that the spontaneous firing of WDR neurons was not altered by blocking the peripheral afferents, while the evoked activities were decreased.[24,31] Besides, spontaneous activities of WDR neurons could be influenced by systemic spinal local administration of chemical compounds.[32–34] These results provide evidence that spontaneous neuronal discharge may arise from the abnormality of local neural circuits in the dorsal horn. Importantly, this phenomenon might be associated with spontaneous neurotransmitter release.[35]

Different administration of anesthesia directly affects the response of WDR neurons to peripheral stimulation. Currently in electrophysiological recordings, intraperitoneal administration of sodium pentobarbital and urethane, along with inhalation anesthesia of isoflurane, are the prevailing methods of anesthesia.[36,37] As reported, inhalation displayed less depression on the firing of WDR neurons compared to intraperitoneal anesthesia.[37] Moreover, inhalation anesthesia facilitates the real-time adjustment of anesthesia depth according to the state of animal during recordings, thereby maintaining an optimal condition of neurons. Therefore, it is beneficial to employ inhalation anesthesia to maintain stable recording.

Besides peripheral afferents, WDR neurons are also regulated by local excitatory or inhibitory interneurons in the local dorsal horn, as well as descending modulation from the higher central nervous system, which will be discussed in detail in the following sections.

Activities of WDR Neurons and Pain

Indeed, the excitability of WDR neurons has a close relationship with hyperalgesia and allodynia pain behavior, especially the C-inputs-mediated neuronal firing.[38] Specifically, a reduction in WDR activities is always accompanied by pain relief. The C-components of WDR neurons, elicited by electrical stimulation, can be precisely distinguished based on their latency, facilitating a detailed analysis of the specific nociceptive activity. Except for increased discharge frequency, the electrical threshold for activating the C-components of WDR neurons is also lower under pathological pain conditions.[17,39] Studies recording in dorsal roots observed that threshold intensity for eliciting C-inputs was significantly decreased in inflamed rats.[40] Meanwhile, neurons in SDH also exhibit far more sensitivity to afferent inputs.[41,42] Therefore, decreased threshold of WDR neurons may be a summative result of peripheral somatosensory afferents and altered synaptic processing in local SDH.

Apart from neuropathic and inflammatory pain, abnormal excitability of WDR neurons is also found under many other pathological pains related to cancer, colorectal distension and surgical incision.[43–45] Capability of WDR neurons in encoding intensity and location of pain has been widely recognized. However, there is little knowledge about whether there exists a difference in the excitability of WDR neurons induced by various pathological pain conditions. In other words, whether the specific property of pain can also be encoded by WDR neurons? Indeed, several studies compared the activities of WDR neurons across neuropathic, inflammation, and osteoarthritic pain. Spontaneous activity, response to non-noxious, noxious mechanical and heat stimuli of WDR neurons inconsistently varied with complete Freund's adjuvant (CFA)- and carrageenin-induced inflammation, spinal nerve ligation (SNL), and monosodium iodoacetate.[31] By using a meta-regression approach, evoked WDR firing rates by different mechanical stimulation across arthritis, inflammation, neuropathy and cancer pain was compared. In contrast to neuropathic pain, the regression slope in the arthritic and inflammatory pain model was significantly higher.[46] Moreover, how activities of WDR neurons were modulated by diverse pharmacology was also observed. These studies suggest that WDR neurons are able to encode not only intensity and location but also the properties of pain. Besides, mechanisms of neuronal firing of WDR neurons responded to different stimulation varies. Studies have demonstrated that activation of TRPV1- and TRPA1-positive nerve may participate in activities of WDR neurons induced by heat but not mechanical stimulation.[47,48] WDR neurons showed less sensitivity to cold than thermal information. Discharge of WDR neurons appeared a significant increase upon stimulation of cold ethanol under neuropathic pain condition.[49] However, cold stimulation does not trigger nociceptive activity in WDR neurons in inflammatory pain rats.[50] Therefore, the susceptibility of WDR neurons to different stimuli may be altered under different pain states.

Due to the responsiveness to noxious stimuli, HT neurons are also known as nociceptive specific (NS) neurons. While both NS and WDR neurons react to nociceptive information, there are significant distinctions between these two neuronal populations. Firstly, the activating threshold of WDR neurons by nociceptive stimulation is lower than NS.[51] Therefore, multiple evidences suggest that WDR neurons are more intimately involved in the generation and process of pain than NS neurons due to their heightened sensitivity to noxious information. NS neurons selectively respond to noxious stimuli, while WDR neurons can be activated by both nociceptive and innocuous inputs, which allows them to reflect the gradual transition from non-noxious to noxious stimulation and provide more specific information concerning the intensity of painful stimulation than NS neurons.[52] Furthermore, activities of NS neurons exhibit a gradual decline over time, whereas responsiveness of WDR neurons to persistent noxious stimuli can sustain for long durations without attenuation.[53] Physiologically, the majority of neurons in the spinal dorsal horn are WDR population.[54] Previous studies reported that the proportion of spinal LTM, NS, and WDR neurons changed under both normal and pathological pain conditions.[55] A decrease in the ratio of NS and WDR neurons along with an increase in LTM neuron count may result from changes in synaptic transmission in the spinal dorsal horn microcircuit.[55–57] Alterations in dendritic spines directly impact the effectiveness of synaptic transmission, and it has been suggested that such modifications are closely related to the excitability of WDR neurons.[58,59] The transition among different neuronal populations highlights the importance of

dynamically analyzing the diversity of these neurons in response to peripheral stimuli. This is of great significance in further understanding the functions and mechanisms of neurons in pain regulation.

