Itch: From mechanism to (novel) therapeutic approaches

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Itch is a common sensory experience that is prevalent in patients with inflammatory skin diseases, as well as in those with systemic and neuropathic conditions. In patients with these conditions, itch is often severe and significantly affects quality of life. Itch is encoded by 2 major neuronal pathways: histaminergic (in acute itch) and nonhistaminergic (in chronic itch). In the majority of cases, crosstalk existing between keratinocytes, the immune system, and nonhistaminergic sensory nerves is responsible for the pathophysiology of chronic itch. This review provides an overview of the current understanding of the molecular, neural, and immune mechanisms of itch: beginning in the skin, proceeding to the spinal cord, and eventually ascending to the brain, where itch is processed. A growing understanding of the mechanisms of chronic itch is expanding, as is our pipeline of more targeted topical and systemic therapies. Our therapeutic armamentarium for treating chronic itch has expanded in the last 5 years, with developments of topical and systemic treatments targeting the neural and immune systems. (J Allergy Clin Immunol 2018;142:1375-90.)

Key words: *Itch, pruritus, treatment, mechanism, pathophysiology, management*

Itch, which is defined as a sensation resulting in an urge to scratch, is normally a benign unpleasant physiologic response. However, when itch becomes severe or chronic (>6 weeks) or occurs in the context of an underlying medical condition, it has a significant effect on the patient's well-being (similar to that of chronic pain).[1] The chronicity of pruritus can affect sleep, mood, and personal relationships, significantly reducing quality of life.[2]

Although still in its infancy, our understanding of the mechanisms and pathways that transduce pruritic stimuli and process itch sensation is expanding. The most well-supported distinction between types of itch is that of histaminergic and nonhistaminergic itch.[3] Differences in these pathways correspond to differences in disease and treatment response. An improved understanding of the underlying mechanisms of itch has permitted us to develop new treatments and retool old ones to combat itch.

As our understanding expands, so does our ability to identify more specific targets for novel treatments, which would be

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Abbreviations used
ACC: Anterior cingulate cortex
AD: Atopic dermatitis
Bhlhb5: Helix-loop-helix family member B5
BTX: Botulinum neurotoxin
CGRP: Calcitonin gene–related protein
GPCR: G protein–coupled receptor
GRP: Gastrin-releasing peptide
GRPR: Gastrin-releasing peptide receptor
JAK: Janus kinase
KOR: κ-Opioid receptor
LPA: Lysophosphatidic acid
MOR: μ-Opioid receptor
Mrgpr: Mas-related G protein–coupled receptor
Na_V: Voltage-gated sodium channel
NGF: Nerve growth factor
NK: Neurokinin
NK1R: Neurokinin 1 receptor
PAR: Protease-activated receptor
PCC: Posterior cingulate cortex
PF: Prefrontal area
SP: Substance P
STAT: Signal transducer and activator of transcription
TrkA: Tropomyosin receptor kinase A
TRPA: Transient receptor potential ankyrin
TRPM: Transient receptor potential melastatin
TRPV: Transient receptor potential vanilloid
TSLP: Thymic stromal lymphopoietin

expected to have improved efficacy and reduced adverse effects. Ideally, the treatment of pruritus should center on targeting the primary instigator of the itch; however, the origin is not always easily identifiable or treatable. Hence treating itch can be an important part of caring for a patient's well-being. In this review we seek to discuss the potential underlying mechanisms and therapies related to itch.

PATHWAYS OF ITCH

Physiologic itch begins at the skin with the introduction of a pruritogen. Pruritogens activate certain receptors on small itch-selective unmyelinated C fibers with cell bodies in the dorsal root ganglia. The majority of these receptors are G protein–coupled receptors (GPCRs). GPCRs promote the opening of ion channels (eg, transient receptor potential cation channels, especially transient receptor potential vanilloid 1 [TRPV1] and transient receptor potential ankyrin 1 [TRPA1], and voltage-gated sodium channels [Na_Vs]) to generate action potentials (Fig 1).[4] In addition to GPCRs, various external stimuli can also activate TRPV1 and TRPA1 (eg, extracellular pH, ATP, prostaglandins, oxidants, capsaicin [for TRPV1], heat [>42°C for TRPV1], allyl isothiocyanate [found in wasabi; for TRPA1], and cold [<17°C for TPRA1]).[5,6]

There are 2 subtypes of itch-sensitive neurons that are entirely separate and independent: histaminergic neurons and nonhistaminergic neurons.[3] Histaminergic and nonhistaminergic itch signals ascend through the spinal cord through separate and distinct tracts[7] and have different patterns of brain activation.[8] Distinguishing between pruritic pathways in itchy conditions has therapeutic implications because certain medications are more effective in combating itch in one pathway but not the other.

Histamine is involved primarily in acute itch. Histamine is released mainly by mast cells, although other immune cells, including basophils[9] and keratinocytes,[10] can also release histamine. H1 and H4 receptors on histaminergic nerves bind histamine and activate TRPV1 through the phospholipase system.[11] Excited histaminergic neurons also release neuropeptides (eg, calcitonin gene–related protein [CGRP] and substance P [SP]), which cause "neurogenic inflammation," including local vasodilation, plasma extravasation, and mast cell degranulation.[12,13] Although histamine induces acute itch (eg, itch in patients with acute urticaria), antihistamines targeting H1 receptors do not improve the majority types of chronic itch.

Chronic itch is induced by the nonhistaminergic pathway.[3,14] Nonhistaminergic neurons can be elicited by endogenous/exogeneous pruritogens other than histamine (eg, proteases, cytokines/chemokines, and amines) and express various receptors involved in itch. These receptors activate TRPV1 or TRPA1 through the phospholipase or kinase system.[4,15] In both histaminergic and nonhistaminergic nerves, TRPV1/TRPA1 activates $Na_V1.7$, and $Na_V1.7$ controls action potentials in neurons. Recently, $Na_V1.7$ has been independently implicated in itch mediation.[16,17] Accordingly, $Na_V1.7$, TRPV1, and TRPA1 are potential therapeutic targets for itch management.[17,18]

PRURITOGENS AND RECEPTORS

To date, a large number of pruritogens and their receptors have been identified (Fig 1 and Table I). Among them, cytokines, proteases and their receptors, SP and its receptor neurokinin 1 receptor (NK1R), and Mas-related G protein–coupled receptors (Mrgprs) have attracted the most attention because of their contribution to chronic itch and their position as potential therapeutic targets.

Cytokines

Allergic and inflammatory cutaneous conditions are frequently pruritic and demonstrate an increased T_H2 immune response. IL-31, a cytokine produced by T_H2 cells, is implicated in patients with various itchy conditions (eg, atopic dermatitis [AD], prurigo nodularis, and cutaneous T-cell lymphoma).[19,20] IL-31 evokes itch through its receptor complex, comprising IL-31 receptor A and oncostatin M receptor β.[19] In addition, IL-31–induced itch requires both TRPV1 and TRPA1 activation.[21]

Thymic stromal lymphopoietin (TSLP), which is secreted primarily by epidermal keratinocytes, is a key cytokine promoting T_H2 immune responses.[22] TSLP directly promotes itch through the TSLP receptor on TRPA1-positive neurons.[23] In turn, scratching induces epidermal keratinocytes to further express TSLP, potentially perpetuating a positive feedback loop of itching and scratching (also referred to as the "itch-scratch cycle").[24] Additional cytokines, such as IL-4 and IL-13, are involved in T_H2 immunity.[25] Recently, it has been shown that IL-4 and IL-13 induce chronic but not acute itch by directly activating sensory neurons through the IL-4 receptor subunit α, which is a shared subunit for both IL-4 and IL-13 and Janus kinase (JAK) 1.[26] IL-33, a promoter cytokine of T_H2 immunity, excites sensory neurons through its receptor (ST2), contributing to itch in a mouse model of poison ivy contact allergy.[27] This pathway might also contribute to pruritus in human subjects.

