Circuit Mechanisms of Itch in the Brain

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Itch is an unpleasant somatic sensation with the desire to scratch, and it consists of sensory, affective, and motivational components. Acute itch serves as a critical protective mechanism because an itch-evoked scratching response will help to remove harmful substances invading the skin. Recently, exciting progress has been made in deciphering the mechanisms of itch at both the peripheral nervous system and the CNS levels. Key neuronal subtypes and circuits have been revealed for ascending transmission and the descending modulation of itch. In this review, we mainly summarize the current understanding of the central circuit mechanisms of itch in the brain.

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INTRODUCTION

Itch (also known as pruritus) is defined as an unpleasant somatic sensation that evokes a desire to scratch (Ikoma et al., 2006). The strong emotional and motivational components of itch play important roles in driving scratching behaviors. The scratching behaviors will not only relieve itchiness but also induce pleasure (Mochizuki et al., 2014), which leads to the vicious itch–scratching cycle. The itch–scratching cycle could cause severe skin damage in patients with chronic itch. These unique characteristics make itch a complex physiological function whose neural mechanism is largely unresolved.

Recent studies have revealed the molecular markers and circuits of itch processing in the spinal cord. Neurons expressing gastrin-releasing peptide receptor (GRPR) are predominantly excitatory neurons, representing a key component of the spinal chemical itch circuit (Sun and Chen, 2007; Sun et al., 2009). Natriuretic peptide receptor A–expressing neurons in the dorsal spinal cord coexpressed with gastrin-releasing peptide (GRP) are located upstream of $GRPR^+$ neurons along the spinal pathway for the chemical itch (Mishra and Hoon, 2013). Spinal inhibitory interneurons, such as galanin-positive neurons and neuronal nitric oxide synthase–positive neurons, form predominant inhibitory synapses with $GRPR^+$ neurons and play an important role in gating chemical itch (Kardon et al., 2014; Liu et al., 2019; Ross et al., 2010). A specific population of interneurons expressing transcription factor *BHLHB5* inhibits itch by releasing opioid peptide dynorphin, and the kappa opioid receptor agonists might have therapeutic potential for treating pruritus (Kardon et al., 2014; Ross et al., 2010). In addition to the chemical itch evoked by pruritogens, itch sensation can also be evoked by light tactile stimuli, known as the mechanical itch. Recent studies found that the mechanical itch is independent of spinal $GRPR^+$ neurons but requires spinal excitatory interneurons expressing Urocortin 3 (UCN3) (Pan et al., 2019). The neuropeptide Y $(NPY)^+$ neurons form functional inhibitory synaptic connections with $UCN3^+$ neurons and gate the mechanical itch circuit in the spinal level (Acton et al., 2019; Bourane et al., 2015; Pan et al., 2019).

Human brain imaging has been employed to study the cerebral mechanisms of itch since the 1990s (Hsieh et al., 1994) and revealed that many brain areas are involved in itch processing, including the primary somatosensory cortex (S1), prefrontal cortex (PFC), insular cortex (IC), and thalamus (Mochizuki and Kakigi, 2015; Mochizuki et al., 2019). Besides human brain imaging studies, the transmission of itch signals has also been examined by in vivo electrophysiological studies in animals. These studies have revealed that the spinothalamic and trigeminothalamic tract neurons are activated by peripheral pruritic stimuli in cats (Andrew and Craig, 2001), rodents (Lipshetz and Giesler, 2016; Moser and Giesler, 2014), and nonhuman primates (Davidson et al., 2009, 2007; Simone et al., 2004). Besides spinal projections to the thalamus, the trigeminoparabrachial tract is also involved in itch processing (Akiyama et al., 2016; Jansen and Giesler, 2015). These studies suggest that several critical nuclei, including the thalamus and the parabrachial nucleus (PBN), are involved in itch processing. Recent studies have begun to dissect the functional roles of these nuclei and central circuits of itch using optogenetic, pharmacogenetic, and genetic approaches. The progress on both peripheral and central neural mechanisms has been well-summarized in several critical reviews (Chen and Sun, 2020; Dong and Dong, 2018). In this review, we will focus on the recent progress on brain circuits in ascending transmission (Figure 1) and descending modulation (Figure 2) of itch.

