What's New in Itch? A Comprehensive Review of Mechanisms and Drug Therapies

Rami H. Mahmoud BS[1], Sarah G. Brooks BA[1], Gil Yosipovitch MD[1]

[1]Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, Miami Itch Center, University of Miami Miller School of Medicine

Background

- The prevalence of pruritus is exceedingly high and has been reported in nearly 40% of adults [1].
- The mechanisms of itch are complex and include peripheral and central pathways and various itch mediators and receptors.
- Numerous drugs targeting type 2 inflammation and neural targets have shown efficacy in ameliorating itch.

Peripheral Mechanisms of Itch

- The sensation of itch begins with the activation of pruriceptive free nerve endings in the skin.
- the vast majority of itch is transmitted by C fibers from the periphery to the central nervous system.

Histamine-Mediated Itch

- Activated mast cells undergo degranulation, releasing histamine and other mediators that stimulate circulating immune cells to occupy the space and clear the potential pathogen.
- There are four histamine receptors, two of which (H1R and H4R) are located on histaminergic neurons and expressed in the dorsal root ganglia (DRG) where they mediate itch [2].

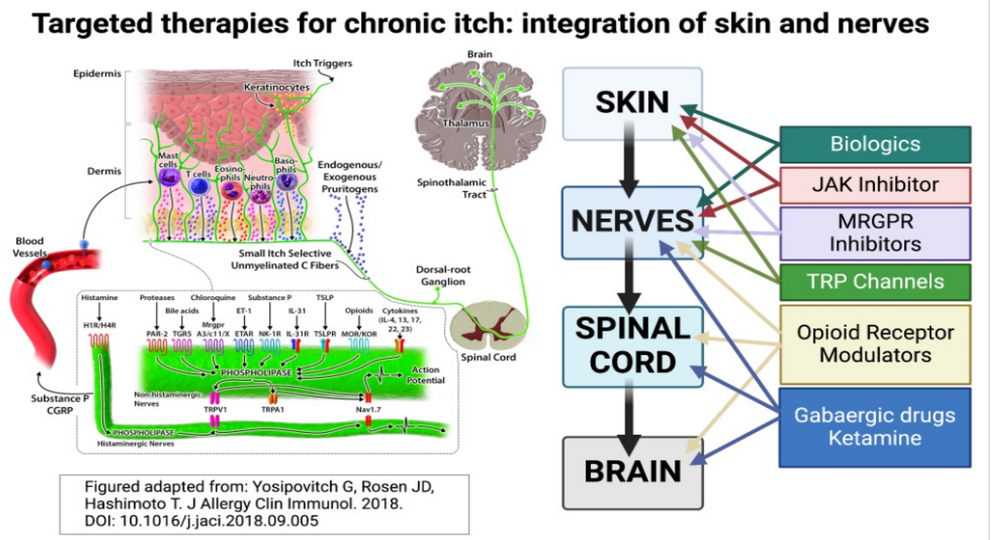
Non-Histamine-Mediated Itch

- The majority of chronic itch types are mediated by non-histaminergic pathways.
- C fibers that are mechanically- and heat-sensitive are activated by an abundance of non-histaminergic pruritogens that may be endogenously secreted (proteases, chemokines, amines) or exogenously introduced (cowhage, capsaicin) [3].
- These pruritogens bind their respective receptors on non-histaminergic neurons and activate TRPV1 or TRP Ankyrin 1 through the phospholipase or kinase system [4], [5].
- This generates an action potential and signaling cascade that is conducted to the dorsal horn of the spinal cord.

