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Review

Neuroimmune interactions in itch: Do chronic itch, chronic pain, and chronic cough share similar mechanisms?

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ABSTRACT

Itch and pain are closely related but also clearly distinct sensations. Pain is known to suppress itch, while analgesics such as morphine can provoke itch. However, in pathological and chronic conditions, pain and itch also have similarities. Dysfunction of the nervous system, as manifested by neural plastic changes in primary sensory neurons of the peripheral nervous system (peripheral sensitization) and spinal cord and brain stem neurons in the central nervous system (central sensitization) will result in chronic pain and itch. Importantly, these diseases also result from immune dysfunction, since inflammatory mediators can directly activate or sensitize nociceptive and pruriceptive neurons in the peripheral and central nervous system, leading to pain and itch hypersensitivity. In this mini-review, I discuss the roles of Toll-like receptors (TLRs), transient receptor potential ankyrin 1 (TRPA1) ion channel, and Nav1.7 sodium channel in regulating itch and inflammation, with special emphasis of neuronal TLR signaling and the interaction of TLR7 and TRPA1. Chronic pain and chronic itch are debilitating diseases and dramatically impact the life quality of patients. Targeting TLRs for the control of inflammation, neuroinflammation (inflammation restricted in the nervous system), and hyperexcitability of nociceptors and pruriceptors will lead to new therapeutics for the relief of chronic pain and chronic itch. Finally, given the shared mechanisms among chronic cough, chronic pain, and chronic itch and the demonstrated efficacy of the neuropathic pain drug gabapentin in treating chronic cough, novel therapeutics targeting TRPA1, Nav1.7, and TLRs may also help to alleviate refractory cough via modulating neuron-immune interaction.

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Contents

1. Introduction

Itch and pain are closely related but distinct sensations. Itch (pruritus) elicits scratching response, whereas pain causes withdrawal responses. In physiological conditions, acute itch can be inhibited by scratching and painful stimuli. The antagonistic interaction between itch and pain is further revealed by the fact that analgesic compounds such as morphine and bile acid can evoke itch [1,2]. Itch and pain also share similarities, especially in

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pathological and chronic conditions [3]. Both itch and pain are detected by primary sensory neurons in dorsal root ganglion (DRG) and trigeminal ganglion. Indeed, pruriceptors and nociceptors are overlapped in DRGs, and the pruriceptors are a subset of small population of C-fiber nociceptors. Pain and itch also employ largely overlapping transduction machinery, such as transient receptor potential ion channel subtype V1 (TRPV1) and A1 (TRPA1), Toll-like receptors (TLRs), and proteinase activated receptors (PARs), although the G-protein coupled receptor (GPCR) MrgprA3 and thymic stromal lymphopoietin (TSLP) receptor are identified as itch-specific receptors [4,5]. Under pathological and chronic conditions, dysfunction of the nervous system, as manifested by neural plastic changes in primary sensory neurons of the peripheral nervous system (peripheral sensitization) and spinal cord, brain stem, and cortical neurons in the central nervous system (central sensitization) will not only result in chronic pain but also lead to chronic itch [3,6]. For example, central sensitization underlies both touch-evoked pain (allodynia) and touch-evoked itch (alloknesis) [7,8]. Loss of inhibitory synaptic transmission (disinhibition) in the spinal cord has also been attributed to both chronic pain and chronic itch; both can be suppressed by spinal implantation of forebrain GABAergic neurons [9,10]. Importantly, both diseases are a direct consequence of immune dysfunction, since inflammatory mediators, produced by immune cells and epithelial cells after tissue injury, can directly activate or sensitize nociceptive and pruriceptive neurons, leading to pain and itch hypersensitivity [3,11]. I focus this review on emerging roles of TLRs, TRPA1, and Nav1.7 in the regulation of pain, itch, and neuroinflammation, an inflammation that is restricted in the nervous system but is particularly important for the pathogenesis of neurological diseases [12]. Finally, I also discuss the shared mechanisms and treatments among chronic pain, chronic itch, and chronic cough.