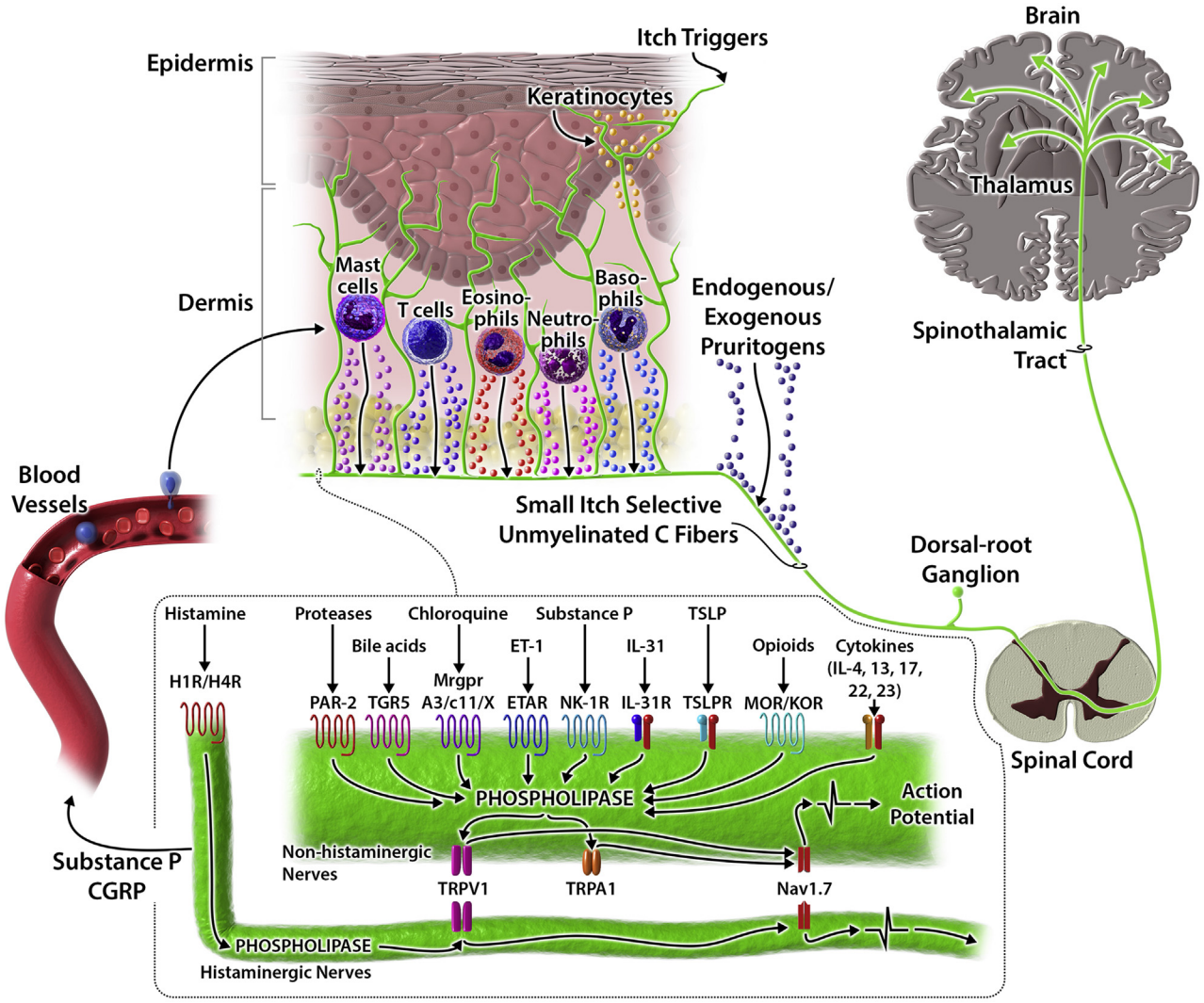

FIG 1. Immune cells, nerves, and receptors involved in itch. Exogenous itch triggers, exogenous pruritogens, and endogenous pruritogens secreted from immune cells (eg, mast cells, T-cells, eosinophils, neutrophils, and basophils) and epidermal keratinocytes stimulate small itch-selective unmyelinated C fibers in the epidermis and dermoepidermal junction. Itch-selective nerve fibers are divided into 2 subgroups: histaminergic nerves and nonhistaminergic nerves. Histaminergic nerves express the histamine type 1 *(H1R)* and type 4 *(H4R)* receptors, are activated by histamine, and are mainly involved in acute itch. Nonhistaminergic nerves respond to a variety of pruritogens other than histamine through corresponding receptors and are involved in chronic itch. *ET-1*, Endothelin-1; *TGR5*, Takeda G-protein receptor 5; *TSLPR*, thymic stromal lymphopoietin receptor.

T_H17-related cytokines, which play a role in psoriasis and the acute phase of AD,[28,29] are also implicated in itch. Ixekizumab, an anti–IL-17A antibody can improve psoriasis-induced itch within 1 week after initiation.[30,31] Genetic expression of IL-17A and IL-23A is upregulated in both itchy atopic and psoriatic skin compared with nonitchy skin from patients with AD and psoriasis.[32]

Whether and how these cytokines elicit itch directly or indirectly remains unclear. The JAK/signal transducer and activator of transcription (STAT) pathway is an intracellular signaling pathway through which various cytokines exert their functions.[33] Cytokine-induced pruritus is mediated partially by the JAK/STAT pathway. The JAK/STAT pathways drive chronic itch not only in patients with inflammatory conditions, such as AD, but also in those with noninflammatory conditions (eg, chronic idiopathic pruritus, which features chronic itch with minimal skin inflammation) and therefore are potential targets for controlling chronic itch.[26,34]

Proteases and protease-activated receptors

Protease-activated receptors (PARs) are a unique type of GPCR that are activated through proteolytic cleavage of their extracellular N-terminus.[35] Nonhistaminergic itch has long been studied using the plant cowhage. Cowhage contains mucunian, a serine protease known to activate nonhistaminergic itch through PAR-2 and PAR-4 activation. Other endogenous and exogenous proteases (eg, tryptase, trypsin, cathepsin S, kallikreins, and dust mite proteases) can also elicit itch through PAR-2 and PAR-4 activation.[36]

TABLE I. Major pruritogens and their receptors

Category	Pruritogens	Receptors
Amines	Histamine	H1/H4 receptors
	Serotonin	5-HT2 receptor
Proteases	Kallikreins	PAR-2
	Tryptase	(PAR-4)
	Trypsin	
	Cathepsin S	
	Exogenous proteases	
Neuropeptides	SP	NK1R
	Endothelin-1	ETA receptor
	NGF	TrkA1
	Opioids	MORs/KORs
Lipid mediators	PAF	PAF receptor
	LPA	LPA5 receptor
Cytokines	IL-4/13	IL-4Rα
	IL-31	IL-31RA/oncostatin M receptor
	TSLP	TSLP receptor
	IL17	IL-17RA-C
Mrgpr agonists	Chloroquine	MrgprX (human)
		MrgprA3 (mice)
Uncategorized	Bile acids	TGR5

ETA, Endothelin receptor type A; *LPA*, lysophosphatidic acid; *IL-4Rα*, IL-4 receptor subunit α; *PAF*, platelet-activating factor; *TGR5*, Takeda G-protein receptor 5.

