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A multidimensional study of itching: from pathophysiological mechanisms to clinical intervention strategies

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Abstract. Pruritus is a highly complex sensory disorder with a large proportion of the population experiencing chronic pruritus. Its occurrence involves multi-level signal transduction of skin receptors, peripheral nerves, central regulation and effectors. Persistent pruritus can lead to scratched skin lesions, pigmentation, and secondary infections, and may even cause sleep disorders, anxiety, and depression, significantly impairing patients' quality of life. In this paper, the physiological and pathological process of pruritus is systematically analyzed based on the reflex arc pathway of "receptor → afferent nerve → nerve center → efferent nerve → effector"; at the same time, it introduces the non-classical signaling mechanisms found in recent years and the clinical research progress of emerging targeted neuromodulators, and pays attention to the psychological, Chinese medicine and physical intervention from multiple dimensions. Such multidisciplinary intervention means can further improve the well-being of patients. At present, there is still a lack of highly effective clinical guidelines for doctors' reference, which makes the prognosis of patients treated with doctors' experience potentially poor. Therefore, the update of guidelines needs to be further strengthened after the publication of new studies.

Keywords: Chinese medicine, physical intervention of pruritus, scratch reflex arc

1. Introduction

Pruritus is a highly complex sensory disorder, and about 10%–20% of the global population has experienced chronic pruritus [1]. Its occurrence involves multi-level signal transduction of skin receptors, peripheral nerves, central regulation, and effectors. Its persistent existence will lead to scratched skin lesions, pigmentation, secondary infection, and even sleep disorders, anxiety, and depression, significantly affecting the quality of life of patients. In this paper, the physiological and pathological process of pruritus is systematically analyzed according to the reflex arc link of "receptor → afferent nerve → nerve center → efferent nerve → effector"; At the same time, it introduces the non-classical signaling mechanisms found in recent years and the clinical research progress of emerging targeted neuromodulators and pays attention to the psychological, Chinese medicine, and physical intervention from multiple dimensions. Such multidisciplinary intervention means can further improve the well-being of patients. This multi-dimensional study holds significant inspirational value, provides new ideas for researchers, and increases the importance of interdisciplinarity, which can promote the further development of pruritus intervention, improve the health level of human beings and even all organisms, and improve the quality of life.

2. Physiological and pathological mechanism of pruritus

There are various causes for pruritus, and the types of pruritus summarized by modern Western medicine are shown in Table 1.

Table 1. Types of pruritus

Pruritus type	Characteristic	Common etiology
Dermatogenic	Localized or systemic with visible skin lesions	Eczema, psoriasis, urticaria
Neurogenic	Often distribute or banded along a single nerve	Post-herpetic neuralgia, dermatitis zoster
Neuroendocrine	No primary rash, often systemic itching	Chronic renal failure, hepatobiliary disease, hyperthyroidism
Psychogenic	Correlates with emotional fluctuations and frequently occurs at night	Anxiety, depression, schizophrenia
Mixed type	Etiology is complex, often alternating attack	Diabetes, systemic lupus erythematosus

2.1. Initial sensation stage of pruritus

2.1.1. Histamine -H1/H4 receptor

Mast cell degranulation releases histamine, which binds to H1 and H4 receptors at the dermo-epidermal junction, and induces the discharge of the underlying C-type unmyelinated nerve fibers, producing a primary pruritus signal. Second-generation antihistamines (loratadine, fexofenadine) are effective for histamine-induced pruritus by competitively blocking the H1 receptor and reducing histamine-mediated receptor activation; Preclinical studies have shown that H4 receptor antagonists (such as JNJ-39758979) significantly reduce scratching behavior in animal models of atopic dermatitis and chronic urticaria, indicating their potential in treating conditions such as chronic spontaneous urticaria, beyond allergic pruritus. However, its side effects such as increased liver enzymes and decreased white blood cells need to be further evaluated, and its long-term safety still needs to be studied. At present, H4 receptor antagonists are still in the stage of preclinical transformation to clinical [2].