SENSORY COMPONENT OF ITCH

Previous human brain imaging studies have examined the difference in brain activity in healthy volunteers in response to histamine or saline injection and showed significant

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Abbreviations: 5-HT, 5-hydroxytryptophan; ACC, anterior cingulate cortex; CeA, central amygdala; CGRP, calcitonin gene-related peptide; CPA, conditional place aversion; GABA, γ-aminobutyric acid; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; IC, insular cortex; NAc, nucleus accumbens; NE, norepinephrine; NPY, neuropeptide Y; PAG, periaqueductal gray; PBN, parabrachial nucleus; PFC, prefrontal cortex; Po, posterior thalamic nucleus; PoT, posterior triangular nucleus; RVM, rostral ventromedial medulla; S1, primary somatosensory cortex; TAC1, tachykinin 1; TACR1, tac1 receptor; UCN3, Urocortin 3; VB, ventrobasal nucleus; VPM, ventral posteromedial nucleus; VTA, ventral tegmental area

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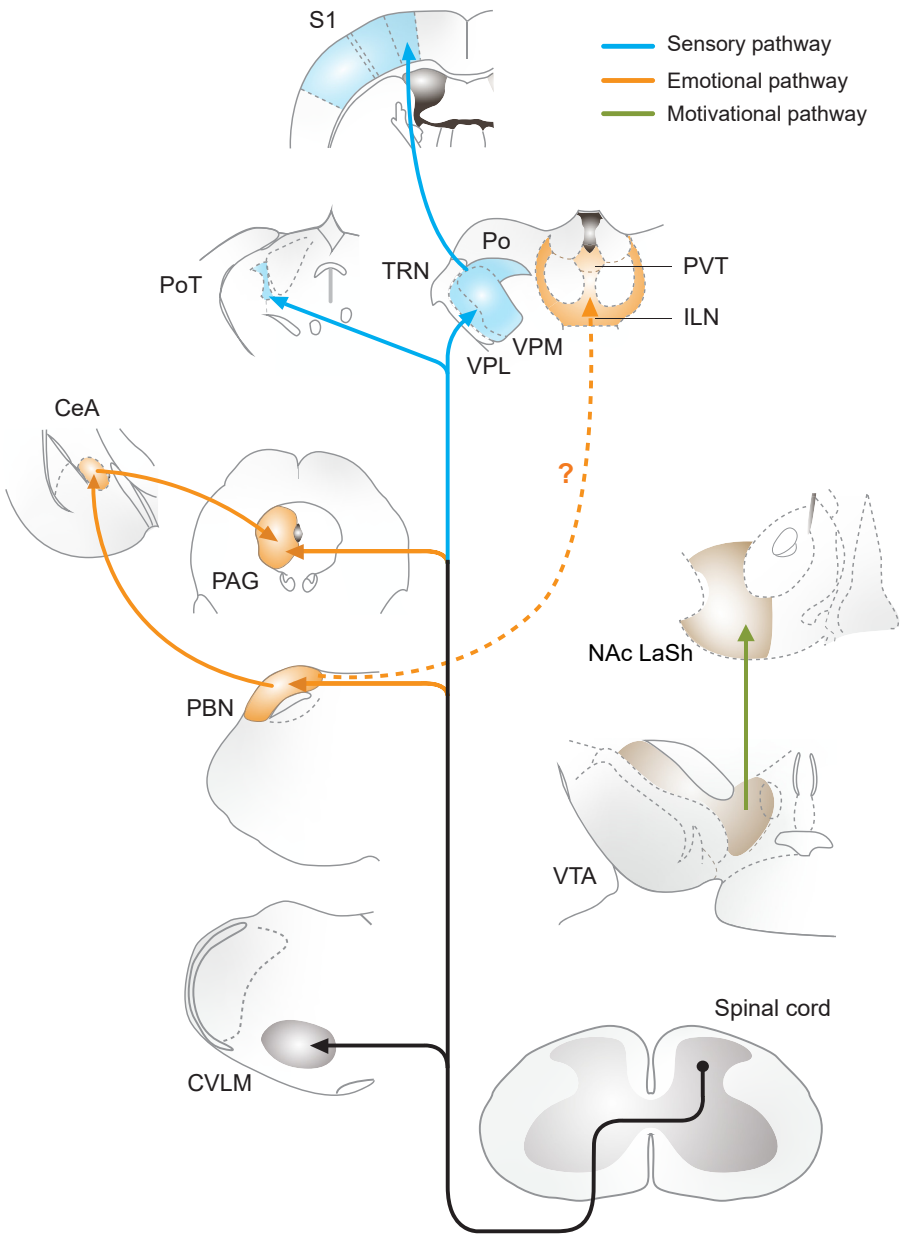

