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·Review·

Population coding of somatic sensations

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Abstract: The somatic sensory system includes a variety of sensory modalities, such as touch, pain, itch, and temperature sensitivity. The coding of these modalities appears to be best explained by the population-coding theory, which is composed of the following features. First, an individual somatic sensory afferent is connected with a specific neural circuit or network (for simplicity, a sensory-labeled line), whose isolated activation is sufficient to generate one specific sensation under normal conditions. Second, labeled lines are interconnected through local excitatory and inhibitory interneurons. As a result, activation of one labeled line could modulate, or provide gate control of, another labeled line. Third, most sensory fibers are polymodal, such that a given stimulus placed onto the skin often activates two or multiple sensory-labeled lines; crosstalk among them is needed to generate one dominant sensation. Fourth and under pathological conditions, a disruption of the antagonistic interaction among labeled lines could open normally masked neuronal pathways, and allow a given sensory stimulus to evoke a new sensation, such as pain evoked by innocuous mechanical or thermal stimuli and itch evoked by painful stimuli. As a result of this, some sensory fibers operate along distinct labeled lines under normal *versus* pathological conditions. Thus, a better understanding of the neural network underlying labeled line crosstalk may provide new strategies to treat chronic pain and itch.

Keywords: developmental neurobiology; dorsal root ganglion; pain pathways; itch; spinal dorsal horn

1 Introduction

In the 1880s, independent studies by Blix, Goldscheider and Donaldson led to the discovery of specific skin spots for cold, warm, or touch/pain sensation[1]. Donaldson further showed that topical applications of cocaine onto the cornea eliminated touch/pain, but not temperature sensitivity[1]. Human microneurographic studies in the 1970s and 1980s further demonstrated that activation of individual sensory fibers is sufficient to evoke a specific somatic sensation[2-4]. These lines of work firmly suggest the existence of specific neural circuits or labeled lines that transmit specific sensory modalities from the skin to the brain, analogous to the "law of specific nerve energies" proposed by Muller in 1826 in explaining other types of sensory coding[1]. The elegance and simplicity of this specificity theory of somatic sensory coding, however, quickly faced complexities by other observations. First, it is not uncommon to observe a mismatch between the nature of sensory stimuli and the actual perception. For example, cold sensation can be evoked from some skin spots by both cold and heat stimuli[5-7]. Similarly, both pain-related and itch-related neurons are able to respond to capsaicin, the pungent ingredient from the chilli pepper, even though intradermal injection of a

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large amount of capsaicin evokes only burning pain[8-11]. Second, it is difficult for the specificity theory to explain why a given sensory stimulus could evoke distinct sensations under normal *versus* pathological conditions. For example, in patients suffering chronic pain following nerve lesions, innocuous mechanical and/or cold stimuli can evoke pain[12,13]. Similarly, in patients suffering chronic itch, capsaicin injection evokes itch, as opposed to pain[14-16]. Several theories have been proposed to explain this coding dilemma[17], and one of them, the population-coding theory, appears to have a lot of support[18-20]. This theory essentially evolved from the pattern theory or the gate control theory proposed since 1898 by many investigators[5,6,21-26], which highlights the interactions of different sensory fibers in generating or reshaping somatic sensations. While the gate control theory of pain proposed by Melzack and Wall initially argued against the existence of specific labeled lines[24,25], the modified population-coding hypothesis emphasizes both the existence of specific labeled lines and the crosstalk among these lines[20], as described below.

2 Population coding of thermal sensations

A population coding of thermal sensations was first indicated by two independent studies reported in 1896[27]. Thunberg discovered the "thermal grill illusion" phenomenon, in which stimulation of adjacent skin areas with innocuous cold and warm led to a hot or burning sensation[27]. Alrutz also found that concurrent activation of cold and warm spots in the skin led to a hot or burning sensation[5,27]. In 1921, Head also reported paradoxical thermal sensations when different parts of the penis were activated alone or together[6]: a strong cold sensation was evoked when the end of the penis was dipped into 45°C water, but an exquisite heat sensation was evoked if it was dipped deeper into the water, covering the corona area without reaching the foreskin. This remarkable observation suggests the existence of different types of sensory afferents that respond to 45°C stimuli, and their isolated *versus* concurrent activation evokes distinct thermal sensations.

