Current Pathogenesis of Pruritus

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Abstract

Pruritus is common complaint in dermatology, which can affect psychological and physical aspects of life. It is estimated that as many as one-fifth of the world's population experience chronic pruritus, which affects the quality of life. An understanding of the pathogenesis and diagnostic approach of pruritus is needed to determine its management. The exact mechanism of pruritus is remain unclear, but recent studies have shown that several mediators, signaling pathways, and neurotransmitters play role in itch sensation. Mediator-related pruritus demonstrated the role of amines (histamine, serotonin), interleukins, proteases, peptides (bradykinin, substance P, opioid peptide) and phospholipid metabolites (cannabinoids, eicosanoids, platelet-activating factor) in the development of pruritus at different stages. Two signaling pathways identified in the mechanism of pruritus are histaminergic and nonhistaminergic pathways. The itching stimulus induce the cells in the skin to release mediators, which will bind to their receptors and activate itch-specific sensory neurons. The itching signal will be transferred via histaminergic or nonhistaminergic pathway, through dorsal ganglia in the spinal cord, spinothalamic tract, thalamus, to cerebral cortex, which will eventually produce pruritus.

Keywords: Pathogenesis; Pruritus; Sensitive Skin; Human and Health.

1. Introduction

Pruritus or itchy sensation is very common complaint in the general population, yet it is difficult to diagnose and manage. Pruritus is one of the symptoms in sensitive skin. Pruritus can be as debilitating as chronic pain. It also had lower overall health-related quality of life than patients with a history of a stroke, including sleep disturbances, mood disorders, negative psychosocial impact culminating in a significant overall reduction in quality of life [1,2].

The lifetime prevalence of chronic itch in the general populations is 22%. It is estimated that one fifth of world's population experience chronic pruritus at least once in their life. The prevalence in general population is 8-38 % worldwide, while the prevalence among elderly 11.5-25% that occur especially over age 85 [1].

Pruritus is the most common complaint in elderly, and one of the main causes is xerosis cutis. Yusharyahya et al reported that there were 127 patients suffered from pruritus during a 6 year evaluation at Cipto Mangunkusumo General Hospital Jakarta Indonesia, with the most common causes being xerosis cutis (63.78%), senile pruritus (19.69%), and pruritus due to systemic disease (7.87%) [3]. While in Dr. Soetomo General Academic Hospital Surabaya Indonesia, xerosis cutis was reported as the most common disease in the elderly who came to the Dermatology and Venereology Outpatient Clinic, as many as 87 of 299 (29.10%) patients in a 2 years period [4].

Based on clinical complaints, pruritus divided in 4 types, namely skin-derived pruritus, neuropathic pruritus, neurogenic pruritus, and psychogenic pruritus. Skin-derived pruritus is caused by skin inflammation, damage or dryness, which results from conduction of C-nerve fibers, such as urticaria, scabies, insect bite dermatitis. Neuropathic pruritus is associated with pathological changes in afferent pathways of sensory nerve

fibers, for example itching that usually occur in post herpetic neuralgia. Neurogenic pruritus originates in central nervous system, through induction and transmission of mediators and receptors without nerve damage, such as bile stasis itching that is caused by opioid peptide acting on μ-opioid receptor. Psychogenic pruritus is pruritus that is caused by psychological factors and psychiatric abnormalities, for example parasitic phobia [2,5].

Pruritus can be caused by various diseases, both dermatological and non-dermatological diseases. Pruritus accompanied by inflammatory skin lesions may be due to dermatological diseases, e.g. atopic dermatitis, psoriasis, contact dermatitis, or lichen planus. Pruritus without inflammatory skin lesions can occur in systemic diseases (such as cholestatic itch, uremic itch, paraneoplastic itch, diabetic-associated itch), neuropathic causes (such as scalp dysesthesia, brachioradial pruritus), and psychogenic causes (such as delusions of parasitosis). In addition, it is necessary to evaluate whether secondary skin lesions are obtained due to scratching or friction, which can be found in dermatological and non-dermatological diseases [6].

Management of pruritus is individualized, according to the underlying disease and its pathogenesis. An understanding of the pathogenesis and diagnostic approach of pruritus is needed to determine its management.