2.1.2. IL-31R/JAK signaling pathway

IL-31 secreted by Th2 cells combines with the IL-31Rα/OSMR complex and activates the downstream JAK1/JAK2-STAT3/STAT5 pathway, promotes the release of various cytokines and enhances the sensitivity of nerve endings. This pathway is blocked by inhibitors of JAK (tofacitinib, rusotinib), which significantly relieve the intensity of itching in atopic dermatitis and chronic itching. Clinical studies have shown that oral administration of JAK inhibitors such as upatinib can provide rapid relief of pruritus in patients with atopic dermatitis, with a reduction in pruritus scores of more than 50% within a few days of dosing in some patients. Common adverse reactions include acne and upper respiratory tract infections. Similar trends have been observed in studies on conditions such as prurigo nodularis [3].

2.1.3. TRPV1/TRPA1 thermal sensing channel

TRPV1 is sensitive to capsaicin and high temperatures, while TRPA1 is highly responsive to cold stimuli and fatty acid metabolites. They are abundantly expressed in mast cells and skin nerve endings and involved in non-histamine itching. The capsaicin patch desensitizes the channels after short-term activation, thus reducing calcium ion influx and the generation of itchy signals for a long time.

2.2. Stages of afferent nerves of pruritus signal

2.2.1. Nav1.7/Nav1.8 sodium channel

Nav1.7 and Nav1.8, located on the axonal membrane of C fibers, are responsible for the generation and maintenance of action potentials. Local anesthetics (lidocaine patch and bupivacaine injection) can inhibit the formation of action potentials and reduce the transmission of pruritus signals to the central nervous system by blocking these sodium channels.

2.2.2. Cav2.2 calcium channel and gabapentin/pregabalin

Cav2.2 is located in the presynaptic membrane, and calcium influx triggers the release of substance P, glutamic acid and other neurotransmitters. Gabapentin and pregabalin combine with the α2δ subunits of the calcium channel to inhibit their activity and

reduce the secretion of neurotransmitters, thereby relieving neurogenic pruritus. Clinical studies have shown that pregabalin has a definite therapeutic effect on uremic pruritus and pruritus related to postherpetic neuralgia, and it can reduce the pruritus intensity of most patients by more than 30%. The main adverse reactions are dizziness and lethargy, which are usually alleviated with the prolongation of medication [4].

2.2.3. High capsaicin depletion

Continuous local application of high-concentration capsaicin can deplete neuropeptides such as substance P and Calcitonin Gene-related Peptide (CGRP), and cause C fiber regression, blocking pruritus signal input for a long time. This approach is suitable for the treatment of localized intractable pruritus.

2.3. Central processing of pruritus signal

Electrical signals reaching the posterior horn of the spinal cord are transmitted to the thalamus and cerebral cortex through the spinothalamic tract, and integrated into pruritus perception in the insula, cingulate gyrus, and prefrontal cortex. Pain and pruritus are cross-regulated in the center.

1. μ-opioid receptor modulation

2. Endogenous opioid peptides (*β*-endorphin and enkephalin) can activate μ-opioid receptors in the spinal cord and brainstem, inhibit presynaptic calcium channels and enhance postsynaptic potassium channels, and reduce neuronal excitability, thereby reducing pain and unconditioned pruritus conduction. However, this process may also enhance the central amplification of pruritus. μ-receptor antagonists such as naltrexone can be used to reverse this amplification.

3. NK1 receptor and regulation of GABA_B/A

4. Substance P acts on the NK1 receptor on central neurons, and can significantly amplify the pruritus signal. Aprepitant antagonizes NK1 receptors and inhibits this amplification pathway. Benzodiazepines (lorazepam) assist in the relief of chronic itching by enhancing GABA_A-mediated inhibitory synaptic transmission and reducing the central nervous system response to pruritus.

2.4. The efferent nerve stage of pruritus reaction

The instructions integrated by the central nervous system are issued through the motor and sympathetic nerves, which not only cause scratching behaviors, but also regulate local vasoconstriction and inflammation through neuropeptides.

1. *β*-receptor blocker

2. *β*-receptors belong to the superfamily of G Protein-Coupled Receptors (GPCR), and are widely expressed in organs and tissues dominated by sympathetic nerves. In the skin, norepinephrine released from the sympathetic nerve endings combines with *β*-adrenergic receptors on vascular smooth muscle cells and causes vasodilation and increases vascular permeability by activating the Gs protein-adenylate cyclase-cAMP signaling pathway, a process that may be involved in the maintenance and aggravation of pruritus-related inflammation. Non-selective *β*-receptor blocker propranolol indirectly relieves itching by competitively antagonizing β-receptor and inhibiting this pathway and reducing neurogenic vasodilation and inflammatory exudation.