SP and neurokinin receptor 1

SP (a tachykinin neuropeptide) and its receptors (neurokinin [NK] 1-3 receptors) are involved in afferent neuronal signal transduction.[37] Among the NK receptors, NK1R is mainly involved in itch. NK1R is expressed by sensory nerve endings, mast cells, keratinocytes, and fibroblasts and is highly abundant in the central nervous system. SP acts on various cells expressing NK1R, resulting in release of additional itch mediators.[38]

Mrgprs

Mrgprs are GPCRs that have 9 subgroups from A to H (in mice and rats) and X (in human subjects). Mrgprs mediate chloroquine-induced itch but not histaminergic itch. Interestingly, Mrgprs are expressed exclusively by peripheral sensory neurons, and Mrgpr-positive neurons also express gastrin-releasing peptide (GRP), which is an itch-selective neurotransmitter in the spinal cord.[39] Recently, human mast cells are reported to express MRGPRX2. MRGPRX2 can be activated by both endogenous and exogenous peptides or molecules (eg, antimicrobial host defense peptides, SP, eosinophilic granules [eg, major basic protein and eosinophilic cationic protein], and even drugs). SP released from peripheral nerves and mast cells themselves can activate MRGPRX2, activating mast cell release of tryptase and IL-31; tryptase and IL-31 can stimulate peripheral neurons, resulting in induction of itch and further release of SP from nerves, causing a vicious cycle.[40,41] Expression of MRGPRX2 mRNA is greater in itchy skin in patients with AD and psoriasis.[30] Hence Mrgprs, including MRGPRX2, might be a potential target in itch therapeutics.[41,42]

ITCH PROCESSING IN THE SPINAL CORD

As pruritic neural signals ascend the spinal cord, activating or inhibitory interneurons in the spinal cord modulate signaling, affecting conscious itch sensation (Fig 2, *B*). Initially, primary sensory neurons respond to pruritic stimuli by releasing glutamate and natriuretic polypeptide B (also known as B-type natriuretic peptide); these molecules activate secondary natriuretic peptide receptor A–positive neurons to release GRP. GRP and its receptor, gastrin-releasing peptide receptor (GRPR), are examples of itch-specific neurotransmitter involved in chemical itch.[43] GRPR-positive neurons then activate pruriceptive projection neurons.[44] Interestingly, primary sensory neurons are also able to release GRP, but this point is still contentious.[45]

In primates (Cynomolgus macaques) with idiopathic chronic itch, GRPR-positive neurons in the dorsal horn of the spinal cord in superficial lamina I and II were overexpressed.[46] In the context of prolonged itch, this circuit can be modulated by astrocytes and Toll-like receptor 4 in the spinal cord. Astrocytes in the spinal cord secrete lipocalin-2 and activate GRPR-positive neurons, which results in a STAT3-dependent increase in itch sensation.[47] Toll-like receptor 4 signaling can similarly exacerbate chronic itch through activation of spinal astrocytes, resulting in astrogliosis.[48]

In addition to the systems of positive feedback, there are also systems of negative feedback that act to mitigate pruritus. Mechanical stimuli, pain (conveyed by TRPV1 and TRPA1 positive nerves), and cooling (transduced through transient receptor potential melastatin [TRPM] 8 positive nerves) can attenuate itch sensation.[49-51] These sensations activate helix-loop-helix family member B5 (Bhlhb5)–positive inhibitory interneurons. These interneurons exert their inhibitory effect on GPRP-positive neurons through releasing inhibitory neurotransmitters: dynorphin, glycine, and gamma-amino butyric acid.[52] Descending inhibitory pathways arising from the supraspinal areas (eg, periaqueductal gray matter) activate Bhlhb5-positive neurons and modulate pruriception.[53-55] This inhibition system is mediated by excitatory α-adrenoceptors on Bhlhb5-positive inhibitory interneurons and by central terminals of primary sensory neurons in the dorsal horn.[56] Conversely, the descending serotonergic system can exacerbate itch sensation by facilitating the GRP-GRPR signaling pathway through serotonin receptor 5-HT1A.[57]

Mechanical itch and other pruritic sensory phenomena, such as alloknesis (normal or nonpruritic stimuli induce are perceived as itchy) and hyperknesis (excessive itch perception to a pruritic stimuli) are conveyed by another itch-related circuit in the spinal cord.[58,59] Neuropeptide Y–positive neurons have demonstrated an inhibitory effect on mechanical itch.[60]

ITCH PROCESSING IN THE BRAIN

After undergoing processing in the spinal cord, itch signals are conveyed through the spinothalamic tract to the thalamus and through the spinoparabrachial pathway to the parabrachial nucleus.[61] After pruritic signals reach the thalamus and parabrachial nucleus, they are projected into various areas and undergo itch processing. Positron emission tomography and functional magnetic resonance imaging has allowed for identification of the specific brain areas involved in itch processing in human subjects (Fig 2, *A*).

The most frequently activated brain regions are the primary and secondary somatosensory cortex. These areas contribute to the localization, intensity, and recognition of itch.[62] Other areas activated by itch include the midcingulate cortex (links to perception and motivation), anterior cingulate cortex (ACC) and insula