Figure 1. Neural circuits underlying different components of itch. VB thalamus, Po, and S1 (cyan) are involved in the processing of the sensory component of itch. PBN, CeA, and PAG (orange) are involved in the processing of the emotional component of itch. VTA and NAc (ocher) are involved in the processing of the motivational component of itch. CeA, central amygdala; CVLM, caudal ventrolateral medulla; ILN, intralaminar thalamic nuclei; NAc, nucleus accumbens; NAc LaSh, lateral shell of the nucleus accumbens; PAG, periaqueductal gray; PBN, parabrachial nucleus; Po, posterior thalamic nucleus; PoT, posterior triangular nucleus; PVT, paraventricular thalamic nucleus; S1, primary somatosensory cortex; TRN, thalamic reticular nucleus; VB, ventrobasal nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus; VTA, ventral tegmental area.

activation of the primary S1 and premotor cortex but not the secondary somatosensory cortex (Darsow et al., 2000; Mochizuki et al., 2003). Similar activation was also detected in human subjects watching video clips of scratching (Holle et al., 2012). In patients with atopic dermatitis, higher activation was detected in the contralateral thalamus, bilateral cingulate cortex, and PFC than in healthy volunteers (Ishiuji et al., 2009; Schneider et al., 2008). By contrast, studies in rodents showed elevated activities in many brain nuclei, including the thalamus, hypothalamus, and brainstem nuclei, but these studies did not detect the activation of S1 and the premotor cortex (Jeong and Kang, 2015; Jeong et al., 2016).

Recent animal studies have begun to examine the functional role of thalamic nuclei in itch processing. The ventrobasal thalamus (VB) is the primary relay nuclei in the thalamus, which can be divided into two subnuclei: the ventral posterolateral nucleus and the ventral posteromedial nucleus (VPM). Lipshetz et al. (2018) found that >70% of the VPM neurons were responsive to one or several kinds of pruritogens. The posterior triangular nucleus (PoT), a high-order thalamic nucleus, has also been shown to be itch responsive. Extracellular recording results showed that the neurons in the PoT responded at higher frequencies than those in the VPM to both histamine-dependent and -independent pruritogens applied to the cheek, indicating that the PoT might be a particularly interesting region for itch transmission from the cheek (Lipshetz et al., 2018). A recent study confirmed that the posterior thalamic nucleus (Po) mediates facial histaminergic itch using fiber photometry and pharmacogenetic manipulation (Zhu et al., 2020). Consistently, previous tracing and electrophysiological studies showed that the Po receives pruriceptive information from the spinothalamic and trigeminothalamic tracts (Chiaia et al., 1991; Gauriau and Bernard, 2004; Lipshetz and Giesler, 2016;