3. Neural control technology

4. Transcutaneous Electrical Nerve Stimulation (TENS) and Spinal Cord Stimulation (SCS) have achieved therapeutic effects in chronic pruritus and neuropathic pain by delivering ectopic electrical impulses at the spinal dorsal horn or on the skin surface, interfering with C fiber signal transduction descending movement command, and reducing the generation and transmission of scratching impulses.

2.5. Effector stage of pruritus response

Effectors include keratinocytes, mast cells, vascular smooth muscle, and skeletal muscle involved in scratching, which react with neurotransmitters and inflammatory mediators.

1. Glucocorticoid and inflammation inhibition

2. Scratching and neuropeptide release activate effector cells, inducing erythema, edema, and inflammation. Glucocorticoids such as dexamethasone can reduce vascular permeability and effectively alleviate inflammatory itching by inhibiting the production of inflammatory factors such as cyclooxygenase -2, IL-6, and TNF-*α*.

3. Barrier repair and anti-leukotrienes

4. Chronic itching is often accompanied by skin barrier dysfunction, and humectants (urea, ceramide) and stratum corneum restorers can repair the barrier structure and reduce exogenous stimulation. Anti-leukotrienes (montelukast) help control pruritus

by inhibiting the production of slow-reactive leukotrienes and reducing the chemotaxis and activation of eosinophils and mast cells.

Notably, in the case of the pain unconditioned reflex, signal transduction also occurred along the same reflex arc. For example, in the "nerve center" stage, activation of μ-opioid receptors can not only reduce pain, but also amplify the itchy sensation [5].

3. Psychological factor intervention

The psychological state affects the pruritus experience through the Hypothalamic-Pituitary-Adrenal axis (HPA axis) and autonomic nervous system. Chronic stress and anxiety can trigger cortisol secretion and pro-inflammatory cytokine release, enhancing the sensitivity of skin receptors; At the same time, an fMRI study found that anxiety and attentional bias could enhance the response of the insula and cingulate gyrus to the itching signal, making patients more vulnerable to perceiving and amplifying the discomfort. Patients with chronic itching often fall into a vicious circle of "itching–scratching–anxiety".

Cognitive Behavioral Therapy (CBT) helps patients to reduce excessive attention to pruritus by identifying and reshaping irrational beliefs (e.g., "grasping can relieve") and behavioral experiments. Mindfulness-Based Stress Reduction (MBSR) teaches patients to observe current pruritus sensations in a non-judgmental manner, thereby reducing emotional responses to pruritus. A multi-center randomized controlled trial such as Staubach showed that for patients with chronic pruritus, the average pruritus intensity was decreased by about 32% after eight weeks of treatment with CBT or MBSR, and the anxiety and depression scores were also significantly improved, with the efficacy maintained during the three-month follow-up visit [6].

4. The application of traditional Chinese medicine in itching intervention

4.1. The holistic view and individuality of treatment based on syndrome differentiation

In traditional Chinese medicine, pruritus is regarded as the pathological product caused by the invasion of pathogenic factors such as wind, cold, dampness, heat, and toxin on the muscle surface, accompanied by the deficiency of vital qi. Clinically, it is usually classified into four syndrome types: wind-heat, wind-cold, damp-heat, and blood deficiency with wind-dryness, with the treatments of clearing heat and detoxicating, expelling wind and relieving itching, removing dampness and turbidity, and nourishing and moistening dryness, respectively. For example, in the case of wind-heat type pruritus, the modified Yinqiao Powder is often used due to red, swollen and hot skin as well as severe scratching. For the blood deficiency and wind dryness syndrome, dry skin and itching at night are more common, and Danggui Yinzi or Xuefu Zhuyu Decoction is used as the main prescription. Treatment based on syndrome differentiation not only alleviates pruritus for local symptoms, but also restores the balance of Yin and Yang at the overall level, thus achieving the goal of addressing the root cause as well as addressing both manifestation and root cause [7].