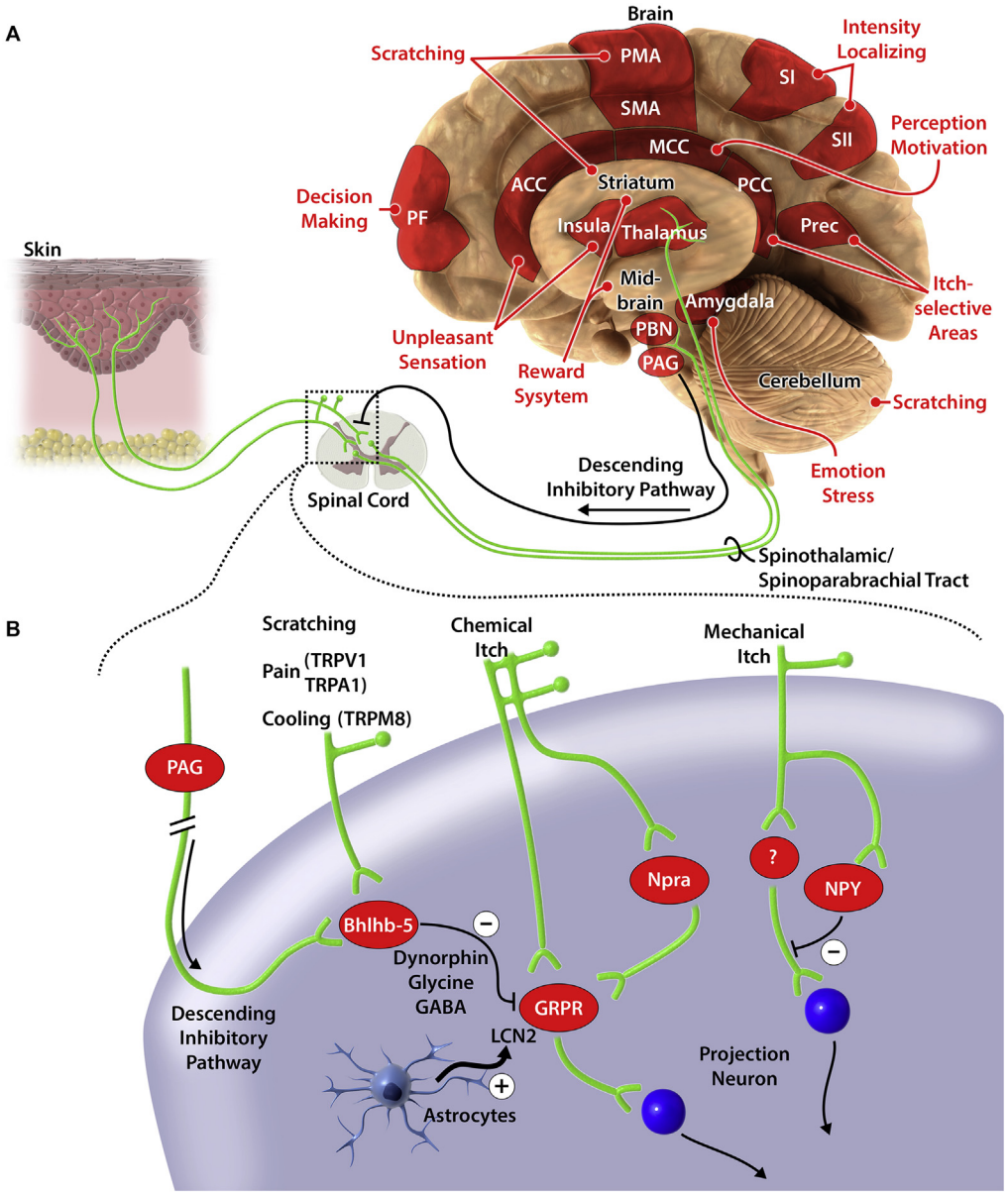

FIG 2. The spinal circuit and brain areas involved in itch perception. **A,** After undergoing processing in the spinal cord, itch signals are conveyed through the spinothalamic tract *(STT)* to the thalamus and through the spinoparabrachial pathway to the parabrachial nucleus *(PBN)*. Then itch signals are transmitted to a variety of areas of the brain that are involved in itch processing. **B,** Once itch signals are transmitted into the spinal cord, they are modulated by interneurons. Chemical itch is transmitted through GRP/GRPR and natriuretic polypeptide B/natriuretic peptide receptor A signaling pathways. Bhlhb5-positive inhibitory neurons attenuate chemical itch by inhibiting the GRP/GRPR signaling pathway through secretion of dynorphin, glycine, and GABA. Bhlhb5-positive inhibitory neurons can be activated by scratching, pain, cooling, and descending inhibitory pathway originated from PAG. Astrocytes activate GRPR-positive neurons by secreting lipocalin-2 in a STAT3-dependent manner. Mechanical itch is transmitted through an as-yet undetermined signaling pathway, and NPY-positive neurons have inhibitory effects on mechanical itch. *GABA*, Gamma-amino butyric acid; *GRPR*, gastrin-releasing peptide receptor; *LCN2*, lipocalin-2; *MCC*, midcingulate cortex; *Nppb*, natriuretic polypeptide B; *Npra*, natriuretic peptide receptor A; *NPY*, neuropeptide Y; *PAG*, periaqueductal gray matter; *PBN*, parabrachial nucleus; *Prec*, precuneus; *PMA*, premotor area; *SI*, primary somatosensory cortex; *SII*, secondary somatosensory cortex; *SMA*, supplementary motor area.

(associated with unpleasant sensation), premotor area, supplementary motor areas, striatum, cerebellum (involved in controlling or initiating scratching behavior), and prefrontal area (PF; implicated in decision making).[63-65] Of note, even though histaminergic and nonhistaminergic itch signals share some similar brain areas (eg, the thalamus, primary and secondary somatosensory cortex, posterior parietal cortex, posterior cingulate cortex [PCC], ACC, and precuneus), cowhage-induced nonhistaminergic itch extensively activates distinct areas, such as the insular cortex, claustrum, basal ganglia, putamen, thalamic nuclei, and pulvinar.[8] "Itch-selective areas" are thought to exist in the precuneus and the PCC.[66] These areas are associated

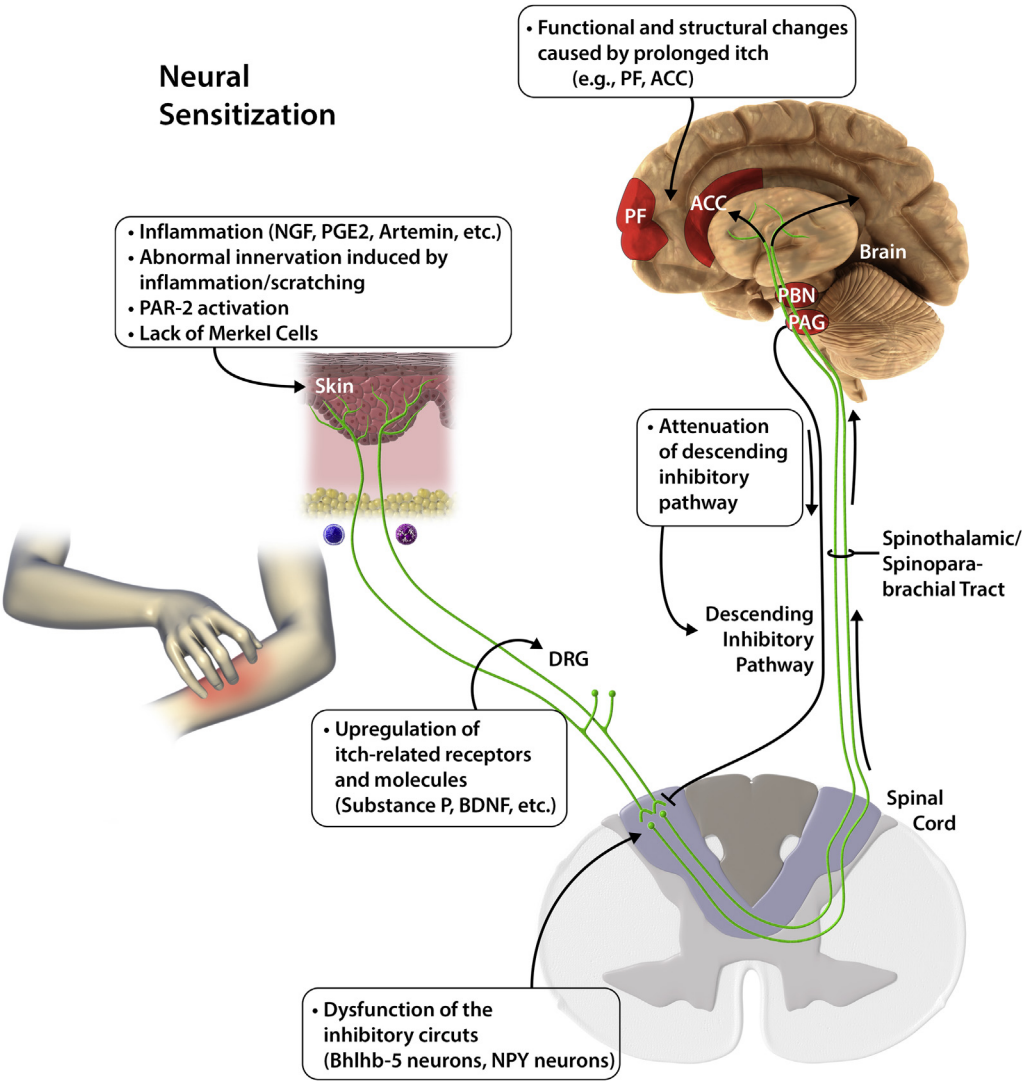

FIG 3. Neural sensitivity to itch. Neural sensitization can be induced by various causes in the skin, dorsal root ganglia, spinal cord, and brain. *BDNF*, Brain-derived neurotrophic factor; *DRG*, dorsal root ganglion; *PGE2*, prostaglandin E_2; *NPY*, neuropeptide Y; *PAG*, periaqueductal gray matter; *PBN*, parabrachial nucleus.

with memory and attention[67] and might be activated by pruritic stimuli alone and not by painful sensation.

NEURONAL SENSITIZATION

Chronic itch is frequently accompanied by alloknesis and hyperknesis.[58,59] These sensory phenomena are likely caused by neural sensitization, which refers to changes in the sensitivity of itch-processing neurons. Various factors acting at targets in the skin, spinal cord, or brain can act to induce neural sensitization (Fig 3).