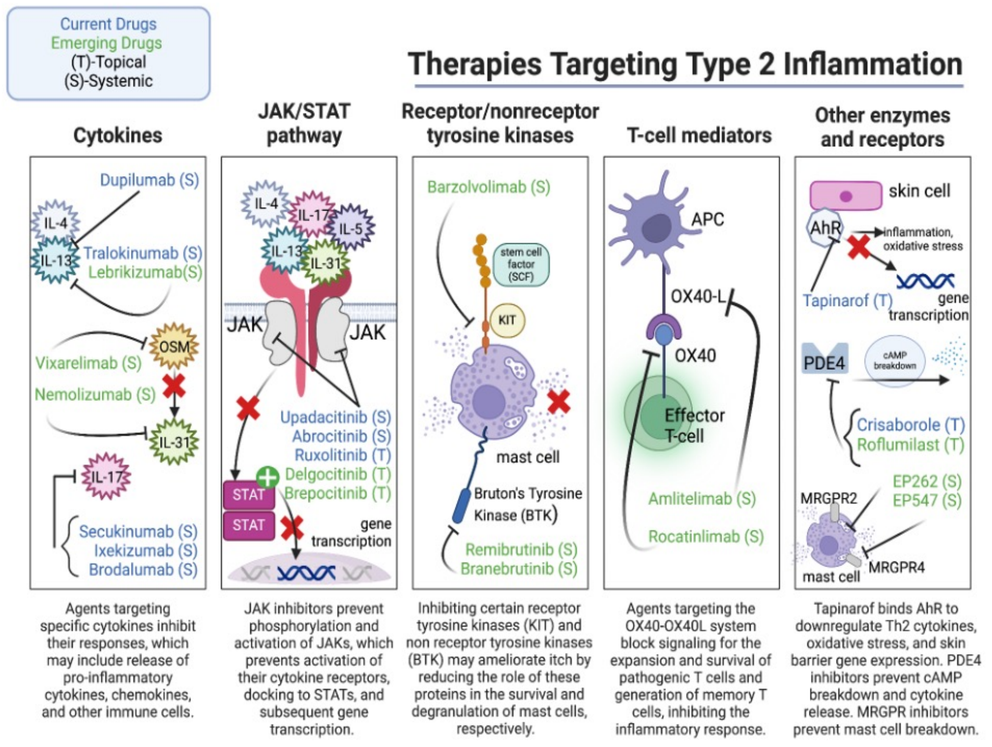
Central Mechanisms of Itch

- Following processing in the spinal cord, itch signals are transmitted via projection neurons to the thalamus and parabrachial nucleus in the brainstem [6].
- From here, information is sent to various regions of the brain.
- Certain areas of the brain nonspecifically play a role in the higher processing of itch, including the thalamus, primary and secondary somatosensory cortices, posterior parietal cortex, insula , superior and middle temporal cortices, posterior and anterior cingulate cortices, precuneus, and cuneus [7] .

Therapeutics



Figured adapted from: Yosipovitch G, Rosen JD, Hashimoto T. J Allergy Clin Immunol. 2018. DOI: 10.1016/j.jaci.2018.09.005



Agents targeting specific cytokines inhibit their responses, which may include release of pro-inflammatory cytokines, chemokines, and other immune cells.

JAK inhibitors prevent phosphorylation and activation of JAKs, which prevents activation of their cytokine receptors, docking to STATs, and subsequent gene transcription.

Inhibiting certain receptor tyrosine kinases (KIT) and non receptor tyrosine kinases (BTK) may ameliorate itch by reducing the role of these proteins in the survival and degranulation of mast cells, respectively.

Agents targeting the OX40-OX40L system block signaling for the expansion and survival of pathogenic T cells and generation of memory T cells, inhibiting the inflammatory response.

Tapinarof binds AhR to downregulate Th2 cytokines, oxidative stress, and skin barrier gene expression. PDE4 inhibitors prevent cAMP breakdown and cytokine release. MRGPR inhibitors prevent mast cell breakdown.

Conclusions

- The field of pruritus research is rapidly and continuously evolving. With that, numerous drugs have been developed, reflecting the diverse array of biochemical targets identified.
- From inflammatory mediators to neural targets and receptors, the possibilities for itch relief are vast and varied and should be curated to the disease context.
- Further research is indicated to assess more long-term outcomes and safety considerations as well as to continue to identify novel treatment modalities.