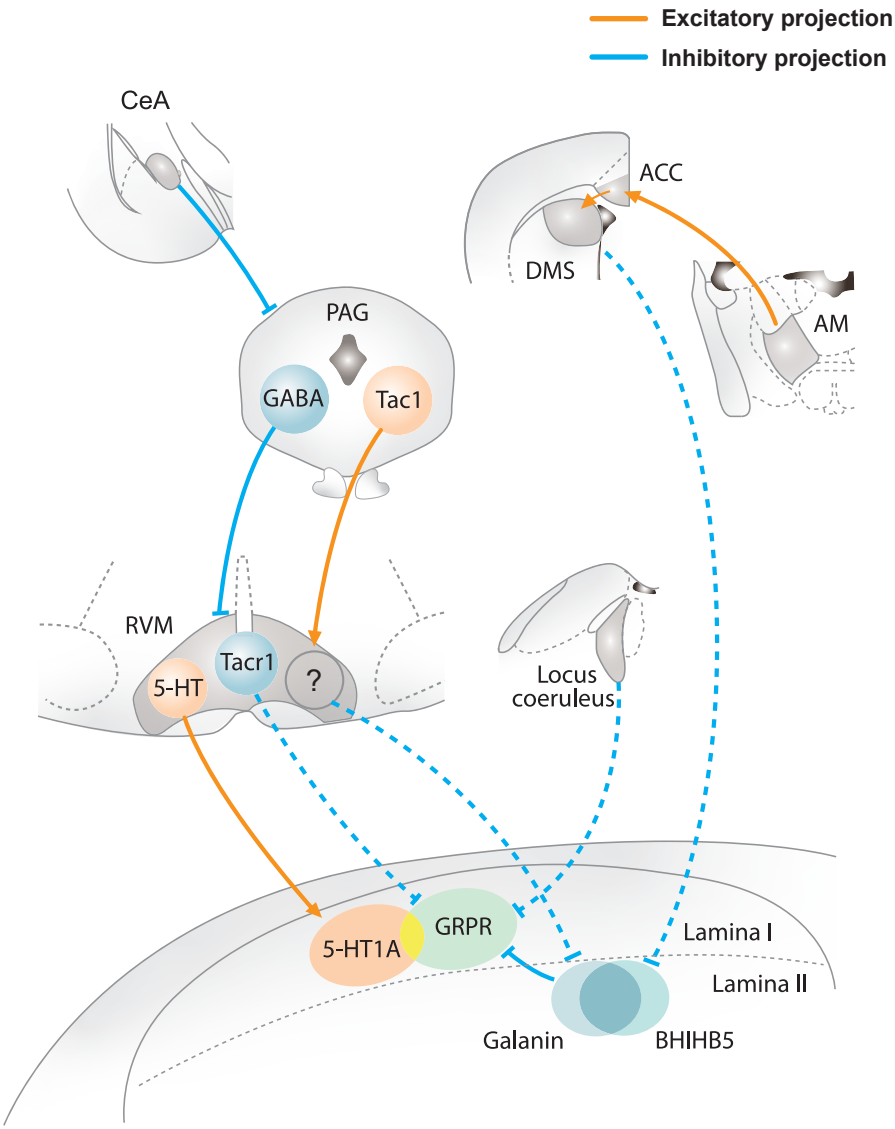

Figure 2. Neural circuit underlying descending modulation of itch. CeA, PAG, RVM, and locus coeruleus are involved in descending modulation of itch through the targeting of spinal GRPR$^+$ neurons, 5-HT1A$^+$ neurons, and Galanin$^+$ neurons. AM thalamic nucleus, ACC, DMS are also involved in modulating Bhlhb5$^+$ neurons in the spinal cord. 5-HT, 5-hydroxytryptophan; ACC, anterior cingulate cortex; AM, anteromedial thalamic nucleus; CeA, central amygdala; DMS, dorsal medial striatum; GABA, γ-aminobutyric acid; PAG, periaqueductal gray; RVM, rostral ventromedial medulla.

Moser and Giesler, 2014; Veinante et al., 2000; Zhang and Giesler, 2005). VB thalamus and Po are also involved in the processing of pain (Saadé et al., 2006; Zhang et al., 2017; Zhu et al., 2021). It is likely that thalamic neurons process different somatosensory submodalities with population coding, given that most spinothalamic tract neurons are responsive to multiple types of stimuli (Simone et al., 2004). However, further studies are warranted to investigate the underlying mechanisms.