Neural sensitization in the skin and sensory neurons

Hypersensitivity of sensory neurons to itch stimuli caused by inflammation and abnormal innervation are the main causes of neuronal sensitization at the peripheral level. Nerve growth factor (NGF), which is released mainly by epidermal keratinocytes and eosinophils, binds to its receptor TrkA, sensitizes TRPV1 on the nerves, and increases sensory nerve sensitivity to SP, CGRP, and brain-derived neurotrophic factor.[68] NGF is also shown to sensitize the skin to cowhage-induced itch[69] and contribute to mechanical hyperknesis.[70] Artemin, a member of the glial cell line–derived neurotrophic factors, is produced by SP-stimulated fibroblasts and keratinocytes in response to air pollutants.[71,72] Artemin decreases the threshold of heat-induced itch sensation.[71] Prostaglandin E_2, which is an eicosanoid and partially involved in skin inflammation,[73] is thought to potentiate histamine-induced itch.[74,75] PAR-2 activation is also shown to sensitize nonhistaminergic itch in mice.[76]

Abnormal innervation is another explanation for peripheral hypersensitivity. Some researchers suggest that abnormal epidermal innervation density can lead to hypersensitivity.[77]

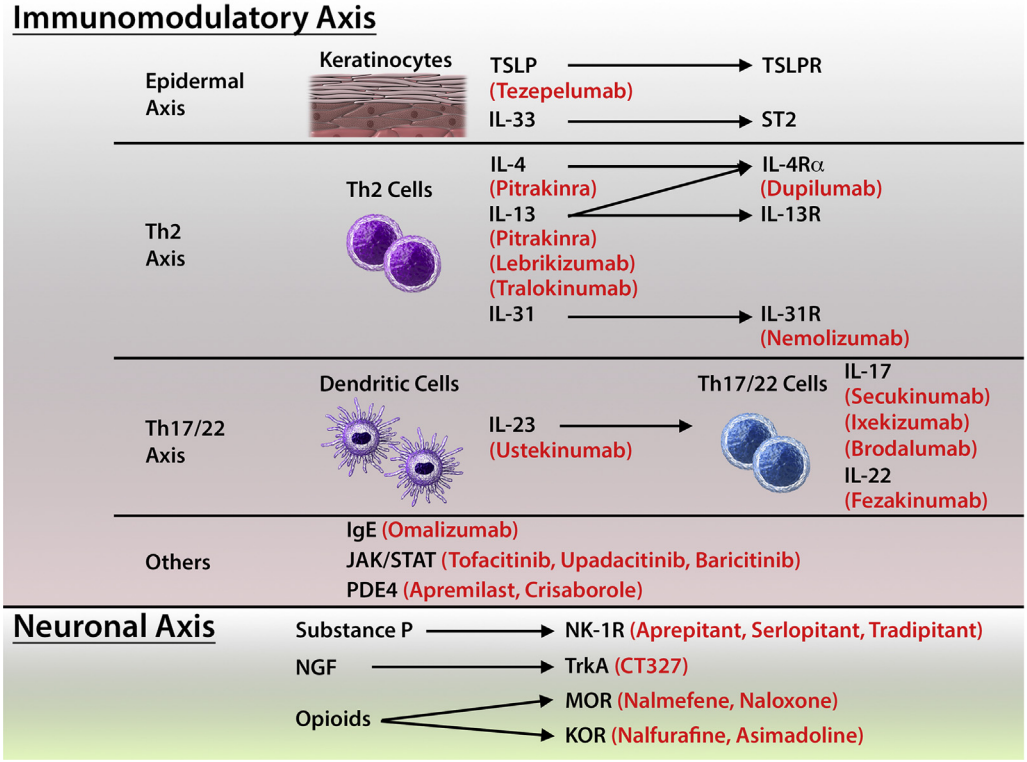

FIG 4. Therapeutic targets. There are 2 main groups for new itch treatments: the immunomodulatory and neuronal axes. The immunomodulatory axis includes the epidermal, T_H2, $T_H17/22$, and other axes. *IL-4R*, IL-4 receptor; *IL-13R*, IL-13 receptor; *IL-31R*, IL-31 receptor; *PDE4*, phosphodiesterase 4; *TSLPR*, thymic stromal lymphopoietin receptor. Adapted from Dr Tey Hong Ley.

Dysfunction of cutaneous touch receptors (eg, piezo2 channel-Merkel cell signaling), potentially caused by aging, also contributes to alloknesis.[78]

Neural sensitization in the spinal cord

In the spinal cord dysfunction of the inhibitory circuits (Bhlhb5-positive neurons and neuropeptide Y–positive neurons) can lead to neural sensitization. Dynorphin, which is released from Bhlhb5-positive neurons, binds κ-opioid receptors (KORs) on GRPR-positive neurons and inhibits these neurons, resulting in attenuation of chemical itch. This inhibition is antagonized by μ-opioid receptors (MORs).[79] Accordingly, imbalance in activation status of KORs and MORs can result in neuronal sensitization; as commonly noted in patients with chronic itch, this imbalance can also occur in the periphery.[80]

Attenuation of the descending inhibitory pathway also leads to neuronal hypersensitivity. This pathway ameliorates itch through α_2-adrenoreceptor.[55] Accordingly, suppressed condition of sympathetic nervous system (eg, in the nighttime) can lead to neuronal hypersensitivity.[81]

Neural sensitization in the brain

In the brain chronic itch modulates activation of particular brain areas, including the ACC, PCC, and PF[82]; alternates functional brain connectivity[83]; and can decrease the gray matter in itch-relating cortical areas, including the PF and precuneus. These can play a role in processing the chronification of itch.[83,84]

In patients with AD with chronic itch, histamine-induced itch robustly activates the ACC and PF. The degree of activation of these areas is closely correlated with disease activity. In addition, the degrees of activation of the PCC and precuneus are greater than those of healthy subjects.[82] These changes might lead to neural sensitization to itch in the brain.

Pleasurability and reward circuits

Scratching temporarily relieves itch and can also be rewarding and even addictive.[85] The degree of pleasure obtained by scratching is correlated with itch intensity.[86,87] Active scratching promotes greater pleasurability and increased inhibition of itch processing in the ACC and insula, which are associated with unpleasant sensation. In addition, activation of areas of the brain reward system (eg, midbrain and striatum) is observed when an itch is scratched.[66,85,88,89] In general, the pleasure from scratching and the discomfort from itching can create an insatiable need to scratch, feeding into the itch-scratch cycle; controlling activation of this reward system might be a therapeutic target for itch.

TREATMENT

The cause of chronic itch is historically divided into 4 categories of itch: dermatologic (associated with primary skin diseases, such as AD and psoriasis), neuropathic (associated with nerve fibers, such as brachioradial pruritus and small-fiber polyneuropathy), psychogenic (associated with psychiatric conditions, such as generalized anxiety disorder and delusions of parasitosis), or

TABLE II. Topical therapies

Class of medication	Medication	Potential antipruritic uses	Notable adverse effects
Corticosteroids	Mometasone, Betamethasone, Clobetasol, etc	AD Inflammatory skin disease itch	Skin atrophy Telangiectasia Striae Changes in pigmentation
Calcineurin inhibitors	Tacrolimus (0.03-0.10%) Pimecrolimus (1%)	Anogenital pruritus AD Cholestatic pruritus Lichen sclerosis Hand dermatitis Neuropathic pruritus Posterior blepharitis Prurigo nodularis Uremic pruritus	Temporary localized pain or burning FDA boxed warning for increased risk of malignancy
Anesthetics	Pramoxine (1%) Lidocaine (2.5% to 5%) Prilocaine (2.5%) Ketamine-amitriptyline-lidocaine	Neuropathic itch Uremic pruritus AD Postburn pruritus Old-age immunosenescence itch Prurigo nodularis	Temporary localized decreased sensation
Ion channels blockers	Capsaicin cream (0.025% to 0.1%) Patch (8%)	AD Aquagenic pruritus Prurigo nodularis Psoriasis Uremic pruritus Neuropathic itch	Temporary localized pain or burning
	Menthol (1% to 3%) Camphor	Pruritus of various causes	Mild localized inflammation or burning
	Strontium chloride (4%)	Localized itch	To our knowledge, no known side effects have been reported thus far.
JAK inhibitors	Tofacitinib (2%)	AD Psoriasis	Skin irritation
Phosphodiesterase-4 inhibitors	Crisaborole (2%)	AD	Temporary localized pain or burning
Topical cannabinoids	N-palmitoylethanolamine	AD Dry skin Lichen sclerosis	Unknown