Activities of WDR Neurons and Central Sensitization

According to the International Association for the Study of Pain, central sensitization involves an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. This phenomenon is manifested in an expansion of receptive fields (RF), enhanced spontaneous activities, and an augmentation of responsiveness to peripheral stimuli.[60] Despite the mechanisms driving its generation, wind-up has been interpreted as a transient neuronal sensitization, potentially contributing to the development of persistent pain and hyperalgesia. Moreover, wind-up in WDR neurons also represents a procession for amplifying the nociceptive signal in the spinal cord, originating from peripheral nociceptors associated with C-fibers as well. Accordingly, this form of neuronal firing serves as a common cellular model for examining the modulation of nociceptive inputs in the primary sensory center. Induction of wind-up generally requires the application of electrical stimulation at RF of neurons or afferent nerves in an intensity- and frequency-dependent manner. The wind-up-like phenomenon occurs in WDR neurons and refers to the progressive amplification in the amplitude of C-fiber evoked responses by repetitive activation of C-fibers. To elicit wind-up of WDR neurons, a train of electrical stimulation with intensity exceeding C-component threshold and frequency beyond 0.3 Hz is usually employed.[8,61]

Most WDR neurons are considered to be projection neurons, while a minority are classified as interneurons. Consequently, the peripheral afferent usually undergoes multiple synaptic transmissions before arriving at WDR neurons. Generation of wind-up is believed to be associated with the alteration of the spinal local micro circuit, post-synaptic receptors, post-synaptic membrane, and pre-synaptic mechanisms.[62] Activation of NMDA has been proposed to play a role in the wind-up of WDR neurons, as evidenced by the attenuation of this form of neuronal sensitization following the administration of ketamine.[63] Besides, activation of endogenous opioid receptors leads to an inhibitory modulation on the development of spinal neuronal sensitization.[12] Broadly speaking, wind-up, a significant procession of central sensitization, occurs when there is enhanced excitatory transmission and decreased inhibitory tone, resulting in a heightened response to stimuli.

In most cases, neurons develop adaption in their responsiveness to persistent nociceptive signals. Windup, which exhibits a constant enhancement of discharge, is associated with a decrease in this adaptability. When inducing the wind-up of WDR neurons, there existed a plateau in evoked discharges, which usually appeared after the 10^{th} stimulus.[64] To prevent the damage caused by excessive nociceptive inputs, supraspinal descending inhibition will be triggered to reduce hyperexcitation of SDH neurons. Therefore, the facilitation of wind-up evoked by persistent stimuli reaching a plateau may be attributed to the limited wind-up capacity of WDR neurons and a strong endogenous inhibition of spinal and supraspinal modulation.

Long-term potentiation (LTP), a long-lasting enhancement of synaptic efficacy, was initially identified in the hippocampus and later found to occur in the SDH. Spinal LTP requires the activation of a cluster of superficial spinal dorsal horn neurons and is also known to contribute significantly to central sensitization thereby promoting hyperalgesia.[65,66] Both LTP and wind-up of WDR neurons involve the enhanced efficiency of synaptic transmission, leading to the amplification of the response to sensory inputs. Wind-up is typically elicited by a series of relatively low-frequency, high-intensity electrical stimuli, while the electrical stimuli that induce LTP are usually of high frequency and intensity.[29] It should be noted that spinal LTP and LTP-like activities of WDR neurons may share some similarities in their discharge mode, but they represent distinct processes. The former reflects the long-term enhancement of post-synaptic current in the dorsal horn, the latter refers to an increase in the reactivity of individual cells.