A series of subsequent human studies then provided key insights into the coding of thermal sensations. From 1975 to 1990, Mackenzie and others found that following a selective blockade of myelinated fibers (A-fibers) by ischemia or compression, innocuous cold stimuli were able to activate unmyelinated C-fibers to evoke burning sensations[28-31]. This finding suggests that (1) cooling sensation is transmitted by cold-sensitive A-fibers (thereby associated with a cold-labeled line), and (2) cold-sensitive C-fibers are associated with a distinct neural circuit whose activation evokes burning pain (a pain-labeled line), but this sensation is dominantly masked by the concurrent activation of the cold-labeled line (Fig. 1A).

Electrophysiological studies carried out by the Craig group then explained how the thermal grill illusion works[32]. They first found that an innocuous cold stimulus can activate two groups of spinal neurons: (1) COLD neurons responding selectively to innocuous cold, thereby likely involved with cooling sensation, and (2) CPH neurons responding to both innocuous Cold and noxious Pinch and Heat, and therefore likely involved with burning sensation. The fact that innocuous cold can concurrently activate these two populations of spinal neurons also suggests that cold-mediated masking of burning pain might operate in the brain, rather than in the spinal cord. They then found that upon thermal grill stimulation, activation of warm fibers in the adjacent skin area prevents the innocuous cold stimulus from activating COLD spinal neurons, without affecting the activation of CPH spinal neurons. In other words, the thermal grill essentially mimics the transduction blockade of cold-sensitive A-fibers by ischemia-compression; as a result, C-fibers responding to innocuous cold are now capable of activating a normally "masked" pain-labeled line to evoke a burning sensation (summarized in Fig. 1A). Thus, through antagonistic interactions among three distinct thermo-sensitive labeled lines (mediated by cold-sensitive A-cold, cold-sensitive C-pain, and C-warm fibers), the same cold stimulus can evoke either cold or burning pain sensation under different conditions. Electrophysiological characterization of other thermosensitive primary sensory afferents, including those responding to noxious cold and heat, further supports a population-coding theory in explaining thermoreception and perception[19,20,27,33,34].