References

1. Silverberg JI, Hinami K, Trick WE, et al. Itch in the General Internal Medicine Setting: A Cross-Sectional Study of Prevalence and Quality-of-Life Effects. Am J Clin Dermatol. 2016 Dec;17(6):681-690.
2. Dong X, Dong X. Peripheral and Central Mechanisms of Itch. Neuron. 2018 May 2;98(3):482-494.
3. Lay M, Dong X. Neural Mechanisms of Itch. Annu Rev Neurosci. 2020 Jul 8;43:187-205
4. Kittaka H, Tominaga M. The molecular and cellular mechanisms of itch and the involvement of TRP channels in the peripheral sensory nervous system and skin. Allergol Int. 2017 Jan;66(1):22-30.
5. Wilson SR, Gerhold KA, Bifolck-Fisher A, et al. TRPA1 is required for histamine-independent, Mas-related G protein-coupled receptor-mediated itch. Nat Neurosci. 2011 May;14(5):595-602.
6. Mu D, Deng J, Liu KF, et al. A central neural circuit for itch sensation. Science. 2017 Aug 18;357(6352):695-699.
7. Papoiu AD, Coghill RC, Kraft RA, et al. A tale of two itches. Common features and notable differences in brain activation evoked by cowhage and histamine induced itch. Neuroimage. 2012 Feb 15;59(4):3611-23.

Adverse Effects

Table 1. Adverse Effects of Current Therapies Used for Chronic Pruritus

Medication Class	Drug	Route	Common Adverse Effects
Topical Corticosteroids	Mild, moderate, or high potency	Cream/ ointment / spray	Skin atrophy, loss of pigmentation, striae
Calcineurin Inhibitors	Tacrolimus	Ointment	Stinging/burning, headache
	Pimecrolimus	Cream	
PDE4 Inhibitors	Crisaborole	Cream	Stinging/burning, headache
	Roflumilast	Cream	Headache, nausea
AhR Activator	Tapinarof	Cream	Folliculitis, nasopharyngitis, headache, contact dermatitis
JAK/Stat inhibitors	Ruxolitinib	Cream	Application-site erythema, UTI, headache, nasopharyngitis
	Upadacitinib	Oral	Acne, URI, folliculitis, abdominal pain, nausea, anemia, transaminitis
	Abrocitinib	Oral	URI, nausea, headaches, acne, AD
Broad Spectrum Immunosuppressants	Methotrexate	Oral	N/V, mucosal ulcers, myelosuppression
	Mycophenolate Mofetil	Oral	Nausea, vomiting, leukopenia
	Azathioprine	Oral	N/V, leukopenia
Monoclonal Antibodies	Dupilumab	SQ	Injection-site reaction, URI, conjunctivitis
	Tralokinumab	SQ	Injection-site reaction, conjunctivitis
	Secukinumab	SQ	Infection, nasopharyngitis
	Ixekizumab	SQ	Neutropenia, URI, injection-site reaction
	Brodalumab	SQ	Infection (bronchitis, nasopharyngitis, pharyngitis, URI, UTI), arthralgia
Anesthetics	Lidocaine	Ointment	Stinging/burning, headache, systemic toxicity
	Pramoxine HCl	Cream/ gel/ lotion/ spray	Rare psychoactive effect with KAL
	KAL	Cream	
Calcimimetics	Strontium	Gel, Salts	Irritating, burning sensation, erythema, edema
TRP Channel Modulators	Capsaicin	Cream	Irritation and burning sensation
	Menthol		
Opioid Receptor Agonists/ Antagonists	Naltrexone	Oral, IM	GI upset, syncope, transaminitis, injection-site reaction, headache, dizziness, insomnia, pharyngitis
	Naloxone	IV, IM, SQ, IN	Headache, joint and muscle pain
	Difelikefalin	IV	Diarrhea, nausea, dizziness, abnormal gait, headache, hyperkalemia
Antidepressants	Sertraline	Oral	GI upset, dizziness, drowsiness, fatigue, insomnia, hyperhidrosis, decreased libido, diaphoresis, ejaculatory dysfunction
	Paroxetine	Oral	
	Fluvoxamine	Oral	
	Mirtazapine	Oral	
GABA Analogs	Gabapentin	Oral	Somnolence, dizziness, insomnia, N/V
	Pregabalin		
Cannabinoids	Dronabinol	Oral	N/V, tachycardia, somnolence, and dizziness

Topical Drugs Targeting Type 2 Inflammation
Systemic Drugs Targeting Type 2 Inflammation
Drugs Targeting the Neural System
KAL: Ketamine/Amitriptyline/Lidocaine, AhR: Aryl Hydrocarbon Receptor, UTI: Urinary Tract Infection, URI: Upper Respiratory Infection, AD: Atopic Dermatitis, SQ: Subcutaneous, IV: Intravenous, IM: Intramuscular, IN: Intranasal, N/V: Nausea/vomiting