Peripheral Receptive Fields

WDR neurons, also known as multi-receptive neurons, possess broad receptive fields (RFs), which refer to the specific region of the sensory inputs. Typically, somatic innervation exhibits a characteristic somatotopic distribution. However, RFs of WDR neurons do not follow a strict spatial arrangement and are characterized by non-somatotopic organization as well as separation between cutaneous and muscle RF. Besides, there can also be a separation between cutaneous and muscle RF. This characteristic has led to the proposal that WDR neurons may play a critical role in encoding the location of stimulation.[7]

Interestingly, WDR neurons exhibit a gradient of sensitivity to the stimulated areas within the peripheral RFs, being more sensitive to inputs from the centers rather than the borders of RFs. This means that stimuli applied to the center of

the RF elicit stronger activities compared to stimuli applied to the border regions. RFs of different neurons often overlap with each other, implying that the central RFs of certain neurons may serve also as the border RFs of another neuron. As a consequence, multiple neurons could simultaneously be activated by stimulus at a given area, yet each neuron may exhibit varying levels of discharge.[6]

Stimulating at the excitatory RF facilitates the discharge of WDR neurons. Additionally, there exists inhibitory fields, usually located near the receptive field, where stimulation signals acting on these areas could exert a suppressive effect on WDR (Figure 2). In general, any region with inhibitory effects on WDR neurons could be identified as inhibitory fields. A recent study compared the regulation of pre-electroacupuncture (EA) with varying intensities at RFs, adjacent or contralateral non-RFs on the nociceptive discharges of WDR neurons evoked by hypertonic saline.[67] The findings revealed that suppression on noxious discharges of WDR neurons varied depending on the distinct location and the intensity of pre-EA stimulation. In the adjacent non-RF, which refers to the neighboring inhibitory field, inhibitory effects can be achieved with non-noxious intensity stimuli. This implies that even a gentle touch or mild stimulus in this area is sufficient to decrease the activity of WDR neurons. In contrast, when stimulation was applied at RF or contralateral non-RF, the noxious intensity was required to inhibit the discharge of WDR neurons. Therefore, stronger or potentially painful stimuli are necessary to exert the suppressive effects in these regions. There appears expansion in RFs of WDR neurons under pathological pain conditions. Stimulating regions that are physiologically expected to have inhibitory effects actually enhance the activity of WDR neurons, which is also considered as the characteristic of central sensitization. It was suggested that this phenomenon might arise from the loss of inhibitory tone in the dorsal horn, resulting in the generation of excitatory signals that normally do not occur.[42,55]

Understanding the variations in the responsiveness of WDR neurons and how they are regulated is important for comprehending the processing of sensory inputs in the nervous system. The mechanisms underlying the modulation of WDR neurons in response to stimulation of different intensities and locations are currently unknown. Inhibitory interneurons in the SDH are more responsive to the low-threshold signal inputs than excitatory low-threshold signal inputs.[42,65] Therefore, it is reasonable to speculate that the activation of inhibitory interneurons may play a crucial role in suppressing WDR neurons, particularly in the inhibitory effects elicited by low-intensity stimulation. Compared to the SDH neurons, the supraspinal nuclei may require a higher intensity of stimulation to be activated.[68] According to this phenomenon, the prevailing viewpoint suggests that the inhibition related to low-intensity afferents may occur at the level of SDH, while the broad inhibitory effects exerted by high-intensity stimulation may involve the participation of supraspinal mechanisms. Noxious stimulation applied to any area of the body can suppress the nociceptive excitability of WDR neurons, known as diffuse noxious inhibitory control (DNIC).[69,70] Regulation of DNIC on WDR neurons will be extensively discussed in the subsequent sections, with a particular focus on certain important central nuclei.

In addition to somatic RFs, there is a portion of WDR neurons that respond to innocuous and noxious stimulation at the visceral organs. Previous studies employed colorectal distension as mechanical stimulation to evoke discharges of WDR neurons.[44,71] Interestingly, a portion of WDR neurons have RFs distributed at both the somato and internal organs

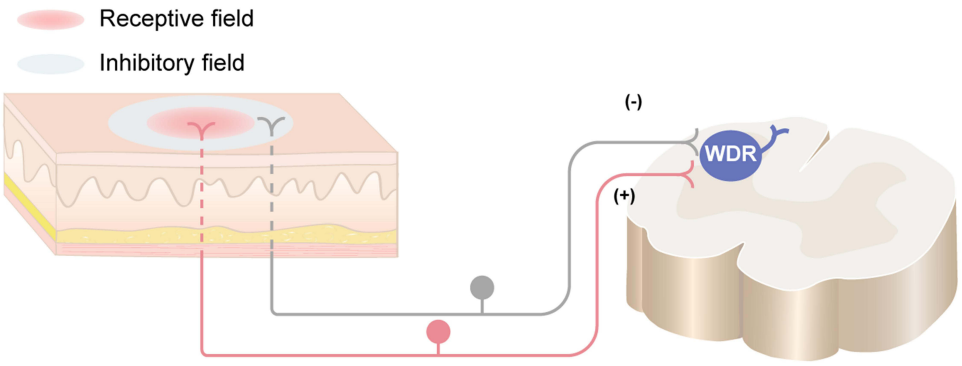

Figure 2 Sensory inputs derived from the receptive field promote the discharges of WDR neurons. WDR neurons exhibit more sensitivities to inputs from the centers of the receptive field. Simultaneously, there exists an inhibitory field that distributed around the receptive fields. Stimulation at the inhibitory field exerts suppressive effects on the activities of WDR neurons.

simultaneously, allowing them to respond to both somatic and visceral afferents. This convergent inputs from external and internal inputs on the same WDR neurons provide an underlying mechanism for referred pain. Indeed, visceral inflammation could facilitate the response of neurons to somatic stimulation.[72,73] More importantly, visceral-somatic or viscera-somatic convergence helps explain the therapeutic potential of somatic interventions, such as acupuncture, in alleviating visceral pain.

