# Research Progress on the Pruritus-Sensing Neural Circuit Mediated by the Anterolateral Posterior Nucleus of the Thalamus

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**Abstract: Pruritus causes a desire to scratch and thus removes skin irritants or foreign objects. Prolonged scratching may lead to skin ulcers and infections or lichenification; both are severe diseases that limit a person's ability to work and live and reduce their quality of life. The core neural mechanisms and circuits in the pathogenesis of pruritus have yet to be identified. The ventral posterolateral nucleus (VPL) of the thalamus is a thalamic nucleus that receives sensory information from the contralateral trunk and limbs, and subsequently transmits pruritus-, pain-, touch- and nociception-related information to the somatosensory cortex to regulate sensation. Collectively, the following are recent developments in VPL-mediated pruritus transmission pathways and regulation. Assess the current state of research on VPL neural circuits in chronic pruritus and propose future directions for research to offer new strategies and theoretical support for developing clinical treatments for chronic pruritus.**

**Keywords: Prurception; Posterior Lateral Nucleus of the thalamus; Neural Circuitry; Mechanistic Regulation; Chronic Pruritus**

## 1. Introduction

Pruritus is an aversive somatic sensation that elicits evolutionarily conserved scratching behaviour in all living things to help defend against infection and protect tissues [1]. Many dermatological diseases are characterised by pruritus, so it can occur in conditions such as neurodermatitis, eczema, liver disease, kidney failure, cholestasis, and mental illness, and is often associated with severe anxiety and other negative emotions.

The above manifestations significantly reduce the quality of life for patients and do not improve treatment results. For many years, traditional textbooks have proposed that pruritus is a type of pain transmitted through shared neural circuits; therefore, it has received relatively little research attention over the past few decades. Recently, studies have shown that the transmission routes for pruritic and nociceptive signals are partially overlapping but also differ among individuals [2–4].

The dorsal horn of the spinal cord is the main processing area for body-pruritus information. Spinal interneurons and descending pathways modify the peripheral pruritic signals at the level of the spinal cord, then these signals are transmitted upwards by projection neurons. The primary processing hub for sensory information in the brain, thalamus gathers all kinds of sensory data from all parts of the body and then sends this information to the cerebral cortex for processing [5–6]. The two functional divisions of the ventrobasal nucleus (VB) in the thalamus are the VPL and the VPM. The VPL is mainly for receiving and transmitting somatic sensory information from the opposite side of the trunk and limbs; the VPM is responsible for sensory data of the head and face. Unlike the other types of sensations, research on the VPL-mediated transmission path and regulatory mechanisms of pruritus is still in its infancy. Systematically review the neural circuits for VPL-mediated pruritus, summarize the current status of research, point out existing problems, and put forward future directions for research in this paper.

## 2. Anatomical Characteristics and Functions of the VPL in Mediating the Itch Sensory Circuit

The indication of an itching feeling, from peripheral stimulation to the emergence of subjective perception, negative emotions and scratching behaviour, is transmitted by multiple levels of neural circuits. VPL is a general-purpose relay station for sensory information from the spinal cord and brainstem, and it extends to the perithalamic nucleus, cerebral

 

cortex, limbic system, etc. As shown in the hierarchical model of pruritus signal processing from the spinal cord to the brain [1], this neural circuit can be divided into three main parts: the primary integration and gating circuit in the posterior horn of the spinal cord; the ascending cortical encoding circuit in the thalamus; and the descending whole-brain regulatory circuit, which includes interactions among thalamic nuclei.