Adapted from Leslie TA, Greaves M, Yosipovitch G (2015)[132] and Tey HL, Yosipovitch G, Bernhard J (2014) Scientific American Medicine, 3rd edition.

systemic (eg, associated with end-stage renal disease and cholestasis). Chronic itch can be a challenging symptom for clinicians to manage; however, various novel treatments are now available, including immunomodulator medications and those targeting the neural system (Fig 4). Currently, many of the therapies used for chronic itch are only supported by case reports and case series rather than controlled trials and are prescribed off-label and at doses different than their primary indication. Although serious adverse effects are rare, relatively mild adverse effects (eg, somnolence and weight gain) are more common with some of the systemic agents. Hence it is vital for clinicians to obtain a thorough history and to personalize treatment plans according to each patient's risk factors and individual preferences.

TOPICAL TREATMENTS

Topical agents are particularly useful in the treatment of localized itch while minimizing systemic side effects. These agents are most effective when used in conjunction with an appropriate emollient or moisturizer (although many patients with dry skin do not complain of itch, barrier damage can induce neural changes associated with pruritus).[90] Various topical agents, each targeting different aspects of the itch pathway, are available for the treatment of pruritus. Depending on the targeted mechanism, certain pruritic conditions can respond better to one topical agent as opposed to another. Topical treatments are summarized in Table II.

Corticosteroids

Topical corticosteroids are nonspecific immunomodulators with a limited utility in the treatment of pruritus. Although reductions in pruritus have been reported, these benefits are largely confined to histaminergic itch[91] and inflammatory skin conditions.[92]

Calcineurin inhibitors

Topical calcineurin inhibitors are relatively safe treatments for pruritus mainly associated with inflammation. Calcineurin inhibitors, such as tacrolimus and pimecrolimus, are immunomodulators that particularly reduce T_H1 cytokines.[93,94] The antipruritic effects of calcineurin inhibitors appear to center on the agonism and desensitization of TRPV1 receptors on primary afferent sensory neurons.[95] Topical calcineurin inhibitors are reported to reduce pruritus in patients with anogenital pruritus,

AD, biliary pruritus, generalized pruritus, lichen sclerosis, hand dermatitis, neuropathic pruritus, prurigo nodularis, and uremic pruritus.[92,95,96] It is important to inform patients that a frequent side effect of topical calcineurin inhibitors is a brief painful burning sensation that is likely mediated by TRPV1 channels.[97]

Phosphodiesterase inhibitors

Crisaborole, a novel topical medication for mild-to-moderate AD that acts on phosphodiesterase 4, inhibiting several itchy cytokines, has been noted to rapidly reduce itch in patients with AD.[98] The most common side effect of crisaborole is burning or stinging at the application site.[99]

JAK inhibitors

JAK inhibitors are exciting potential antipruritic agents. A number of topical JAK inhibitors are being developed, such as JTE-052, to combat itch.[100] Topical tofacitinib, a JAK inhibitor, can substantially reduce itch in patients with AD and psoriasis.[101] Likewise, oral JAK inhibitors have shown significant antipruritic effects in patients with psoriasis and atopic eczema (discussed further in the text below).[102]

Topical cannabinoids

Topical cannabinoid receptor agonists (eg, N-palmitoylethanolamine) can offer itch relief in conditions, such as AD, prurigo nodularis, lichen sclerosis, postherpetic neuralgia, or aquagenic pruritus.[103-105] It is thought that these medications derive their antipruritic affects from activating cannabinoid receptors in the skin or by enhancing the activity of endocannabinoids.[106] Recently, it has been suggested that the antipruritic effects of cannabinoids are independent of descending inhibitory serotonergic pathways.[107]

Anesthetics and drugs targeting transient receptor potential channels

Topical anesthetics, a widely used class of medications for various indications, derive their anti-itch properties from the reduction of nerve activity. This effect is achieved through Na_V antagonism, resulting in decreased nerve impulse production and conduction of action potentials.[108] Commonly used antipruritic topical anesthetics include pramoxine (1% to 2%), lidocaine (2.5% to 5%), and prilocaine (2.5%).[92] These agents are particularly effective in treating neuropathic pruritus and might also be efficacious in reducing itch in patients with other conditions, including uremic pruritus.[109]

Topical therapies that directly antagonize TRPV1 have not demonstrated a significant reduction in itch in human subjects compared with placebo.[110] However, the antipruritic effects of capsaicin likely center on its activity on TRPV1, although it can also act on PAR-2 or through the suppression of SP.[111,112] Capsaicin is available as a 0.025% to 0.1% cream or as an 8% patch. Capsaicin cream typically requires repeated application to achieve a significant reduction in itch. Capsaicin might be useful in neuropathic forms of pruritus, as well as AD, aquagenic pruritus, psoriasis, and uremic pruritus.[92,112] The 8% capsaicin patch is typically applied for 1 hour and can maintain lasting localized effects after a single application, although repeated application might be necessary.[113-115] Similar to calcineurin inhibitors, treatment with capsaicin is associated with a transient burning sensation (prior application of local anesthetic can be used to mitigate these symptoms).

Although evidence is limited, the combined topical application of ketamine-amitriptyline-lidocaine has demonstrated antipruritic properties effective in the treatment of chronic itch.[116,117] Ketamine, a versatile compound with a number of medical uses, can treat intractable pain and depression but is perhaps most well-known for its use intravenously in the induction of anesthesia. The mechanism of action of this topical combination is unknown and likely acts peripherally. Despite being known to antagonize N-methyl-D-aspartate receptors in the central nervous system when applied systemically, topical ketamine is likely to behave similarly to topical analgesics by modifying neural activity peripherally.[118] Centrally, amitriptyline behaves largely as a serotonin-norepinephrine reuptake inhibitor; however, the topical effects of amitriptyline are believed to include antagonism of voltage-gated ion channels and a number of other receptors (eg, adrenergic, cholinergic, histaminergic, muscarinic, and N-methyl-D-aspartate receptors).[119]

Applying cool temperatures to the skin can reduce itch intensity and duration.[120] This mechanism involves activation of TRPM8 on afferent neurons, which can then activate inhibitory pathways to reduce itch (Fig 2).[51,121] Menthol is able to achieve temporary improvement in itch through activation of TRPM8.[51,92,122] Patients who report improvements in pruritus with cool stimuli are more likely to have a favorable response to these cooling agents.