WDR Neurons Regulated by Spinal Inhibitory and Excitatory Tone

The neuronal circuits in the spinal dorsal horn encompass a wide array of highly diverse neurons, with the WDR neurons constituting the largest neuronal population and being subject to the regulation of this modular architecture.[74] Despite the currently ambiguous phenotype of WDR neurons, research has observed the influence of specific pain-related molecules on their regulation, especially the glutamate and gamma-aminobutyric acid (GABA).

The balance between excitatory and inhibitory tone is directly linked to pain occurrence. Spinal dorsal horn neurons are categorized as either excitatory or inhibitory based on their primary neurotransmitter.[75] The majority of excitatory neurons in the spinal dorsal horn are glutamatergic and express vesicular glutamate transporter 2 (VGLUT2), whereas the inhibitory neurons release GABA and/or glycine. The excitatory or inhibitory nature of WDR neurons remains uncertain, but these primary neurotransmitters do influence their activity. Local application of glutamate receptor agonists or antagonists can respectively enhance or suppress the responsiveness of WDR neurons to peripheral stimulation.[32,33] Additionally, sensitization of WDR neurons, including wind-up and LTP responses, relies on enhanced glutamate signaling.[63,76,77] Conversely, GABA and glycine play an inhibitory role in WDR neurons. Restoring reduced spinal GABAergic inhibition in rats with neuropathic pain decreased the excitability of WDR neurons.[78,79] However, it is not yet clear whether the glutamate, GABA, and glycine signals affect the activity of WDR neurons indirectly through the involvement of other modulatory neurons, or by directly interacting with the receptors located on the WDR neurons themselves. Cutting-edge neuroscience techniques offer insights into this issue. In addition to pharmacological interventions targeting neurotransmitter signaling, a recent study utilized optogenetic technology and found that suppression of spinal inhibitory neurons significantly facilitated the responsiveness of WDR neurons.[80] This suggests that as a crucial and diverse population of modulatory neurons, WDR neurons are integral to the local spinal microcircuitry and are subject to regulation by other interneurons.

WDR Neurons Regulated by Descending Pathways

As noted above, DNIC is initially identified through electrophysiological recordings, which revealed inhibition on nociceptive activities of WDR neurons, while not affecting NS or LTM neurons, through heterotopic application of noxious stimulation.[69,70] Analgesic effects induced by DNIC are significantly diminished or completely absent in animals with spinal cord injury or spinalization.[70,81] Elimination of DNIC in these animals emphasizes the participation of supraspinal components in descending pain modulatory network. Numerous earlier studies employed electrical stimulation, pharmacological intervention, optogenetic and chemogenomic techniques to manipulate those central nuclei to explore their effects on WDR neurons. In summary, the regulation of WDR neurons involves various projection pathways, including the spinothalamic tract, descending modulatory pathway, and the prefrontal cortex. The following section will offer a comprehensive overview of these findings related to the modulation of WDR neurons and summarize the identified projection pathways involved (Figure 1).

Central Nucleus (CeA)

The amygdala has been widely recognized for its contribution to the processing and integration of pain-like and anxiety-like behaviors.[82] Additionally, kappa opioid receptors (KOR) signaling in this limbic brain region also plays a significant role in aversion and other negative emotions associated with pain.[83] Dysfunction of DNIC appears in various pathological pain, partly caused by failure of sensory transmission or activation of descending facilitation. Microinjection of KOR antagonist into contralateral CeA restored the inhibition of DNIC on WDR neurons in rats undergoing SNL.[81] CeA contains a high concentration of corticotrophin-releasing factor (CRF) neurons. These neurons in the CeA have extensive projections to various brain regions that are involved in the processing and modulation of nociceptive signals, such as

PAG and RVM.[84,85] Optogenetic inhibition of hyperexcitation of CeA-CRF neurons reduced evoked response of spinal WDR neurons to both non-noxious and noxious mechanical stimulation.[86] Interestingly, administration of KOR agonist increases activities of amygdala CRF neurons through synaptic disinhibition, resulting in pain-like behavior and emotion.[87] Moreover, potentiating effects of KOR activation on spinal WDR neurons were blocked by ablation of CRF neurons in the CeA.[88] These findings highlight the significance of KOR activation of CRF neurons in the CeA for the descending modulation of spinal WDR neurons.