2. Itch mediators and transduction mechanisms

As one of the best studied itch mediators, histamine is released from mast cells and binds to histamin H1 receptor (H1R), which is coupled with Gαq, phospholipase Cβ3, and TRPV1 in DRG neurons to evoke itch [13,14]. Although antihistamines are widely-used as anti-itch drugs, chronic itch is often resistant to anti-histamine treatments [15]. It is generally believed that unmyelinated C-fibers especially TRPV1-expressing C-fibers are responsible for generating both histamine dependent and independent itch, although some myelinated fibers were also implicated in cowhage-induced itch [16]. Nonhistaminergic itch (e.g., cowhage and chloroquine) activates distinct neural signaling pathways via PAR2, MrgprA3, and TRPA1 [17–19]. Thymic stromal lymphopoietin (TSLP) is an epithelial cell produced cytokine, which can directly act on primary sensory neurons to elicit itch via activation of TRPA1 [5]. At spinal cord level, the neuropeptides gastrin releasing peptide (GRP), substance P, and neuropeptide natriuretic polypeptide b (Nppb) have been implicated in itch sensation by activating respective GRPR, NK-1, and Npra in spinal cord neurons [20–22]. These peptides may also modulate itch via peripheral mechanisms. Some of these itch mediators and transducers are summarized in Table 1.

Oxidative stress has been strongly implicated in the pathogenesis of chronic pain [23]. Interestingly, oxidative stress also induces histamine-independent itch via activation of TRPA1 [24] (Table 1). Intradermal injection of the oxidants hydrogen peroxide and tert-butylhydroperoxide into the nape of mouse was shown to evoke robust scratching behavior. Although TRPV1 as a transduction molecule is dispensable for oxidants-induced itch, TRPV1-expressing C-fibers are indispensable for oxidant-induced itch. Furthermore, hydrogen peroxide-induced itch was suppressed by TRPA1 antagonist and antioxidants such as vitamin E [24,25].

Sodium channel subunit Nav1.7 has been strongly implicated in human pain sensation, based on gain-of-function and loss-of function mutations [26,27]. It was also reported that paroxysmal itch results from gain-of-function mutation of Nav1.7 [28]. In particular, a monoclonal antibody targeting the voltage sensor paddle of Nav1.7 can suppress both histaminergic itch (induced by compound 48/80) and non-histaminergic itch (induced by chloroquine) by inhibiting TTX-sensitive sodium currents and action potentials in C-fiber DRG neurons [29] (Table 1). This monoclonal antibody can also suppress acute inflammatory pain and inhibit synaptic transmission in spinal nociceptive circuit [29]. Given the efficacy of this antibody in inhibiting both pain and itch, it should act on the common neural circuit of pain and itch.

Chronic itch models are critical to study the molecular and cellular mechanisms of refractory itch and test new anti-itch therapies. These models include dry skin model induced by a mixture of acetone/ether (1:1) and water (AEW), contact dermatitis model induced by diphenylcyclopropenone (DCP), and allergic contact dermatitis model induced by 2,4-Dinitro-1-fluorobenzene (DNFB). Remarkably, TRPA1 is not only necessary for dry skin-induced chronic itch but also essential for dry skin-induced pathological changes triggered by dry skin-evoked itch and scratching

Table 1
Peripheral itch mediators and transducers in pruriceptive sensory neurons. The mediators can be produced by immune cells, epithelial cells, keratinocytes, and even neurons after tissue injury and infection. They act on their respective receptors in pruriceptive neurons to elicit itch via transducers (e.g., TRPA1 and TRPV1).

Challenges	Cell types	Mediators	Receptors	Effectors
			Pruriceptive sensory neurons	
Tissue injury	Keratinocytes	NGF	TrkA	TRPV1?
		ET-1	ET_A	TRPA1
		TSLP1	TSLPR	TRPA1
	Mast cells	Serotonin	5HTR	TRPA1
		Tryptase	PAR2	TRPV1
		Histamine	H1	TRPV1/Nav1.7
	Macrophages	TNF	TNFR1	TRPV1?
	T cells	IL-31	IL-31R	TRPV1/TRPA1
	Neurons	SP	NK1	TRPA1/TRPV1?
		GRP	GRPR	Unknown
		miRNAs (ss)	TLR7	TRPA1
Bacteria and virus infection	LPS	TLR4	TRPV1/TRPA1?	
	RNAs (ds)	TLR3	TRPA1?	
	RNAs (ss)	TLR7	TRPA1	
Drugs	Chloroquine	MagprA3	TRPA1/Nav1.7	
Oxidative stress	ROS (H_2O_2)	Unknown	TRPA1	

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