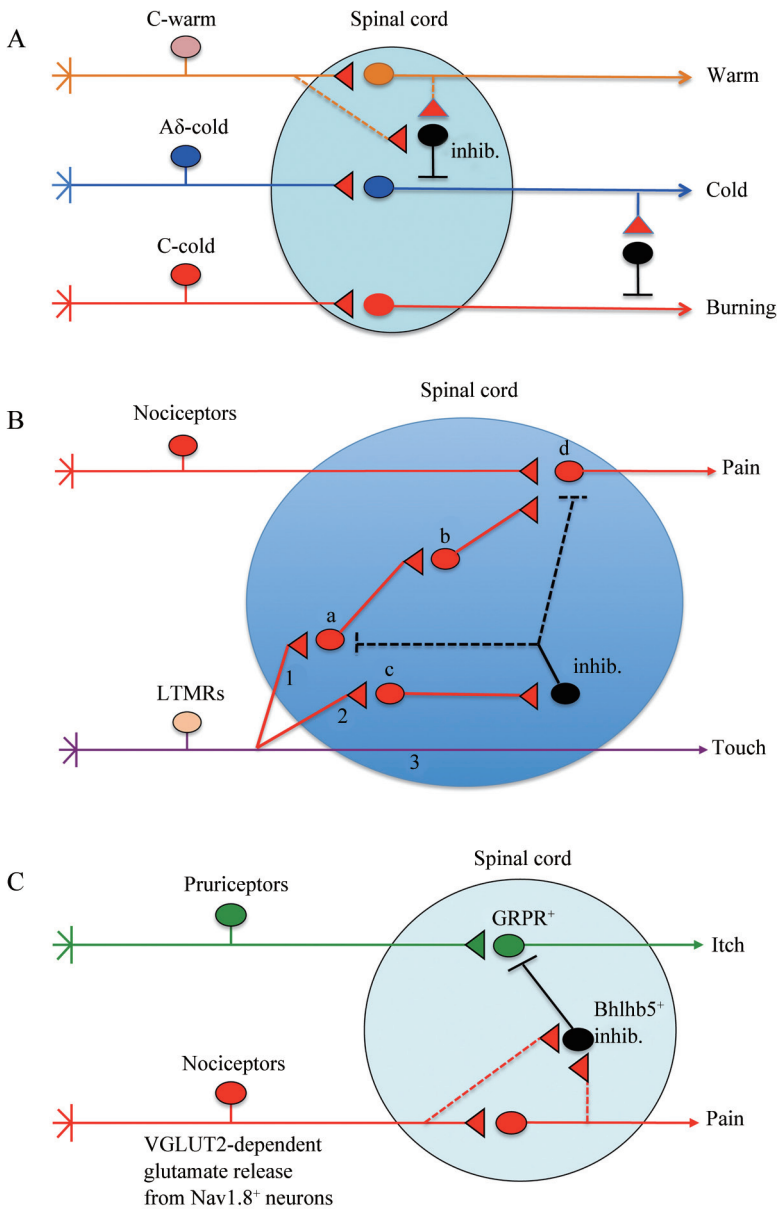

Fig. 1. Crosstalk among sensory-labeled lines. A: Interaction of three innocuous thermosensitive sensory-labeled lines. The pain-labeled line mediated by C-cold fibers is inhibited by the activation of the Aδ-cold labeled line, and the inhibition may occur in the brain. The activity of the Aδ-cold labeled line can be suppressed by the activation of C-warm fibers from the adjacent skin area, and this inhibition starts at the spinal level[32]. Blockade of Aδ-cold fiber activity by the thermal grill or ischemia-pressure, or through central disinhibition following nerve lesions, allows C-cold fibers to activate the normally masked burning pain-labeled line. B: The neural circuits linking low-threshold mechanoreceptors (LTMRs) to pain output neurons (modified from Takazawa *et al*. Ann N Y Acad Sci 2010[39]). Aβ-LTMRs participate in three pathways. Pathway "1" is composed of polysynaptic connections of local excitatory interneurons ("a" and "b") in laminae III and II onto a pain output neuron ("d") in lamina I. Pathway "2" is connected to a local excitatory neuron ("c"), which is synaptically connected to an inhibitory neuron ("inhib.") that provides potential inhibitory inputs onto neurons in pathway "1". Pathway "3" represents an ascending pathway for normal touch percepts. Following central disinhibition induced by nerve lesions, LTMRs can directly activate pain through pathway "1", leading to the development of mechanical allodynia. C: Itch inhibition by pain (modified from Ma QF. J Clin Invest 2010[20]). Pain and itch are processed along two different labeled lines. VGLUT2-dependent glutamate release from Nav1.8$^+$ neurons is required for pain sensation, and these pain-processing neurons might form, directly or indirectly, synaptic connections with Bhlhb5-expressing inhibitory neurons in the superficial laminae of the dorsal spinal cord, which in turn suppresses itch-related gastrin-releasing peptide receptor (GRPR)-expressing spinal neurons. It should be noted that although the schematics point out potential labeled line crosstalk in the spinal cord, this could in principle occur in the brain.

3 Cross talk between low-threshold mechanoreceptors (LTMRs) and pain-processing neurons

Neurons in the dorsal root ganglia (DRGs) and the trigeminal ganglia also include a variety of LTMRs that are critical for touch-related percepts, such as texture, shape, pressure, and vibration. LTMRs are divided into heavily-myelinated Aβ, thinly-myelinated Aδ, and unmyelinated C subtypes[35,36], which terminate in distinct laminae within the deep dorsal horn[37]. The linkage of LTMRs with pain is suggested from two fronts. First, under normal situations, inputs from LTMRs can inhibit pain, and this forms the key basis for the gate control theory of pain[24,25]. In fact, Head already proposed in 1905 the theory of "protopathic (for pain)" *versus* "epicritic (for touch, cold, and others)" systems, with the former inhibited by the latter[21]. Electrophysiological studies show that lamina I spinal neurons responding to noxious stimuli can be inhibited by the concurrent activation of large myelinated LTMRs[38]. Second, under pathological conditions, pain can be evoked by LTMRs, a phenomenon called mechanical allodynia (see below).

Recent electrophysiological studies have now revealed quite complex neural circuits linking Aβ LTMRs to putative pain output neurons in the dorsal spinal cord, as illustrated in Fig. 1B[39]. First, LTMRs form a polysynaptic excitatory circuit to connect with putative high-threshold pain output neurons in lamina I (pathway "1" in Fig. 1B)[40-43]. This pathway is normally masked due to concurrent activation of a separate inhibitory circuit (pathway "2" in Fig. 1B). Electrophysiological recordings show that under normal conditions, stimulation of Aβ fibers fails to activate pathway 1 neurons, but does so after application of GABA or glycine receptor antagonists to block inhibitory input[40,41,44]. The polysynaptic nature of pathway "1" is indicated by the finding that Aβ fiber input exhibits both failures and variable latency when lamina I output neurons are recorded at high stimulation frequencies[41]. The activation of the inhibitory neurons by Aβ fibers in pathway "2" is indirect, requiring activation of a local excitatory neuron[39,45]. It was proposed that the inhibitory input may suppress the activity of a lamina II interneuron in pathway "1"[39] (Fig. 1B). However, other studies show that inputs of LTMRs are able to inhibit spinal neurons normally responding to noxious stimuli[38], suggesting that the LTMR-mediated inhibitory pathway might additionally and directly suppress pain-processing output neurons in lamina I (Fig. 1B). Finally, it should be noted that neurons forming either pathway "1" or pathway "2" can be heterogeneous, indicating the existence of multiple excitatory and inhibitory pathways activated by LTMRs in the dorsal horn[39,41,43,44]. In summary, the above discussion highlights the existence of preexisting pain pathways that respond to innocuous thermal (Fig. 1A) or mechanical stimuli (Fig. 1B), and their activity is normally masked by the concurrent activation of anti-pain systems. As discussed below, following central disinhibition induced by nerve lesions, these masked pain pathways would become open, thereby contributing to the development of pathological pain.