2. Pathomechanism of Pruritus: from Skin to Brain

Itch originates in the epidermis and dermal-epidermal junction, that is transmitted majority by itch-selective C nerve fibers. Some of these fibers are sensitive to histamine, but the majority are not. A complex interplay among T cells, mast cells, neutrophils, eosinophils, keratinocytes, and nerve cells (along with increased release of cytokines, proteases, and neuropeptides) leads to exacerbation of itch. The C fibers form synapses with second-order projections in the dorsal horn, and the itch signal ascends in the contralateral spinothalamic tract, with projections to the thalamus. From the thalamus, itch is transmitted to several regions of the brain that are involved in sensation, evaluative processes, emotion, reward, and memory [6,7].

Sensory nerve fibers involved in itch transmission. C and Aδ fibers are responsible for peripheral itch transmission. Two subgroups of C fibers have been identified. Intraepidermal mechano-insensitive afferences C-fibers (CMIA) are activated by histamine via the transient receptor potential vanilloid-1 (TRPV1) ion channel, and mechano-heat sensitive C-fibers (CMH) that respond to cowhage, express TRPV1, transient receptor potential ankyrin-1 (TRPA1), protease-activated receptor-2 (PAR2), and Mas-related G protein–coupled receptors (Mrgprs). CMH fibers also act as polymodal nociceptors. Recently, the role of Aδ fibers, which also express TRPV1, has been acknowledged in itch transmission. Properties of peripheral nerve fibers are shown in the **Table 1** [7,8].

Table 1. Nerve fiber in itch transmission [7]

Peripheral nerve fiber	Diameter	Myelin coating
C	0.2-1.5 μm	No
Aδ	1-5 μm	Yes
Aβ	6-12 μm	Yes
Aα	12-22 μm	Yes

3. Molecular anatomy of itch

Mediator of itch or pruritogen is substance that after induction into the skin, elicit sensation of itch & an urge to scratch. Pruritogen interact with molecular detector G-protein coupled receptor (GPCR) or transient receptor protein (TRP) channel on keratinocyte cell surfaces and sensory nerve endings. Receptors and channels respond to pruritogens such as proteases, histamine, etc, then itch signal will be transmitted to the

dorsal root ganglia (DRG) and spinal cord (**Figure 1**) [7,8].

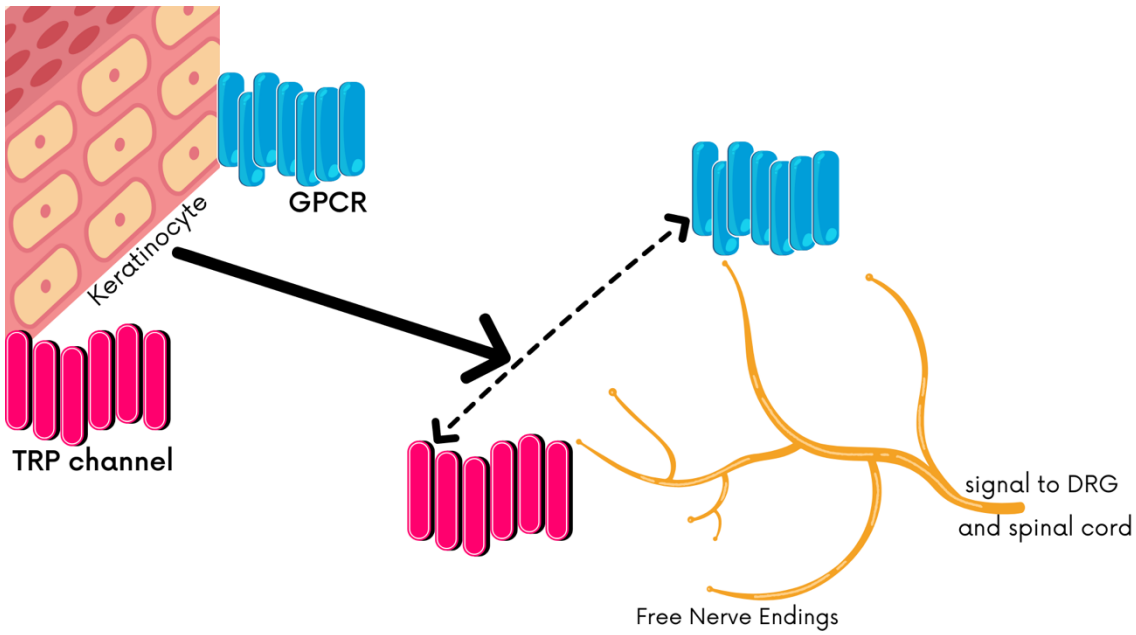

Figure 1. Molecullar anatomy of itch. Adapted from Garibyan, L., Rheingold, C.G., and Lerner, E.A., 2013 [8]

Mediator-related pruritus demonstrated the role of amines (histamine, serotonin), interleukins, proteases, peptides (bradykinin, substance P, opioid peptide), phospholipid metabolites (cannabinoids, eicosanoids, platelet-activating factor). Each mediator has spesific receptor, as describe in **Table 2** [8,9].