The antipruritic effects of topical strontium have been described in patients with experimentally induced (with cowhage) pruritus.[123] Strontium is a calcimemetic, which can reduce pruritus by altering ion channel permeability or neurotransmitter release.[123]

Tropomyosin receptor kinase A antagonist

Tropomyosin receptor kinase A (TrkA) inhibitors are a new class of prospective topical agents targeting the peripheral nerves in the skin. These agents exert their effects by reducing the activity of the NGF-TrkA-TRPV1 itch pathway.[124] A clinical trial demonstrated isolated itch reduction in patients with psoriasis treated with the TrkA antagonist CT327.[124]

Botulinum toxin

Botulinum neurotoxin (BTX) is an invasive yet effective treatment for many forms of localized pruritus. The antipruritic mechanism of BTX has not been fully elucidated and is likely to be multifactorial. BTX induces cleavage of soluble N-ethylmaleimide–sensitive factor attachment protein 25 (synaptosomal-associated proteins of 25 kDa), which prevents release of neurotransmitters from presynaptic vesicles.[17] This results in inhibition of acetylcholine, which has been shown to induce itch in patients with AD.[125] In addition, BTX inhibits the release of several neuropeptides with implicated roles in neuropathic pruritus and inflammation; these include SP, glutamate, and CGRP, as well as downregulation of TRPV1 and TRPA1.[126,127] Injection of BTX at the site of localized pruritus has been reported to reduce localized itch in patients with conditions like brachioradial pruritus, notalgia paresthetica, and lichen simplex chronicus.[128]

TABLE III. Systemic therapies

Class of medication	Medication	Dosage	Antipruritic indications	Notable adverse effects
Antihistamine H1 blockers	First generation	Varies depending on medication	Nocturnal itch	Somnolence
	Second generation	Varies depending on medication	Reaction to insect bites Urticaria or chronic idiopathic urticaria Mastocytosis	Somnolence (less severe)
Anticonvulsants	Gabapentin	300-1200 mg thrice daily	Neuropathic itch Prurigo nodularis Postburn pruritus Uremic pruritus Paraneoplastic pruritus	Somnolence Weight gain Gastrointestinal symptoms Lower extremity swelling
	Pregabalin	25-225 mg twice daily		
Antidepressants	SSRIs			
	Paroxetine	10-40 mg daily	Paraneoplastic pruritus	Somnolence
	Sertraline	75-100 mg daily	Cholestatic pruritus	Insomnia
	Fluvoxamine	25-150 mg daily	Pruritus coexisting with depression or anxiety	Gastrointestinal symptoms Reduced sexual desire or ability to reach orgasm
	TCAs			
	Doxepin	10-100 mg nightly	Neuropathic itch	Anticholinergic side effects
	Amitriptyline	25-75 mg nightly	Chronic idiopathic urticaria	Hypotension and other cardiovascular effects
	Mirtazapine	7.5-15 mg nightly	Nocturnal itch Paraneoplastic pruritus AD Systemic itch	Somnolence Weight gain
Opioid κ agonists and μ antagonists	Butorphanol	1-4 mg/mL nightly	Generalized severe intractable pruritus	Somnolence Disorientation Bizarre dreams Gastrointestinal symptoms
	Nalfurafine	2.5-5 micrograms daily	Uremic pruritus	Insomnia
	Naltrexone	25-50 mg daily	Cholestatic pruritus AD Chronic idiopathic urticaria Uremic pruritus	Skin reaction Gastrointestinal symptoms
	Nalbuphine, extended release	120 mg	Uremic pruritus Prurigo nodularis	Gastrointestinal symptoms
	Asimadoline		AD	Phase II, clinical trials completed
	CR845		Uremic pruritus	Phase III, clinical trials ongoing
NK-1 inhibitors	Aprepitant	80 mg daily	Paraneoplastic pruritus Prurigo nodularis	Gastrointestinal symptoms
	Serlopitant Tradipitant		Chronic pruritus Prurigo nodularis AD	Mild somnolence, diarrhea Phase II-III, clinical trials ongoing
Immunosuppressants	Thalidomide	100-200 mg daily	Prurigo nodularis Uremic pruritus Actinic prurigo	Peripheral neuropathy Teratogenicity in female subjects Somnolence
	Dapsone	0.5-1 mg/kg daily	Dermatitis herpetiformis	Neuropathy Hemolytic anemia Methemoglobinemia
	Methotrexate	15 mg weekly	Psoriasis AD Prurigo nodularis Old-age immunosenescence itch	Gastrointestinal symptoms Decreased hematopoiesis Liver function abnormalities
	Cyclosporine	2.5-5 mg/kg daily	Generalized pruritus AD Psoriasis Prurigo nodularis Chronic idiopathic urticaria	Hypertension Renal toxicity Hirsutism

(Continued)

TABLE III. *(Continued)*

Class of medication	Medication	Dosage	Antipruritic indications	Notable adverse effects
	Mycophenolate Mofetil	2 g daily	AD Immunosenescence itch	Gastrointestinal symptoms Leukopenia
	Azathioprine	25-275 mg daily	Chronic pruritus AD	Transaminitis Gastrointestinal symptoms Hypersensitivity drug reaction Myelosuppression Skin cancer
Biologics and small-molecule inhibitors	Dupilumab (anti–IL-4Ra)	600 mg, followed by 300 mg biweekly	AD	Injection-site reaction Conjunctivitis
	Ixekizumab (anti–IL-17A)	160 mg, followed by 80 mg biweekly for the first 12 weeks, then monthly	Psoriasis	Injection-site reaction Upper respiratory tract infection Systemic infections Rare IBD
	Secukinumab (anti–IL-17A)	300 mg weekly for 5 weeks, then monthly	Psoriasis	Upper respiratory tract infections Rare IBD
	Nemolizumab (anti–IL-31Ra)		AD Prurigo nodularis	Phase II, clinical trials ongoing
	Omalizumab (anti-IgE)	150-375 mg, biweekly or monthly	Chronic idiopathic urticaria Aquagenic pruritus Bullous pemphigoid Solar urticaria	Anaphylaxis Injection-site reaction Viral infection Upper respiratory tract infection
	Apremilast (anti-PDE4)	Over 1-wk titrate up to 30 mg twice daily	Psoriasis AD	Gastrointestinal symptoms Weight loss Rare depression
JAK inhibitors	Tofacitinib	5-10 mg daily	Psoriasis	Upper respiratory tract infection Systemic bacterial and fungal infections FDA boxed warning for increased risk of malignancy
	Baricitinib	2 mg daily	AD	Nausea Upper respiratory tract infection Herpes simplex or zoster infection
	Oclacitinib		Allergic dermatitis in dogs AD in dogs	Used in veterinary medicine

Adapted from Leslie TA, Greaves M, Yosipovitch G (2015)[132] and Tey HL, Yosipovitch G, Bernhard J (2014) Scientific American Medicine, 3rd edition.
FDA, US Food and Drug Administration; *IBD*, inflammatory bowel disease; *SSRI*, selective serotonin reuptake inhibitor; *PDE4*, Phosphodiesterase 4; *TCA*, tricyclic antidepressant.

Pruritus normally returns within months of receiving botulinum toxin treatment, and desensitization can occur with repeated treatments.[128]

SYSTEMIC TREATMENTS

Systemic therapies might be required to manage more generalized or treatment-refractory chronic itch. Many of these medications act on cutaneous or central pathways to achieve their antipruritic effects. Although it is important to be wary of adverse effects, combining systemic agents might be necessary to better control pruritic symptoms. However, systemic therapies should be started one at a time, and the addition or switch to other medications should only be considered once the maximum tolerable therapeutic dose is reached. Systemic treatments are summarized in Table III.

Antihistamines

Although the histaminergic pathway is involved in some forms of itch (typically more acute).[3] Antagonism of histamine receptors, specifically H1 or H2 receptors, has no role in the majority of cases of chronic itch, except in patients with chronic urticaria.[129] The perceived antipruritic effects of first-generation antihistamines are likely due to the sedative effects secondary to their activity in the central nervous system. Despite being less sedating, the effect of second-generation antihistamines on itch is limited to the treatment of urticaria or mastocytosis.[130]

Interestingly, H4 receptor antagonism is antipruritic in mice and could potentially be targeted by novel therapeutic agents.[129] Overall, H1 and H2 antihistamines are generally not recommended in the treatment of chronic itch.