Paraventricular Nucleus (PVN)

The PVN of the hypothalamus plays a crucial role in maintaining the homeostasis of the body by regulation of the endocrine and autonomic nervous systems. Besides, it has been demonstrated that oxytocin neurons in the PVN project to the brainstem and spinal cord, contributing to analgesia by releasing oxytocin.[89,90] Electrical stimulation of the PVN or intrathecal oxytocin decreased Aδ- and C-fiber evoked responses and post-discharges of WDR neurons, without affecting Aβ-response.[91,92] This effect diminished after intrathecal administration of a specific oxytocin antagonist or bicuculline, indicating the importance of oxytocin and GABAergic neurotransmission in this antinociceptive pathway.[93] In a recent study, chemogenic activation of oxytocin neurons in the PVN promotes the activation of GABAergic neurons in the SDH and alleviates hyperalgesia in inflammatory pain rats.[94] Accordingly, it is highly likely that the regulation of spinal WDR neurons by PVN and the consequent analgesic effects are achieved through the descending oxytocinergic pathway mediated by GABAergic transmission.

Parabrachial Nucleus (PB)

The PBN has been widely recognized as a sensory relay that receives and processes diverse sensory information related to taste, digestion, pain modulation, and various aspects of autonomic condition.[95] Peripheral sensory information, like nociception, itch, and temperature, is transmitted directly from the SDH to PB through the spino-parabrachial tract.[96] As a primary supraspinal region that receives spinal nociceptive projection, PB is of great importance in modulating somatic and visceral nociceptive information. Behavioral and electrophysiological experiments reported that inactivation of the lateral PB area reduced the DNIC-induced analgesia and inhibition of nociceptive activities of WDR neurons.[97] Besides, PB has been suggested to be involved in descending control of pain through its dense projection to the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM).[98,99] Therefore, PB simultaneously participated in both ascending pain-transmission and descending pain-modulation pathways. Although the neural tracing study emphasized the involvement of PB in ascending pathways of DNIC, the indirect pathways through which the PB modulates the descending segment of this circuit have yet to be clarified.

Periaqueductal Gray (PAG)

It is well known that the PAG exhibits remarkable analgesic effects through direct modulation of spinal nociceptive transmission or indirect pathways involving projections to the RVM. Importantly, the PAG has been considered a key structure for mediating endogenous opioid-induced pain suppression, primarily attributed to its high levels of mu opioid receptors (MORs) expression.[100] Electrophysiological recordings provided the results that the administration of morphine in the PAG enhanced the inhibitory effects on WDR neurons in neuropathic animals.[101] Likewise, microinjections of endogenous ligands of the opioid receptor into the PAG yielded a significant enhancement in both the C-components and post-discharges of WDR neurons.[102,103] The descending control from the PAG on spinal nociception is characterized by dual dynamics, eliciting either facilitatory or inhibitory effects. The balance between descending facilitation and inhibition directly influences the spinal integration and processing of sensory information, resultant modulation of nociceptive output. Activation of the cyclooxygenase (COX)-prostaglandin E2 signaling pathway within the ventrolateral PAG not only enhances spinal transmission of C-nociceptor inputs but also increases spinal sensitivity to A-nociceptor inputs, and subsequently leads to hyperalgesia and algesia in rats.[104] Interestingly, modulation of PAG on spinal WDR neurons appears a separation as to the responses to A- vs C-inputs. Neuronal encoding of C-nociceptor information of WDR is disrupted upon inhibition of COX-1 descending facilitation, whereas the encoding of A-nociceptor information remains unaffected.[105] Accordingly, integration of A- and C-afferents in spinal WDR neurons is under distinct regulation

of descending control from the PAG. Morphological studies have revealed that the efferent fibers from the PAG primarily projected to the locus coeruleus (LC) and the RVM, rather than the SDH.[85,106] Therefore, it is likely that the analgesic effects of the PAG are mediated through nuclei in the LC and RVM complex.

Locus Coeruleus (LC)

As a main noradrenergic nucleus in the brainstem, LC provides primary noradrenergic innervation to the SDH.[107] Descending noradrenergic projections terminating in the SDH is recognized as a key participation of the endogenous pain modulation system. Additionally, ascending LC projections to the prefrontal cortex (PFC) are related to pain-related negative emotion. Research findings indicate that activation of the noradrenergic projections from the PFC to the LC is associated with the manifestation of spontaneous pain, aversion, and anxiety-like behavior. Conversely, activation of noradrenergic fibers projecting from the LC to the SDH exerts inhibitory effects on pain and decreases the firing frequency of WDR neurons.[108] The direct modulation is through the noradrenergic descending pathway, which is dependent on the α2 adrenergic receptors.[109] Spinal application of α2-adrenoceptor agonists can effectively decrease the noxious discharges of WDR neurons through both pre-synaptic and post-synaptic mechanisms.[30] Significantly, opto-activation of local LC noradrenergic neurons was found to mitigate, rather than abolish, the DNIC effects in an α1 adrenergic receptors-dependent manner.[110] Overall, the suppressive action of LC on WDR is achieved through direct projections to the dorsal horn as well as indirect engagement in DNIC.