Table 2. Mediator and its receptor in pruritus pathogenesis [8]

Mediator	Receptor
Histamine	H1, H4
Tryptase, cowhage, cathepsin S, kallikreins, dust mite protease allergen	PAR2
Interleukin-31 (IL-31)	IL-31R
Leukotriene B4	LTB4
Substance P	NK1

4. Neurobiology of pruritus in the skin

The free endings of sensory nerves are found in the epidermis and papillae of the dermis. Electron microscopy shows that neurons communicate with keratinocytes by means of "signal invagination" into the cytoplasm of keratinocytes. Cutaneous nerves function through afferent mechanisms (pruritus, pain, touch, temperature, etc.) and efferent mechanisms (through the release of neuropeptides in the skin) [6,7].

The epidermis and the peripheral nervous system play a role in the skin's first sensory processing upon exposure to the skin. The cutaneous nerves will transmit information to the central nervous system after the exposure, such as parasites, toxins, allergens, chemicals, ultraviolet, pH disturbances, or stress. This mechanism corresponds to the protective mechanism of the skin, which normally can cause a reaction to

protect the affected area, for example by scratching, or resisting stimuli [6,7].

When there is stimulation to the skin, sensory nerves will be activated by proliferating and extending. Receptors and channels found on the surface of keratinocytes and sensory nerve endings interact with pruritogens. Sensory nerve endings will produce neuropeptides (substance P) and will activate the immune system, which can release inflammatory mediators that also play a role in the pathogenesis of pruritus. This itching signal will be transmitted through sensory nerve fibers to the brain, and is received by the individual as itchy sensation [6,7].

5. The Role of Skin Barrier in Pruritus

The epidermal layer plays an important role in the skin barrier, especially in the stratum corneum. The skin barrier maintains the balance of water content (permeability barrier), protection against microorganisms and antigens, protection against ultraviolet, and protection against the effects of oxidative stress. A well-functioning skin barrier will produce healthy skin, with the occurrence of invisible desquamation, smooth skin texture, elasticity, and resistance to shearing forces [10,11].

The stratum corneum consists of corneocytes and intercellular lipid membranes arranged in a 'brick and mortar' manner. Corneocytes represent the brick, and intercellular lipid membrane represents the mortar. This composition maintain the water gradient and proper acidic pH within the stratum corneum so that the enzymatic mechanisms can function optimally. Corneocytes are composed mainly of keratin macrofibrils, which are protected by a cornified cell envelope, and are held together by corneodesmosomes. The intercellular lamellar lipid membrane is mainly composed of ceramides, cholesterol and fatty acids. A mixture of several small hygroscopic compounds present in corneocytes, referred to as natural moisturizing factor (NMF), plays an important role in the physiological maintenance of stratum corneum hydration (**Figure 2**) [10–13].