Oral corticosteroids

Similar to topical corticosteroids, oral corticosteroids are not directly antipruritic and are not advocated as treatments for chronic itch. However, these agents can reduce levels of the itchy cytokine IL-31 and reduce itch in the context of inflammation (eg, urticaria, bullous pemphigoid, and cutaneous lymphoma).[131,132] Given the limited efficacy and propensity for adverse effects, corticosteroids are generally avoided or only used for short periods of time.

Anticonvulsants

Anticonvulsant medications, in particular gabapentinoids (eg, gabapentin and pregabalin), can be used to manage chronic pain, as well as a number of pruritic conditions; the mechanism likely involves a reduction in central neural hypersensitization.[133,134] Oral gabapentin can be very effective in the treatment of neuropathic forms of itch (eg, brachioradial pruritus, notalgia paresthetica, and prurigo nodularis) and might also have some utility in treating itch associated with major burns, chronic kidney disease, or cutaneous lymphoma.[132,135,136] Gabapentin is generally started at night at low doses (300-600 mg) and gradually increased to achieve a total daily dose of 900 to 3600 mg (often taken in smaller doses 3 times per day).[132] If there is failure to respond or tolerate gabapentin, a trial of pregabalin might be reasonable (or *vice versa*). Despite belonging to the same class of medication, patients can respond to gabapentin or pregabalin but not the alternative. The dose of pregabalin is increased incrementally to reach a target of 25 to 225 mg twice daily.[132] Weight gain, lower-extremity swelling, somnolence, and gastrointestinal symptoms are some of the more frequent side effects associated with either agent.

Antidepressants

A number of medications classically used in the treatment of depression can also be used to mitigate pruritus. Selective serotonin reuptake inhibitors, such as paroxetine, sertraline, or fluvoxamine, might be effective in dermatologic, psychogenic, or secondary forms of pruritus.[132,137] Low-dose oral mirtazapine (7.5-15 mg at night) can decrease neural sensitization and reduce nocturnal pruritus and can be used in combination with a gabapentinoid for those patients not responding to monotherapy.[138] Low-dose mirtazapine can also have antinociceptive effects.[139,140] Amitriptyline, a tricyclic antidepressant, has demonstrated efficacy in patients with neuropathic pruritus.[141] The aforementioned therapies can improve itch through various mechanisms, including modulation of histamine and serotonin.[142] Overall, these agents represent effective adjuvant therapies.

Opioids

Although MOR agonists, such as morphine, are associated with increased itch, MOR antagonists and KOR agonists are associated with decreased itch.[132] Naltrexone (a MOR antagonist),[143] nalfurafine (a novel KOR agonist available in Japan),[144,145] and butorphanol (an intranasally administered KOR agonist and MOR antagonist that acts on central and possibly peripheral targets)[146,147] can effectively reduce itch in patients with a number of pruritic conditions, including those secondary to an underlying systemic conditions.[148] Novel MOR antagonists and KOR agonists have successfully reduced itch in phase 2 studies (Table III).

NK-1 inhibitors

The perception of itch decreases with inhibition of the NK-1 receptor, the primary receptor of SP. The NK-1 inhibitor aprepitant demonstrated efficacy in the treatment of prurigo nodularis, Sezary syndrome, and paraneoplastic itch; however, interactions with other medications restrict its use in some patients.[132,149] In a phase II clinical trial, serlopitant, another NK-1 inhibitor, significantly reduced pruritus in patients with chronic itch of different types with minimal adverse effects.[150] However, this drug failed to achieve its antipruritic end points in patients with AD.

Immunosuppressants

Immunosuppressant antipruritic therapies previously consisted solely of agents such as dapsone, thalidomide, methotrexate, cyclosporine, or azathioprine. These medications are efficacious in many forms of chronic pruritus, but potentially serious adverse effects limit their long-term use. The advent of safer biologic targeted therapies has introduced a new era of antipruritic agents. For instance, dupilumab (anti–IL-4 receptor subunit α antibody) and nemolizumab (anti–IL-31 receptor A antibody), ixekizumab and secukinumab (anti–IL-17A antibodies), and omalizumab (anti-IgE antibody) can dramatically curtail itch in patients with AD, psoriasis, and chronic idiopathic urticaria, respectively.[132,151-155] Biologics targeting other factors (eg, TSLP, IL-33, and chemoattractant receptor–homologous molecule expressed on T_H2 cells) are being investigated. Apremilast might begin to reduce the pruritus associated with psoriasis as early as 2 weeks after beginning treatment.[156,157] The anti-TNF inhibitors adalimumab and etanercept can also decrease itch in patients with psoriasis.[158,159] However, compared with etanercept, ixekizumab (anti–IL-17A antibody) and tofacitinib (a JAK inhibitor that diminishes cytokine production and T_H17 differentiation) have each demonstrated a more pronounced reduction in psoriatic itch.[160-162] Other JAK inhibitors (eg, baricitinib, GSK2586184, and tofacitinib) are also useful in reducing psoriatic itch.[163,164] Moreover the antipruritic effects of JAK inhibitors extend to other types of chronic itch, including AD and itch associated with aging.[165]

Phototherapy

Phototherapy (eg, UV-A, narrow-band UV-B, and psoralen and UV-A) has been reported for decades to improve pruritus of different types.[132,166] The antipruritic effects of phototherapy can be associated with reduced nerve fiber density, reduced NGF, and reduced semaphorin 3A levels in the epidermis.[167] However, the antipruritic benefits of phototherapy are limited, and better systemic treatments are available.

Treatments on the horizon

Autotaxin is a phosphodiesterase that facilitates the conversion of lysophosphatidylcholine into lysophosphatidic acid (LPA).[168] Autotaxin and LPA levels are increased in patients with pruritus secondary to cholestatic disease.[169-171] LPA receptor antagonists and autotaxin inhibitors are an exciting new potential agent in

neuropathic pain and can offer similar benefits in the treatment of chronic itch, particularly those occurring secondary to hepatic disease.[168,172]

Other exciting potential treatments are those targeting $Na_V1.7$; as discussed previously, $Na_V1.7$ is involved in action potential propagation of neurons involved in the mediation of itch. In animal models compounds inhibiting $Na_V1.7$ have demonstrated reductions in itch and pain.[173,174]

Holistic treatments

Given the psychological toll of chronic itch, it is not surprising that methods of stress or anxiety reduction can also reduce itch.[175] The effects of cognitive-behavioral therapy on reducing itch have been reported in patients with AD.[176] Similar benefits can be seen with other techniques, such as acupuncture or progressive muscle relaxation.[175,177,178]

CONCLUSION

Our understanding regarding mechanisms of itch in the skin and brain continues to evolve. In the skin novel itch mediators and pruritogens transduce and modulate itch. In the spinal cord specific inhibitory interneurons and neurotransmitters are involved in itch conduction. Moreover, growing evidence regarding itch-related brain areas and the reward system has elucidated features that might be central to driving the itch-scratch cycle. Our improved understanding has already led to development of new therapeutic medications. Continued interest in understanding pruritic mechanisms can help to identify additional therapeutic modalities and to usher in a new era of targeted anti-itch treatments.

What do we know?

- **Itch has a distinct neuronal pathway that differs from pain in the peripheral and central nervous systems.**
- **The 2 major itch pathways are histaminergic and nonhistaminergic; numerous mediators have been linked to each of these pathways.**
- **Nonhistaminergic itch is responsible for the majority of chronic itch types.**
- **Neural sensitization in the skin, peripheral nerves, spinal cord, and brain contributes to the processing of chronic itch.**
- **A variety of novel treatments are now available, including targeted immunomodulatory drugs.**

What is still unknown?

- **The pathophysiology of different types of chronic itch**
- **How the new neural and immunomodulatory treatments target different types of itch**
- **How to best treat idiopathic itch**

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