### 2.1 Integration and Gating within Spinal Circuits

Both mechanical and chemical pruritogens can stimulate peripheral receptors; neurons in the posterior horn of the spinal cord form localised microcircuits through synaptic connections to conduct preliminary integration and gating modulation of the incoming pruritic signal. Neurons that express gastrin-releasing peptide receptors (GRPR) are required components of the transmission pathway for chemical itch signals, according to the above studies. Excitatory interneurons (e.g., those expressing urocortin-3 or neuropeptide Y receptors) specifically drive mechanical itch, and the intensity of pruritic signals is regulated by changes in their balance with inhibitory interneurons (e.g., GABAergic neurons expressing neuropeptide Y, prokineticin, or bradykinin) [1,7,8]. Pruritic information processed at the spinal level is then transmitted to supraspinal centres by spinothalamic tract neurons (STT neurons) and spinoparabrachial neurons (SPB neurons). Research has shown that STT neurons specifically responding to pruritogens, including both histamine-reliant and histamine-autonomous types, mainly project to thalamic areas such as the VPL and the posterior inferior thalamic nucleus. STT neurons in the superficial dorsal horn show an increase in discharge amplitude and duration after exposure to pruritogens, and thus act as a primary source of pruritic input to the VPL [9]. fMRI studies have further shown that during active scratching to relieve itch, neuronal activity in the VPL is positively correlated with the extent of pruritic relief; thus, VPL is also involved in both perception and behaviour in itch processing [10]. A considerable number of VPL neurons are selectively activated by pruritic stimuli and show partial functional segregation from nociceptive neurons [5], thus showing the special features of the pruritic signal pathway in the spinal cord and thalamus.

### 2.2 Intracerebral Encoding and Emotional Responses

The thalamus transmits sensory information to the somatosensory cortex for spatial organisation, and connections between the parabrachial nucleus and emotional centres in the limbic system, such as the amygdala and prefrontal cortex, are involved in processing emotions and triggering defensive responses, such as scratching [1]. Thalamocortical projections extend to both the primary (S1) and secondary (S2) somatosensory cortices, and the VPL relays information related to itch, pain, touch and nociception to the S1 for sensory modulation [9–12]. fMRI investigations have demonstrated that localized pruritic stimulation of the limb selectively activates the contralateral VPL and S1 regions; the cortical activation elicited by mechanical scratching alone is spatially adjacent to, yet distinct from, the itch-related activation zone, confirming the capacity of the VPL to discriminate between pruritic and general tactile signals [10]. O'Reilly and others (2021) have proposed the basic features of thalamocortical circuits in rodents, indicated a high density of synaptic connections between VPL and S1 that facilitate rapid conduction of somatosensory information, and different synaptic efficiencies under various stimulus conditions [11]. Other studies have also found shared parallel ascending pathways for sensory information in the "thalamus-S1-S2" network, but their feedback regulation mechanisms are different: S1 provides prolonged inhibition, and S2 increases inhibition upon stimulation. Although thalamic cortical projections to S2 involve multiple lateral and central thalamic nuclei, this study did not precisely identify the nucleus that carries thalamic cortical signals - VPL.

### 2.3 Downstream Regulation and Neural Modulation

In the spinal cord, it is generally accepted that ascending fiber tracts constitute sensory conduction pathways, while descending fiber tracts form motor conduction pathways, with the largest descending neural fiber tract being the corticospinal tract. Studies demonstrate that the corticospinal tract comprises not only fibers descending from the motor cortex to the spinal cord but also fibers directly extending from the sensory cortex to the spinal cord [13]. Brain

 

imaging reveals that peripheral pruritic stimuli activate the S1 region. Research has identified descending projection fibers from S1 that pass through the VPL and predominantly cross at the inferior end of the pyramids to reach layers III–V of the contralateral dorsal horn of the spinal cord; these S1–posterior horn projection neurons exertfeedback inhibition on spinal pruritic information [14]. Diffusion tensor imaging (DTI) studies have shown that fibres in the central anterior pathway to the spinal cord are closely associated with those in the central posterior pathway; thus, a direct projection from the sensory cortex to the spinal cord in humans has been suggested. Recently, our research group has found that the VPL also has descending fibres that participate in the transmission of pruritic signals and serve as relay stations.Downward pathways from the brainstem (e.g., the locus coeruleus norepinephrineergic system) and neurotransmitters (e.g., serotonin, endogenous opioid peptides) exert bidirectional regulation on the spinal pruritic processing circuit via VPL and spinal neurons [3,7,8]. The above mechanisms show how emotions or changes in attention affect itch sensitivity and supply new aims for management of chronic itch. Research has shown that S2 extends to various areas of the cortex and below, and among these, VPL and Posterior Complex Nuclei (Po) receive relatively dense projections [15], areas that receive limb sensory information from the spinal cord. These projections are probably both feedback loops and components of the cortex-thalamus-cortex circuit.