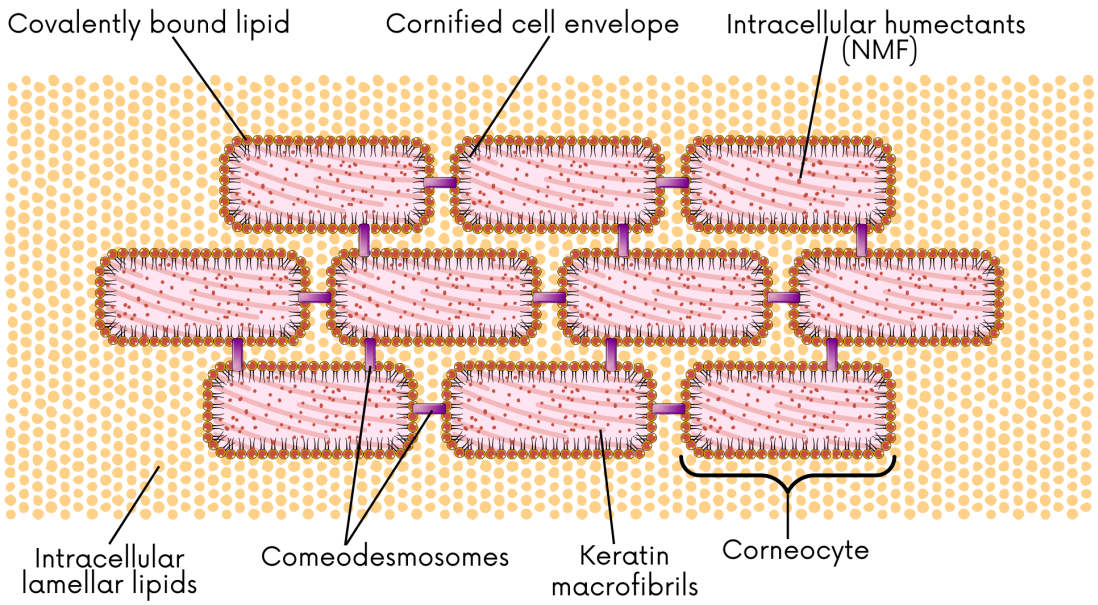

Figure 2. 'Brick and mortar' manner of stratum corneum. Adapted from Damayanti, 2017 [13]

Many skin disorders are associated with the skin barrier impairment. Skin disease is frequently associated with xerosis and pruritus, with underlying disease that may vary according to age group. Structural

and physiological changes of the skin barrier that occur due to aging, accompanied by the presence of comorbid factors and polypharmacy, can increase the risk of abnormal skin barrier in the elderly. The main cause of skin barrier-related pruritus or sensitive skin in elderly is xerosis, which is reported as a cause of 69% of chronic pruritus in elderly. Whereas in children and adults, the main cause of pruritus is atopic dermatitis, one of the diagnostic criteria is the presence of xerosis due to skin barrier impairment [14,15].

Skin barrier impairment is one of the main factors in the itch-scratch cycle. Dry skin or chronic scratching on the skin may cause skin barrier damage, which can activate pruriceptors through inducing the release of epithelial cell-derived cytokines such as thymic stromal lymphopoietin (TLSP) and IL-33. Kallikrein and cathepsin S can also trigger itch via cleavage-based activation of PAR2 and MrgprC11, although the mechanism by which Kallikrein triggers neuronal PAR2 is still not completely clear. Immune cells can trigger pruriceptors, including IL-4 which is produced by T helper-2 (Th2) cells, mast cells, basophils; and IL-31 which is produced by Th2 cells. Histamine and tryptase produced by mast cells and basophils activate the G-protein-coupled receptors (Histamin-1/4-Receptor and PAR2) [16].

6. Itch-scratch cycle

Itching or pruritus is an uncomfortable cutaneous sensation, which causes the urge to scratch. This suggests that itching and scratching are interdependent symptoms. The association between itching and automatic scratching response leads to an itch-scratch cycle [7,17].

Scratching is the self-protection mechanism and inflammatory defense from harmful agents on the skin. Although it is a self-protection mechanism, scratching may disrupt epidermal barrier and cause complication such as secondary infection. Scratching can relieve pruritus, because it causes 'localized pain', that suppress intolerable itch. In addition, scratching can reduce itch through the emergence of a sense of comfort due to the release of serotonin when scratching the skin [9,16,17].

The exact mechanism by which scratching causes chronic itching is not completely understood. Several factors, that play a role in itch-scratch cycle, include humidity and inflammation of the skin. Itch scratch cycle is a multifactorial mechanism, including network between the stromal system, immune system and sensory system. Epithelial cells, immune cells and neurons can promote pruritus, so that their activation caused by repetitive scratching behavior, may induce itch-scratch cycle which is the main symptom of chronic skin disease [16].

Itching and scratching behavior are mutually dependent symptoms, known as the itch-scratch cycle. Scratching may increase itch through the disruption of epithelial barrier due to scratching. In addition, scratching will stimulate epithelial cells to release cytokines, proteases, and antimicrobial peptides (AMP) that play role in immune cells activation and cause an inflammatory state. Keratinocytes may also activate itch sensory nerves directly through soluble mediators such as cytokines and proteases. Neuropeptide released by neurons may cause neurogenic inflammation. In contrast, cytokines and proteases produced by immune cells, interact with the sensory nervous system and activate itch transmission through the dorsal root ganglia (DRG) (**Figure 3**) [16].