As shown by human brain imaging studies (Gross et al., 2007; Kim et al., 2017; Vierck et al., 2013), the S1 is a critical cortical region for the sensory component of itch processing. A recent in vivo electrophysiological study examined the responses of S1 neurons to the application of mechanical stimuli and intradermal injections of pruritic and algesic chemicals in anesthetized rats (Khasabov et al., 2020). They found that most of the recorded neurons were activated by one or more stimuli and that no neurons were excited exclusively by pruritogens, arguing against a specificity theory for the sensation of itch. Thus, how S1 neurons encode and process different sensory modalities remains elusive.

EMOTIONAL COMPONENT OF ITCH

Itch sensation is associated with a strong negative emotional component, and scratching behavior induces pleasure and itch relief. In addition, chronic itch is associated with increased stress, anxiety, and other mood disorders. These disorders further exacerbate itch, leading to a vicious cycle that worsens the disease prognosis and reduces QOL (Golpanian et al., 2020; Marron et al., 2016; Oh et al., 2010; Sanders and Akiyama, 2018; Simpson et al., 2016). Human brain imaging studies have found that patients with chronic itch exhibited higher activation in several brain areas that are involved in emotion, including the IC and PFC (especially the cingulate cortex), in response to pruritic stimuli, indicating altered neural activity in chronic conditions (Ishiuji et al., 2009; Napadow et al., 2014; Schneider et al., 2008). Animal studies also confirmed that both the IC and cingulate cortex are involved in negative emotions associated with

aversive somatosensation (Gehrlach et al., 2019; Juarez-Salinas et al., 2019; Meda et al., 2019; Wu et al., 2020; Zang et al., 2020; Zhou et al., 2018).

Animal studies have begun to reveal the mechanisms underlying negative and positive emotional components of itch (Mu and Sun, 2017; Sanders et al., 2019; Su et al., 2019). It is thought that the spinoparabrachial tract and the PBN are involved in pain processing (Basbaum et al., 2009; Dunckley et al., 2005; Youssef et al., 2016). Several tracing and in vivo electrophysiological studies in rodents have shown that the PBN is also involved in itch processing (Akiyama et al., 2016; Jansen and Giesler, 2015; Li et al., 2021b). A study found that the PBN serves as a critical itch-processing nucleus (Mu et al., 2017). Inhibition of the PBN neurons impairs itch-induced scratching behaviors, and silencing synaptic transmission in the PBN alleviates both acute itch and chronic itch. However, it is noteworthy that this study did not determine whether the manipulation of the PBN affects the sensory component or affective component. A more recent study showed that a subtype of PBN neurons expressing calcitonin gene-related peptide (CGRP) are activated by noxious and pruritic stimuli and that silencing of $CGRP^{+}$ neurons attenuates fear responses and itch-induced scratching behaviors, indicating that the PBN might be involved in various affective–behavioral states, including both itch and pain (Campos et al., 2018).

The PBN sends projections to various brain areas, with the central amygdala (CeA) being the most critical downstream target, which is also thought to be the primary center for anxiety and fear (Chiang et al., 2020). Previous human brain imaging studies have shown that the amygdala was activated by itch stimuli and deactivated by scratching, indicating that the CeA might contribute to processing itch-induced unpleasure (Papoiu et al., 2013, 2012; Vierow et al., 2015). A rodent study has shown that pruritic stimuli activate the lateral external subdivision of PBN that projects to CeA (Sanders et al., 2019). Furthermore, selective activation of itch-responsive CeA neurons could enhance both scratching and anxiety-like behaviors but not in some aversive and appetitive behaviors previously ascribed to CeA neurons, indicating that itch-activated CeA neurons are critical for mediating sensory and affective components of itch (Samineni et al., 2021; Sanders et al., 2019).