Rostral Ventromedial Medulla (RVM)

The RVM consists of the nucleus raphe magnus (NRM) and its adjacent ventral reticular formation, which primarily receive inputs from the PAG and the PBN, along with inputs from structures like the prefrontal cortex, hypothalamus, and amygdala. The descending fibers from the RVM predominantly project through the dorsolateral and ventrolateral tracts to the dorsal horn of the medulla and spinal cord.[111] Previous studies established that the organization of RVM-spinal cord circuits was of significant importance in the descending pain control system.[112,113] Within the RVM, there are both on-cells that facilitate the spinal transmission of nociceptive information to amplify pain, and off-cells that enhance the descending inhibitory control of SDH neurons, thereby exerting analgesic effects.[99] Administration of NK1 receptor agonists into the RVM, which enhances the activities of on-cells, results in a pronounced increase in the sensitivity of WDR neurons to mechanical and thermal stimuli.[114] Meanwhile, pharmacological activation of off-cell attenuates C-fiber-evoked responses via DNIC.[115] Significantly, there is growing evidence implicating the involvement of serotonin in the modulation of pathological pain.[116] The NRM serves as the primary site of aggregation for serotonergic neurons in the brain and projects serotonergic fibers to the SDH. The WDR neurons exhibit a high sensitivity to 5-HT, which is dependent on the involvement of supraspinal structures.[117] However, the antinociceptive and pronociceptive effects of the descending serotonergic pathway in pain modulation remain controversial.[118] According to multiple studies, there are notable variances in the effects of various subtypes of 5-HT receptors on the A-components, C-components, and post-discharges of WDR neurons.[119–121] The heterogeneous effects of the serotonergic descending pathway on nociception, as observed in WDR neurons, may be attributed to the activation of different receptor subtypes on the neuronal surface. Consequently, it is necessary to consider the receptor expression profile of the dorsal horn neurons themselves to determine whether the serotonin released by the RVM into the SDH exerts descending inhibitory or facilitatory effects.

Subnucleus Reticularis Dorsalis (SRD)

Brainstem reticular formation refers to an intricate and intertwined structure that is composed of a complex and dense network of various neurons. Due to its specific anatomical characteristics, the investigation of pain modulation involving the RF is greatly restricted. Nevertheless, the transmission and modulation of nociceptive information in this area have been widely acknowledged.[122] SRD, also known as dorsal reticular nucleus (DRt), is a reticular nucleus located dorsally in the brainstem, that extends from the spinomedullary junction to the rostral border of the area postrema. Neurons in the SRD can be activated by noxious input from any region of the body and their response level shows a linear relationship with the intensity of the stimulus. Noxious information from different regions converges onto the same SRD neurons, which enables this structure to share a similar function with WDR neurons in integrating nociceptive input.[123] Contrarily,

SRD neurons exhibit a plateau response, characterized by a potential decrease in activity when the stimulus intensity surpasses or reaches a specific threshold. Electrophysiological experiments documented that activation of local SRD neurons by glutamate enhances the response of spinal WDR neurons to electrical stimulation.[124] Conversely, blocking ipsilateral SRD neurons with lidocaine results in a significant decrease in the response of WDR neurons.[125] Meanwhile, blocking opioidergic signaling in the DRt had no effect on spinal neuronal responses to innocuous and noxious stimulation but abolished the phenomenon of DNIC.[126] Taken together, this spinal-SRD-spinal circuit endows SRD neurons with a pivotal contribution to feedback modulation of pain, especially through the descending pathway of DNIC.

WDR Neurons in Acupuncture Analgesia Research

It has been proposed that mechanisms underlying acupuncture analgesia involve central summation.[127] Acupuncture signals transmitted through primary sensory fibers encounter with nociceptive information in the dorsal horn of spinal cord. The capacity of spinal WDR neurons to comprehensively integrate somatosensory inputs renders them highly suitable for investigating the mechanisms underlying acupuncture-induced analgesia. EA stimulation elicits a dose-dependent response in WDR neurons, leading to an augmentation in their firing frequency with the increasing intensity of intervention.[128] Significantly, discharges of WDR neurons excited by different manipulations are analyzed to quantify the specific intensity of EA.[129] Importantly, under pathological pain conditions, the acupuncture signal and nociceptive information simultaneously encounter in WDR neurons, leading to integrated neuronal activities. Thus, EA intervention exerts analgesic effects by suppressing the excitability of WDR neurons in response to nociceptive inputs. Indeed, studies have shown that EA or transcutaneous electrical acupoints stimulation (TEAS) intervention can effectively dampen the abnormal activities of WDR neurons.[130]