4 Population coding of pain *versus* itch

Itch and pain are two distinct modalities of nociception, evoking withdrawal and scratching responses, respectively, and the molecular and anatomical basis of itch has been extensively reviewed[46-51]. Many theories had been proposed to explain the coding of pain *versus* itch[17,46,52,53], but in recent years the population coding theory has gained considerable support[18,20,49,54]. The discovery of primary and relay sensory neurons responding selectively to noxious stimuli suggests the existence of a pain-related circuitry[55-58]. Itch-selective neurons or pruriceptors also exist. Using the microneurographic technique, Schmelz *et al.* reported the existence of histamine-sensitive mechano-insensitive primary afferents whose activation is correlated with the itch sensation in humans[59], and in cats there are histamine-sensitive neurons in the dorsal horn that do not respond to mechanical or thermal stimuli[60]. Cell ablation experiments in mice show that spinal neurons expressing the gastrin-releasing peptide receptor (GRPR) are required to sense itch, but not pain[61,62]. Furthermore, a very small subset of DRG neurons marked by the expression of the

Mrgpr family of G protein-coupled receptors, such as MrgprA3 and MrgprC11, are promising candidates of pruriceptive neurons[63-65].

However, itch fibers are polymodal and respond to stimuli that normally generate pain, such as capsaicin, which activates the transient receptor potential channel TRPV1 (vanilloid)[66-69], and/or mustard oil that activates TRPA1 (ankyrin)[63-65]. Nonetheless, intradermal injection of a high dosage of capsaicin or mustard oil evokes burning pain[70]. This coding puzzle is explained by a suppression of itch by pain (Fig. 1C)[18,71-76]. Accordingly, itch is evoked if a stimulus selectively activates itch-related fibers. If a stimulus activates both pain and itch fibers, pure pain sensation can emerge if the evoked pain is sufficient to mask itch, as occurs with intradermal capsaicin injection. However, if the amount of pain is insufficient to mask itch, both pain and itch sensations can be evoked. Indeed, delivering a small amount of capsaicin into the epidermis, in a region likely enriched in itch fibers[51], can evoke both itch and nociceptive sensations[76,77].

The neural basis of itch inhibition by pain is beginning to be understood. Two studies show that VGLUT2-dependent glutamate release from a group of primary sensory afferents marked by the expression of the Nav1.8 sodium channel is required to sense pain and suppress itch in mice[75,78]. Removal of VGLUT2 from these neurons leads to pain attenuation, itch sensitization, and the spontaneous development of excessive scratching and skin lesions. More strikingly, with an apparent loss of itch inhibition by pain, injection of capsaicin is now switched to activate a normally "masked" itching pathway in these knockout mice[75]. Interestingly, Nav1.8-expressing neurons include both pain-related and itch-related neurons[75], suggesting that with a loss of pain, glutamate release from itch fibers is dispensable for the transmission of itch-related information, although in wild-type mice, synaptic glutamate release from itch fibers could play a modulatory role, such as removing tonic itch inhibition from pain-related neurons[75,79]. The next question is to understand where itch inhibition by pain occurs in the nervous system. Electrophysiological studies in cats and primates suggest that itch inhibition by pain-processing neurons starts to occur in the dorsal spinal cord or in the spinal trigeminal nuclei[60,80]. For example, histamine-sensitive spinal neurons are normally silent[60], and scratching can directly inhibit histamine-evoked firing by these neurons[80]. Ross *et al*. then showed that a group of spinal/hindbrain inhibitory neurons, whose development is dependent on the bHLHb5 transcription factor, is essential for itch inhibition[81]. Conceivably, VGLUT2-dependent glutamate release from pain-processing sensory fibers could activate Bhlhb5-dependent inhibitory neurons to suppress itch (Fig. 1C).