Previous studies have shown that the periaqueductal gray (PAG) is involved in emotion regulation (Etkin et al., 2015; Motta et al., 2017). A recent study revealed that the PAG is critical for modulating the affective component of itch. Pharmacogenetic activation of PAG γ-aminobutyric acid (GABA)ergic neurons impairs itch-induced scratching behaviors and itch-associated conditional place aversion (CPA), suggesting the PAG GABAergic neurons also play a prominent role in modulating sensory and affective components of itch (Samineni et al., 2019). Furthermore, the ventral tegmental area (VTA) GABAergic neurons are critical in encoding the unpleasant or aversive aspect of itch sensation (Su et al., 2019). VTA GABAergic neurons positively regulate scratching behaviors during acute itch and contribute to itch-associated CPA.

The mechanism underlying scratching-evoked pleasure in itch is a fascinating question. The VTA is a well-known reward-related center in the brain. Brain imaging studies found that the VTA is involved in the processing of scratching and in encoding the reward perceived in the scratching of itch (Mochizuki et al., 2014; Papoiu et al., 2013). Mochizuki et al. (2014) showed that the VTA was significantly activated during scratching in the pleasant condition (on-target scratching) compared with that in the control condition (off-target scratching). Besides, Papoiu et al. (2013) showed that the VTA is activated during the active scratching by subjects themselves but not during the passive scratching by an investigator. These studies indicate that the VTA could contribute to the pleasure and the addictive features of scratching. In addition, Su et al. (2019) found that dopaminergic neuron activation lags behind GABAergic neurons and is dependent on the scratching of the itchy site. Inhibition of VTA dopaminergic neurons reduced scratching behaviors and attenuated scratching-associated conditional place preference (Su et al., 2019). These studies suggest that VTA dopaminergic neurons are critical in scratching-evoked pleasure.

MOTIVATIONAL COMPONENT OF ITCH

The motivational component of itch plays a key role in driving scratching behavior. The earlier brain imaging study has unraveled a coactivation of the anterior cingulate cortex (ACC), motor cortex, and premotor cortex that depicts a motor intention of the urge to scratch (Hsieh et al., 1994). This is consistent with the finding that scratching in the pleasant condition (on-target scratching) deactivated the cingulate cortex and the primary motor cortex (Mochizuki et al., 2014), supporting the idea that these brain regions could be involved in motivation for scratching behavior. The negative emotional component of itch could also drive the scratching behavior. The VTA GABAergic neurons, which are involved in the emotional component of itch, might also be involved in generating motivation for scratching (Su et al., 2019).

It is well known that VTA dopaminergic neurons play an important role in motivation, and dopamine receptors have been shown to be involved in itch-evoked scratching behavior (Akimoto and Furuse, 2011; Bromberg-Martin et al., 2010). Yuan et al. (2018) strictly defined the different characteristics of scratching behaviors recorded by the magnetic induction system. Scratching induces a cluster of voltage peaks (each peak during scratching is defined as a scratching event). Some scratching events are closer to each other, and a cluster of adjacent scratching events is defined as a scratching bout. A cluster of adjacent scratching bouts is defined as a scratching train (Yuan et al., 2018). By precisely manipulating the VTA dopaminergic neurons, Yuan et al. (2018) found that brief photoinhibition of VTA dopaminergic neurons significantly shortened the duration of the scratching train, suggesting that the activation of dopaminergic neurons near the onset of scratching behavior likely codes the motivation driving subsequent scratching. This result is in line with the ability of dopaminergic neurons to process aversive signals (Bromberg-Martin et al., 2010). This is also supported by the human imaging study showing that the VTA was activated during itching without scratching (Mochizuki et al., 2014).

The VTA dopaminergic neurons are reported to mediate the reward to scratch-induced relief of itch and code motivation driving subsequent scratching in different studies (Su et al., 2019; Yuan et al., 2018). The complex functions of dopaminergic neurons might be mediated by different subpopulations of dopaminergic neurons or different dopaminergic receptors in the downstream brain regions of the VTA, especially the nucleus accumbens (NAc). Previous studies have found that dopamine 1 receptor and dopamine 2 receptor in the NAc have different functions in learning and behavioral plasticity.