## 3. Current Issues and Research Prospects

### 3.1 Constructing a Comprehensive Map of VPL-Mediated Pruritus Neural Circuits

VPL acts as a relay station for itch sensation, but how different types of neurons within this nucleus are functionally specialised and which specific areas in the cortex are reached by ascending pathways for various aspects of itch sensation are not fully understood. Interactive circuits between VPL and brain regions such as the thalamic reticular nucleus, amygdala and prefrontal cortex have not been systematically identified. A thorough diagram of the neural networks accountable for managing itch information in the VPL has not yet been obtained. Advanced methodologies—including morphological analyses, Fiber photography, optogenetics/chemical genetics procedures, integrated behavioral and electrophysiological assessments, transcriptomics, proteomics, and connectomics—should be employed to delineate the key neuronal subtypes involved in VPL-mediated pruriceptive processing and their regulatory mechanisms.

### 3.2 Deepening Research on Molecular Mechanisms

Current investigations into pruritus predominantly concentrate on neurotransmitters and ion channels, rather than the role of coding RNA, epigenetic modifications, and inflammatory factor pathways within the VPL have been scarcely explored. The molecular mechanisms through which the VPL regulates chronic pruritus remain insufficiently clarified. It is imperative to further elucidate the functional mechanisms of microglia and astrocytes within the VPL, examine the contributions of non-coding RNAs and epigenetic regulation to central sensitization, identify novel drug targets with high selectivity and low adverse effects, and develop next-generation centrally acting antipruritic agents. The cutaneous immune system is also a part of how we feel an itch. The precise manner in which the central nervous system regulates the skin's immune response via sympathetic nerves to modify the sensation of itch remains incompletely understood, and this is of great interest to research on chronic itchy skin diseases.

### 3.3 Optimization of Animal Models for Pruritus Research

Most of the research on pruritus has been carried out in rodent models, and there are notable species-specific variations in the structure of the thalamic nucleus, spinothalamic tract projection patterns and receptor expression profiles among rodents, primates and humans. Investigations using non-human primates are often limited by small sample sizes, and invasive electrophysiological studies in human subjects are subject to methodological and ethical restrictions; thus, the results from animal studies have not been directly applied to clinical practice [9]. Therefore, the improvement of animal models for pruritus research is needed. At the same time, the focus of strategic efforts should be to expand the model system for chronic pruritus in mice, develop non-human primate

 

models, and advance research that uses human-derived samples. Utilizing new technology such as organoid platforms, the research on pruritus will be shifted from rodents to primates to achieve a new understanding of its pathogenesis and better guide treatment.

## 4. Summary

The VPL in the thalamus is a central component of the itch-sensing pathway. This paper will systematically introduce the VPL-mediated pathway of pruritic signal transmission and its regulation, as well as its overall impact on the perception of itch and behaviour. As a relay station for sensory information, the VPL receives input via the spinothalamic tract, and among its neuronal populations, some are functionally heterogeneous; that is, separate subpopulations process pruritic and nociceptive signals independently. Interactions among the VPL and both S1 and S2 are required for spatial localisation and intensity coding of itch perception. The downstream regulatory path of S1 is VPL, and in conjunction with other areas in the brain such as the thalamic reticular nucleus and locus coeruleus, affective responses and pruritic perception are integrated.

Although some positive outcomes have been accomplished lately, there are still some issues. The functions of the various neuronal subpopulations are not clear, there has been no study of interactive dynamics between VPL and other brain areas, and differences exist in animal models and human neuroanatomy. In the future, scholars will integrate the best technologies to explore in more depth how VPL reduces itching, discover new targeted therapies, develop effective management strategies for chronic pruritus, and ultimately provide support for enhancing the quality of life of patients.

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