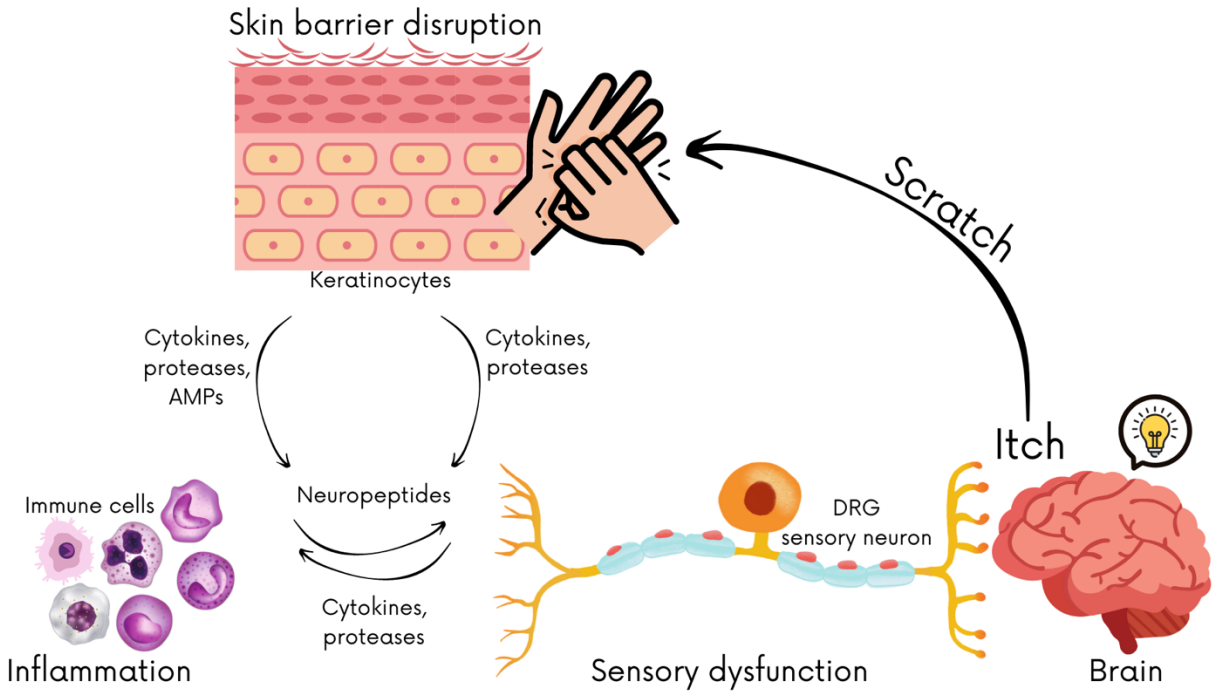

Figure 3. The itch-scratch cycle. Adapted from Mack, M.R. and Kim, B.S., 2018 [16]

7. Approach to pruritus

Pruritus can occur localized or generalized. In localized pruritus, it is necessary to evaluate whether a skin lesion is present. If skin lesions are found in localized pruritus, then treatment can be carried out according to the underlying skin disease, and a skin biopsy can be performed to support the diagnosis of the underlying skin disease. Meanwhile, if no skin lesions are found, then this localized pruritus can be caused by psychogenic or neurogenic causes [2,18].

Treatment of generalized pruritus with skin lesions, may be administered according to the protocol, or a skin biopsy may be performed to assist in establishing the diagnosis. Whereas in generalized pruritus without skin lesions, xerosis cutis should be ruled out first, then followed by an evaluation of whether systemic disease is involved. Pruritus is often a sign of severe systemic disease. Systemic disease is present in 14-24% of pruritic patients without skin lesions [2,18].

The first stage in the management of pruritus is basic management, in the form of giving emollients, antihistamines, and avoiding allergens. For pruritus with established underlying disease, targeted therapy can be given according to the underlying disease. Meanwhile, in chronic pruritus which cause is unknown or refractory, symptomatic therapy can be given. In addition, the management of pruritus is given according to the accompanying manifestations, such as the presence of sleep disorder, reactive depression, etc., which can be given at all stages of pruritus management [2,7,19].

8. Conclusion

Pruritus is not a form of low intensity pain. Itch originates in the epidermis and dermal-epidermal junction and is transmitted majority by itch-selective C nerve fibers. Pruritus manifest in many

dermatological, systemic & psychogenic conditions, that require holistic and multidisciplinary management, based on the underlying diseases.

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