DESCENDING MODULATION OF ITCH

The neuromodulatory system plays important roles in gating sensory processing (Dasgupta et al., 2018; Gil and Metherate, 2019; Jacob and Nienborg, 2018). Among them, norepinephrine (NE, or noradrenaline) and serotonin have been shown to be involved in descending control of itch signal processing. NE-positive neurons are located in several brainstem nuclei, including the locus coeruleus, which is a small brain area located deep in the brainstem and provides broad noradrenergic projections through the CNS (Chandler et al., 2019; Poe et al., 2020). Previous studies have shown that NE is involved in regulating spinal itch signal processing through both α1 and α2 adrenoceptors (Gotoh et al., 2011a, 2011b). Recent studies have revealed that α1 adrenoceptors are preferentially expressed in spinal inhibitory interneurons and that α1A adrenoceptors are expressed in spinal dynorphin-positive interneurons (Häring et al., 2018; Serafin et al., 2019). Koga et al. (2020a) showed that the descending locus coeruleus noradrenergic pathways control acute and chronic itch by facilitating inhibitory synaptic inputs onto spinal $GRPR^+$ neurons. Furthermore, the projection from locus coeruleus to the ACC is also involved in the modulation of itch (Koga et al., 2020b), suggesting that the locus coeruleus has complex modulatory effects on itch according to diverse efferents and adrenergic receptors. Serotonin (5-hydroxytryptophan [5-HT]) is another neuromodulator that plays a vital role in descending control of the spinal itch signal processing. Depleting the spinal $5\text{-}HT^+$ fibers attenuates pruritogen-induced scratching behavior (Zhao et al., 2014), suggesting a facilitating role of 5-HT in itch. This effect is mediated by the 5-HT1A receptor, which facilitates GRP–GRPR signaling by directly interacting with GRPR. Many other types of receptors for 5-HT are also expressed in the spinal cord (Majczyński et al., 2020; Xie et al., 2012), and their functional roles in descending control of itch remain to be determined.

The PAG is a critical hub that modulates nociceptive signals in the descending pathway (Basbaum and Fields, 1984; Huang et al., 2019; Kuner and Kuner, 2021; Ossipov et al., 2010). A human brain imaging study showed that the PAG was activated during simultaneous stimulation of itch and cold pain but not during itch alone (Mochizuki et al., 2003), and the PAG was found to be significantly deactivated by scratching during itch in humans (Papoiu et al., 2013). Rodent imaging studies also detected increased activity of the PAG during itch (Jeong and Kang, 2015; Jeong et al., 2016). These studies suggested that PAG might be involved in itch modulation. PAG could integrate the itch-related information from both the ascending and descending pathways because PAG receives itch-related information from both the CeA and the PBN (Li et al., 2021a; Samineni et al., 2021). Recent studies have revealed diverse roles of different subtypes of neurons in PAG in itch (Gao et al., 2019; Samineni et al., 2019, 2017). Gao et al. (2019) found that a subpopulation of PAG glutamatergic neurons expressing tachykinin 1 (PAG^{Tac1}) facilitates the itch–scratching cycle through the descending mechanism (Gao et al., 2019). They showed that ablation or inhibition of these neurons reduced itch-induced scratching behaviors, and activation of these neurons induced spontaneous scratching behaviors. They also found that ablation of $TAC1^+$ neurons did not cause significant changes in mouse behavioral responses to thermal or mechanical stimuli or to a formalin-evoked nociceptive insult, indicating that PAG $TAC1^+$ neurons are differentially involved in the modulation of itch and pain processing. Moreover, $TAC1^+$ neurons form glutamatergic synapses with the rostral ventromedial medulla (RVM) neurons, and the PAG^{Tac1} activation–induced scratching behavior is reduced by ablation of spinal $GRPR^+$ neurons, suggesting that the PAG^{Tac1}–RVM circuit modulates $GRPR^+$ neurons in the descending modulation of itch. Given that RVM neurons form strong inhibitory synapses with $GRPR^+$ neurons (Liu et al., 2019), it is possible that the PAG^{Tac1} neurons facilitate spinal itch processing through a disynaptic disinhibition circuit. However, a recent study showed that the TAC1 receptor (TACR1)-positive neurons in RVM are GABAergic and have an inhibitory effect on itch (Follansbee et al., 2021[1]). Thus, the specific subpopulation of PAG^{Tac1} downstream in RVM is still elusive.