Acupuncture has the potential to produce both segmental and systemic analgesic effects. Segmental analgesic effects refer to alleviating pain at the same neural segment as the intervention site, typically employing non-nociceptive intensities. Systemic analgesia, on the other hand, aiming at relieving pain in distant regions of the body, often necessitates higher intensity of intervention. Research has shown that electro-acupuncture (EA) intervention with A-fiber intensity at the local pain site can effectively inhibit the spontaneous firing of WDR neurons caused by muscular inflammatory pain.[131] Meanwhile, EA with an intensity beyond C-fiber has also been validated to reduce the nociceptive activity of WDR neurons. In a study conducted on rats with migraines, EA with high-intensity C-fibers significantly reduced the elevated firing frequency of WDR neurons in the spinal trigeminal nucleus caudalis region.[132] It should be noted that the effective intensity of EA in inhibiting the excessive activities of WDR neurons varies depending on the stimulation site. In the inhibitory regions adjacent to the RF, EA with the intensity of Aβ is sufficient to diminish the nociceptive discharges of WDR neurons. However, when EA is applied directly at the RF or in contralateral regions, a higher intensity is necessary to effectively elicit the inhibitory effects.[67] Overall, the nociceptive discharges of WDR neurons can be effectively suppressed not only by innocuous A-inputs within the same segment but also by noxious stimuli applied to any region of the body, which are referred to as gate control and DNIC effect, respectively. Research shows that remote acupuncture of mild-intensity is difficult to alleviate pain.[133] Consequently, when EA is administrated at a distance far away from RF, higher intensity is usually required to exert an analgesic effect, potentially involving the participation of supraspinal nuclei and resulting in the descending inhibition of WDR neurons. However, the specific structures involved in the systemic analgesic effects of high-intensity acupuncture at distant sites are currently unclear.

This characteristic highlights the comprehensive convergence of inhibitory control mechanisms across multiple sensory sources and establishes a promising basis for further unraveling the neural integration perspective of segmental and systemic analgesic effects of acupuncture (Figure 3).

In addition to somatic sensory, acupuncture also exhibits intensity-dependent modulation on WDR neurons that receive visceral inputs.[134] Visceral pathology typically leads to somatic hyperalgesia, while the inherent pain originating from the organs themselves may be less prominent. Therefore, the majority of studies focused on somatic hyperalgesia involved with visceral pathology. The WDR neurons, which receive inputs from both visceral and somatic afferents, provide a valuable perspective for exploring the mechanisms underlying acupuncture treatment of visceral and referred pain.

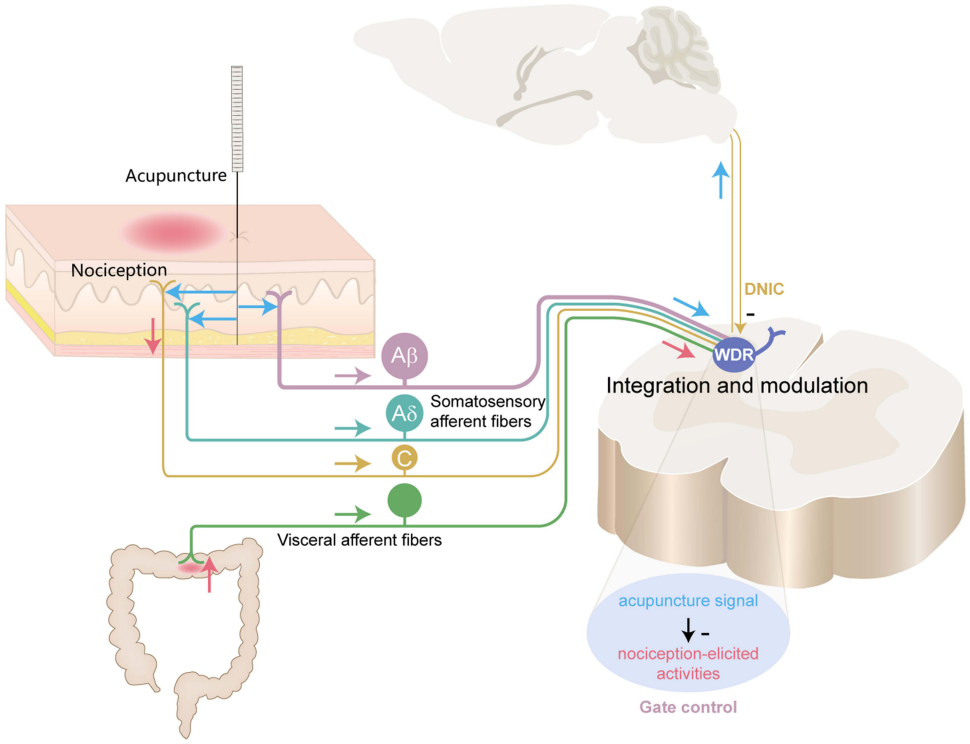

Figure 3 Acupuncture signals transmitted through various types of primary sensory afferents encounter with nociceptive information in the spinal dorsal horn. Low or high intensity of acupuncture exert analgesic effects through the gate control or the diffuse noxious inhibitory control (DNIC), respectively. The integrative and modulatory capacities of WDR neurons made them highly suitable for investigating the mechanisms underlying acupuncture-induced analgesia in both somatic and visceral hyperalgesia and referred pain.