5 Changes in labeled line crosstalk could lead to neuropathic pain and itch

One hallmark of neuropathic pain symptoms is pain evoked by innocuous mechanical or cold stimuli, referred to as mechanical or cold allodynia[12,13,82]. The underlying mechanisms are quite complex, as described in recent reviews[12,13,83-86]. Here we only discuss one of those mechanisms: disruption of labeled line crosstalk caused by injury-induced central disinhibition.

In terms of mechanical allodynia, human psychophysical studies demonstrated that myelinated A-fibers are required for the readout of dynamic mechanical allodynia[87-90], suggesting that activation of LTMRs is switched to promote rather than inhibit pain. This switch is at least partly caused by a loss of central inhibition through multiple mechanisms[12,39,82,91,92]. One is a direct loss of inhibitory neurons in the dorsal spinal cord, but controversies remain[93,94]. The other is that nerve lesions induce the release of brain-derived growth factor from activated microglia, which in turn causes (1) down-regulation of the expression of the potassium-chloride co-transporter KCC2 channel, (2) a change in the anion equilibrium potential, and (3) a loss of GABA- or glycine-mediated inhibition in post-synaptic neurons[91,95,96]. In an extreme situation, the loss of KCC2 could reach a degree that allows GABA or glycine to drive excitation, rather than inhibition[91]. As a result of this disinhibition, Aβ LTMRs are now able to activate the normally masked pre-existing neural circuit linked to pain-processing neurons in superficial laminae (pathway "1" in

Fig. 1B). Consistent with this model, intrathecal injection of GABA or glycine receptor antagonists is sufficient to generate mechanical allodynia in animals[91,97-99].

Besides mechanical allodynia, human patients suffering neuropathic pain also complain of burning pain in response to innocuous cold stimuli, such as grabbing a cup containing ice water or placing a spoonful of ice cream onto the tongue. In Fig. 1A, we show a mechanism by which activation of the Aδ cold-labeled line can dominantly mask a C-fiber pain-labeled line that also responds to innocuous cold. Apparently, the masking of pain by the Aδ cold-labeled line is abolished in patients with neuropathic pain. This in principle could be caused by the selective degeneration of Aδ cold fibers, or by central disinhibition induced by nerve lesions, as in the development of mechanical allodynia. Other mechanisms involving sensitization of nociceptors have also been proposed[100].

A failed labeled line crosstalk is also seen in patients suffering chronic itch. Scratching and other painful stimuli do not just fail to suppress itch, but are switched to promote it in these patients[14-16,46]. The simplest interpretation is that the circuits involved with pain-induced itch inhibition might be impaired in patients with chronic itch. Because itch fibers are polymodal, capable of responding to painful and mechanical stimuli, central disinhibition might allow painful stimuli to activate the normally masked itch pathways (Fig. 1C). This central disinhibition mechanism is indirectly supported by animal studies, showing that a loss, or failed activation, of inhibitory neurons in the mouse dorsal spinal cord results in the development of chronic neurogenic itch that shares the symptoms seen in human patients, including the promotion of itch by painful stimuli[75,81]. In summary, one of the common themes associated with chronic pain and itch is the failed antagonistic interactions among sensory-labeled lines, which allows anti-pain and anti-itch systems to activate normally masked pro-pain and pro-itch pathways, respectively.

6 Conclusion

The coding of somatic sensory information might be best explained by the population-coding theory that highlights the existence of distinct sensory-labeled lines, the polymodal nature of most sensory fibers, and antagonistic interactions among different sensory-labeled lines, such as pain suppression by Aδ cool fibers and LTMRs, cool suppression by C-warm fibers, and itch suppression by pain. Because of the polymodal nature of most sensory fibers, a given stimulus often activates multiple labeled lines, and antagonistic interactions among these labeled lines are required to generate a dominant sensation. Following central disinhibition induced by nerve injury, the coding of somatic sensation can be changed, such that pain can be evoked by innocuous cold and mechanical stimuli through pre-existing neural circuits. These observations suggest the existence of multiple “pre-assembled” pain-labeled lines that are mediated by low or high threshold primary sensory neurons. Some sensory fibers, such as LTMRs, could then operate along different labeled lines (touch *versus* pain) under normal and pathological conditions, respectively (Fig. 1C, pathways “1” *versus* “3”). Finally, one of the key features of neuropathic pain and chronic itch is the failed antagonistic interaction of sensory-labeled lines, with anti-pain or anti-itch systems switched to become pro-pain or pro-itch. Future characterization of the neural circuits involved with labeled line crosstalk may therefore provide new thinking for chronic pain and itch treatment, such as by restoring the lost anti-pain or anti-itch systems.

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