4.2. Application of classical prescriptions and modern TCM preparations

Classical prescriptions such as Xiao Jing Jie Decoction, Xiao Huo Luo Dan, and Xiao Feng Powder are widely used in the treatment of pruritus. Xiaofeng Powder, for example, is composed of Herba Schizonepetae, Radix Saposhnikoviae, Periostracum Cicadae, Kochiae Fructus, and Cortex Moutan, which has the effects of dispelling wind, clearing heat, removing dampness, and relieving itching. Clinical randomized controlled trials have shown that compared with the control group treated with conventional antihistamines, the Xiaofeng Powder group had a significantly greater average reduction in pruritus scores ($\geq 30\%$, $p < 0.01$), and it effectively relieved the scratching behavior of patients with chronic eczema and urticaria. The modern Chinese medicine preparation technology enables the classical prescriptions to be standardized and granulated for production, which improves the drug stability and ease of administration, and promotes the clinical promotion and application [8].

4.3. Mechanism research on TCM monomers and compounds

With the deepening of modern pharmacology, the mechanism of a variety of Chinese medicine monomers in the pruritus model has gradually become clear. Studies confirmed that intraperitoneal injection of matrine (20 mg/kg) could significantly inhibit the degranulation of mast cells and down-regulate the expression of TNF-α by about 40%, reducing the number of histamine-induced scratches in mice by more than 50%. Astragalus polysaccharide inhibits the chronic skin inflammatory reaction by regulating the ratio of CD4+/CD8+ T cells to close to normal level and promoting IL-10 secretion (increased by about 35%). For the compound, in vitro and in vivo experiments have shown that Xiaofeng Powder significantly inhibited the activation of the NF-κB pathway (the inhibition rate was more than 50%), and reduced the production of IL-6 and IL-31 (by about 45% and 38%, respectively), thereby relieving itching and prolonging the disease-free period in model animals [9, 10].

4.4. Multi-modal combination of acupuncture and external therapies

External therapies in Traditional Chinese Medicine (TCM), such as acupuncture, moxibustion, scraping, herbal fumigation, and washing, exert synergistic effects in the management of pruritus. Acupuncture exerts the effects of analgesia and antipruritic by stimulating the nerve endings to release endogenous active substances such as endorphins. For fumigation and washing, the volatile components can directly reach the lesions to inhibit local inflammation. For patients with atopic dermatitis, the acupoints of "Fengmen (HT 7)" and "Dazhui (GV 14)" were selected for acupuncture, together with the fumigation and washing of Ageratum and Radix Sophorae Flavescentis. After eight weeks, the Visual Analogue Scale (VAS) for pruritus was decreased by 2.5 points on average, and the sleep quality and quality of life were significantly improved [11].

5. Application of various physical therapies in pruritus management

Massage therapy is a safe, non-pharmaceutical traditional intervention for pruritus, regulating the skin–nerve–immune axis by mechanical stimulation.

Based on the gate control theory, mechanical stimulation of low-threshold Aβ fibers "occupies" the neural pathway in the spinal dorsal horn, blocking the introduction of pruritus the signal of C fibers. At the same time, it can promote local blood and lymphatic circulation, accelerate the removal of metabolites, and stimulate the release of endorphins, VIP, and other neuropeptides. Table 2 presents the effects of each physical intervention on pruritus.

Table 2. Physical intervention methods

Intervention approach	Frequency and period	Core content	leading indicator	source
Aerobic running (mouse model)	30 minutes per day, 4 weeks	Free run wheel	Number of scratches, skin IL-31&TNF-α	[12]
yoga (atopic dermatitis patients)	3 times per week, 60 minutes, 8 weeks	Moderate intensity kinesthetic + respiratory training	Pruritus score, sleep quality score, anxiety score	[13]
Targeted massage	2 times per week, 20-30 minutes, 4-6 weeks	Swedish sliding push + meridian pressing + fascial lysis	VAS average ↓2.3 points	[14]

6. Conclusion

The new technologies at this stage play an unprecedented role in supporting the research and development of new drugs. The new drugs provide a new solution for inhibiting the sensation of pruritus, overcoming the limitations of traditional drugs, which are not durable or stable and have large side effects, and gradually enabling different patients to have different optimal solutions. At the same time, multidisciplinary interventions can further ensure the well-being of patients. However, there are still many challenges in the current development, such as how to design clinical trials for personalized drugs tailored to individual patients and the lack of experience due to the insufficient treatment for the root causes of pruritus in the current world. Therefore, financial and policy support in the biological field of pruritus needs to be strengthened to accelerate the research process and realize the understanding of the whole process of pruritus and whole-link intervention as soon as possible.

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