Summary and Outlook

In this review, we provide a comprehensive overview of the characteristics of the spinal WDR neurons and discuss their involvement in pain modulations. As the initial relay station for sensory information, the SDH undergoes intricate processing of both peripheral afferents and upper central projections, contributing to comprehensive signal integration. Neurons within the SDH receive peripheral sensory inputs while undergoing modulation by supraspinal nuclei, concurrently engaging in intricate local microcircuits within the dorsal horn. The convergent view of pain holds that this pathological sensation is an integrated state represented by a pattern of convergent somatosensory activity within a complex network.[7] WDR neurons are not exclusively localized in the dorsal horn of the spinal cord but are also found in other central nuclei, such as ventral posterolateral thalamus[135] and parabrachial nucleus.[136] Extensive distribution of WDR neurons in the central nervous system further demonstrates the multi-integration and modulation of signal transmission. As a crucial convergence of various inputs, spinal WDR neurons serve as vital loci for various sensory processing. The encoding ability of this neuronal population, specifically in terms of pain intensity and location, may exert a noteworthy impact through both spinal and supraspinal mechanisms. Importantly, WDR neurons play a pivotal role in pain research, particularly in relation to the gate control theory, which explains the interaction between innocuous and noxious inputs in the SDH. Additionally, they are involved in the modulation of SDH neurons by supraspinal structures, as observed in the DNIC effects. Furthermore, WDR neurons also provide a crucial foundation in unraveling the complex mechanisms underlying acupuncture analgesia, such as the primary integration of acupuncture and nociceptive signals in the central nervous system, along with the modulation of visceral sensation by acupuncture.

The central integration of sensory inputs heavily requires the participation of WDR neurons, nonetheless, the current understanding of these neurons remains limited. The present definition of WDR neurons is primarily based on their responsive patterns to external stimuli, with the identification method exclusively relying on electrophysiological

recordings. Consequently, this methodology allows for the differentiation of only WDR, HT, and LTM neuron types. However, the morphological characteristics of these different types of neurons remain unclear. Research findings have demonstrated that lamina III antenna neurons in the dorsal horn possess the capability to integrate inputs from low- and high-threshold primary afferents, enabling them to function as WDR neurons.[137] However, this study adopted a predominantly functional perspective, and the investigation of their morphological characteristics was primarily based on the assessment of axon-to-dendrite ratios. In practice, such classification fails to provide a comprehensive and intricate understanding of spinal cord cell types and their complex regulatory effects.

It is generally thought that the majority of WDR are modulatory neurons, with a small proportion being categorized as projection neurons.[136] In regards to their positioning, WDR neurons distribute at a depth of 500–1200 μm beneath the surface of the spinal dorsal cord, and are concentrated in lamine V–VI. Therefore, signals conveyed by WDR neurons to higher central centers primarily comprise integrated non-nociceptive information or nociceptive inputs modulated by non-nociceptive factors, demonstrating contrasting characteristics compared to the nociceptive outputs from $NK1^+$ projection neurons in the superficial laminae. Moreover, in terms of distribution, lamine IV and VI contain a greater proportion of inhibitory interneurons, whereas the lamine V is primarily populated by excitatory interneurons.[138] Thus, WDR neurons may possess both excitatory and inhibitory characteristics simultaneously. Single-cell RNA sequencing unveiled the gene expression signature and molecular organization of spinal neurons.[139] These findings demonstrate the significant heterogeneity of SDH neurons and provide a foundation for advanced genetic manipulation and targeted whole-cell patch clamp recordings of specific neuronal populations. However, the presence of specific molecular markers of WDR neurons remains elusive posing a challenge in manipulating these neurons using techniques like optogenetics and chemogenetics. This knowledge gap could be a critical obstacle in advancing our understanding and exploration of WDR neurons.

Abbreviations

SDH, spinal dorsal horn; WDR, wide dynamic range; LTM, low-threshold mechanoreceptor; HT, high-threshold; SRD, subnucleus reticularis dorsalis; CeA, central nucleus; PVN, paraventricular nucleus; PB, parabrachial nucleus; PAG, periaqueductal gray; LC, locus coeruleus; RVM, rostral ventromedial medulla; CV, conduction velocities; CFA, complete Freund's adjuvant; RF, receptive fields; LTP, long-term potentiation; SNL, spinal nerve ligation; CRF, corticotrophin-releasing factor; MORs, mu opioid receptors; COX, cyclooxygenase; PFC, prefrontal cortex; NRM, nucleus raphe magnus; DRt, dorsal reticular nucleus; TEAS, transcutaneous electrical acupoints stimulation; EA, electro-acupuncture; GABA, gamma-aminobutyric acid; VGLUT2, vesicular glutamate transporter 2; KOR, kappa opioid receptors; NS, nociceptive specific.

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Disclosure

The authors report no conflicts of interest in this work.

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