The ACC, a higher-order cortical region, is also involved in the modulation of itch. Several brain imaging studies suggested that the cingulate cortex is activated by both itching and pain (Herde et al., 2007; Mochizuki et al., 2007, 2003). They also found that subregions of the cingulate cortex might be more involved in itch than in pain (Herde et al., 2007; Mochizuki et al., 2007). Besides, rodent studies found that chronic itch could potentiate synaptic transmission in the ACC (Zhang et al., 2016). Recent studies have shown that the anteromedial thalamic nucleus–ACC–dorsal medial striatum circuit modulates histaminergic itch likely through a spinal $BHLHB5^+$ interneuron-dependent mechanism (Deng et al., 2020; Lu et al., 2018).

CONCLUSION AND FUTURE DIRECTIONS

In summary, dramatic progress has been made in deciphering the central circuit mechanisms of itch. Several critical brain regions and neural circuits have been revealed for the processing or modulation of itch. The mechanism of contagious itch has been partially elucidated (Holle et al., 2012; Yu et al., 2017). Despite all these exciting findings, several key issues of itch signal coding and processing remain to be addressed.

First, how is itch encoded and perceived? The coding mechanism of the itch is still controversial (Braz et al., 2014;

[1] Follansbee AT, Domocos D, Nguyen E, Nguyen A, Bountouvas A, Velasquez L. Descending inhibition of itch by neurokinin 1 receptor (Tacr1) - expressing ON cells in the rostral ventromedial medulla. bioRxiv 2021.

Koch et al., 2018; Ma, 2010; Prescott et al., 2014). A series of extracellular recording studies have been performed to examine the responses of spinothalamic, trigeminothalamic, thalamic, and cortical neurons to pruritic stimuli (Davidson et al., 2012; Khasabov et al., 2020; Lipshetz et al., 2018; Moser and Giesler, 2014). These studies found that the majority of recorded neurons were excited by both pruritic and nociceptive stimuli. Thus, the coding principle of itch and how itch is perceived remain elusive. It will be critical to perform large-scale in vivo extracellular recording or cellular calcium imaging to examine the activity of thalamic or cortical neurons during itch processing in awake animals. The PBN, CeA, PAG, and other nuclei are also closely involved in pain sensation, and it is likely that different neuronal populations are involved. For example, the PAG $TAC1^+$ neurons regulate itch rather than pain. However, how these nuclei are discriminately processing itch and other modalities need further research. Further transcriptomic analyses and genetic manipulation should decipher the cellular mechanism underlying itch and pain modulation.

Second, the circuit mechanisms underlying the itch-associated emotion and motivation need further examination. Several brain areas and subtypes of neurons have been implicated in itch-associated emotion and motivation. How these neurons or brain areas receive itch-associated emotion and motivational components is still unknown. It is also important to further study the functional role of itch-associated–negative and –positive emotions in itch–scratching cycle.

Finally, the central mechanisms underlying chronic itch are largely unknown. Recent studies in chronic pain have recognized that synaptic plasticity could function as a critical mechanism underlying pathological pain (Kuner, 2010; Kuner and Flor, 2016; Luo et al., 2014). The chronic itch, including the psychogenic itch, is likely resulted from the central sensitization and loss of descending control (Misery, 2020; Misery et al., 2018). It will be necessary to further study the neural plasticity during chronic itch and show the involvement of synaptic plasticity in the development of chronic itch.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

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