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Substance P and the itch-scratch response

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Abstract: Substance P (SP), a neuropeptide diffusely scattered in the nervous system and immune system, participates in various physiological and pathological processes, including pain perception and inflammatory response. However, the regulatory mechanisms of SP in itch perception and its downstream pathophysiological responses, such as the chronic itch-scratch vicious cycle, have not been systematically elucidated. Based on an analysis of the existing literature, this review summarizes the biological functions of substance P in the itch-scratch response, and explores its mechanism of action in signal transduction, inflammatory response and nerve sensitization.

Keywords: pruritus, Substance P, scratching, chronic itching, inflammatory response

1. Introduction

Substance P is a neuropeptide that mediates neurogenic inflammation, pain transmission and pruritus. Both central and peripheral nervous systems contain this molecule. Substance P is identified as a neuropeptide causing inflammation and a potent endogenous pruritogen in mice and human subjects. It mainly acts through Neurokinin 1 Receptor (NK-1R) and Mas-related G protein-coupled receptors, and promotes the occurrence of pruritus by interacting with sensory neurons, immune cells such as mast cells, T cells, and non-neural cells such as keratinocytes. Studies have shown that substance P is not only involved in acute pruritus, but also involved in the development of chronic pruritus, making it an important therapeutic target [1]. Based on the existing literature, this paper discusses the role of substance P in the itch-scratch response. An in-depth knowledge of the function of substance P in pruritus will help us to reveal the nature of pruritus and provide new targets for some new anti-pruritus drugs. Substance P is also one of the key substances of pain sensation. This study hopes to provide ideas for the combined study of pain sensation and itch sensation.

2. The mechanism of Substance P secretion in itch sensation

Substance P is encoded by the Preprotachykinin A (PPT-A) gene. After transcription and translation, the precursor protein is generated, and then undergoes. A series of enzyme digestion and modification processes to form bioactive SP. In neurons, SP is primarily generated in the endoplasmic reticulum of the soma and subsequently encapsulated in secretory vesicles, which are sent along the axon to the nerve terminal for storage. When a neuron is stimulated, these vesicles move to the presynaptic membrane and rapidly release substance P [2].

The signals that stimulate the secretion of substance P during pruritus are mainly divided into mechanical and chemical signals. Mechanical pruritus is mainly mediated by hypomyelinated Aδ fibers or unmyelinated C fibers. When the skin surface is subjected to pressure, stretch, or hair movement, Aδ cutaneous nerve terminals located in the dermis are activated and secrete substance P [3]. Chemical pruritus is mediated by hypomyelinated cutaneous sensory nerve endings Aδ and nonmyelinated fiber nerve endings C [4]. They contain multiple membrane receptors specific for both exogenous and endogenous pruritogens. When the concentration of these pruritogens rises in the blood, nerve terminal Aδ and nerve terminal C activate and stimulate the secretion of substance P.

Chemical pruritus in the skin Pruritogens are generally secreted by keratinocytes and immune cells, including T lymphocytes, mast cells, and granulocytes, and act on skin nerve endings through local release. These molecules are speculated to be related to G Protein-Coupled Receptors (GPCRs) and may also be involved with Janus Kinase (JAK) Signal Transduction and Activate Transcription (STAT) factor signaling pathways (i.e., cytokine/chemokine receptor) coupling. The receptors mentioned mediate substance P secretion by activating ion channels, such as Transient Receptor Potential Vanilloid 1 (TRPV1), instant Receptor Potential ion channels (Transient Receptor Potential Ankyrin 1, TRPA1), and voltage-gated sodium channels (NaV) [3].

Substance P is found to be synthesized and secreted by T cells, macrophages, mast cells and other immune cells apart from sensory neurons, indicating that substance P has a broader role in the neural-immune regulatory network [5].

3. The main receptor of Substance P in the itch-scratch cycle

3.1. Neurokinin 1 Receptor (NK-1R)

NK-1R, a member of the G Protein-Coupled Receptor (GPCR) family, is the major receptor of substance P. NK-1R is widely expressed by the spinal dorsal horn, trigeminal ganglion, skin, gastrointestinal tract, respiratory tract and other parts of the body [6]. In the dorsal horn of the spinal cord, the projection neurons in the superficial layers I and II are the main neurons to express NK-1R. In skin, cells related to the initiation and transmission of pruritus, keratinocytes included, are the main resources of NK-1R. These results suggest that substance P can directly or indirectly regulate the function of skin cells and immune cells by binding to NK-1R [6, 7].

After being secreted by the synaptic terminals of peripheral neurons, substance P binds to the NK-1R of dorsal root neurons and activates secondary neurons in the spinal cord, which transmits the itch signal to the higher centers. Results showed that NK-1R knockdown or usage of NK-1R antagonist remarkably reduced the scratching behavior of mice in response to pruritus stimuli [6]. NK-1R is also involved in the conduction of pruritus in the skin. SP binds to NK-1R on skin cells, which can stimulate keratinocytes to secrete cytokines and chemokines, attract immune cell infiltration, and promote the occurrence of inflammatory response. At the same time, the activation of NK-1R can also lead to the degranulation of mast cells, and the secretion of histamine and other pruritus mediators, which further aggravate the symptoms of pruritus [2, 8].

3.2. Mas-associated G protein-coupled receptors (Mrgprs)

Mrgprs constitute a recently identified family of GPCRs, predominantly expressed in sensory neurons and immune cells. Substance P is capable of binding to several Mrgprs. In mice, substance P mainly binds to MrgprA1 expressed in the peripheral dorsal root ganglion and MrgprB2 in mast cells. In humans, substance P mainly binds to MrgprX2, which is expressed in both peripheral ganglia and mast cells [9, 10].

MrgprA1 is an important member of the Mrgprs family, which is mainly expressed on sensory neurons. Through genetic and pharmacological approaches, the researchers confirmed that MrgprA1 plays an important role in SP-induced scratches behavior [9]. In experiments, blocking MrgprA1 receptors in neurons in the dorsal root ganglion reduced the number of scratching to the baseline, suggesting that substance P, after being released by prickly primary afferents, interacts with Mrgprs in the postsynaptic membrane to activate excitatory interneurons in the dorsal root neurons, which eventually transmit to the cerebral cortex to produce itch sensation and trigger pruritus.

MrgprB2 is the only Mas-associated G protein-coupled receptor expressed in mouse mast cells. Substance P may bind to these receptors and mediate IgE-independent mast cell degranulation, promoting the body's inflammatory response [11, 12]. In addition, MrgprB2 can also be activated by various pruritogenic substances, both endogenous and exogenous, and is involved in the occurrence of a variety of itch-related diseases [2, 7].

MrgprX2 is the cognate receptor of MrgprB2 in human mast cells and mainly mediates the degranulation response induced by cationic compounds such as morphine and LL-37.

4. Interactions of Substance P with the immune system during the itch-scratch cycle

4.1. Effects of Substance P on the immune system

4.1.1. Activation of immune cells

Substance P can activate multiple immune cells and promote the release of immunoactive substances.

Mast cells are an important immune cell type, widely distributed in the skin, gastrointestinal tract, respiratory tract, and other tissues. Substance P can activate mast cells by binding to MrgprX2/B2 on mast cells [9, 11]. After binding to its receptor, substance P activates the downstream signaling pathways, leading to the increase of intracellular calcium concentration in mast cells, triggering degranulation and the secretion of histamine, leukotriene, prostaglandins and other inflammatory mediators. These medium seepages can cause vasodilation and plasma cells, thereby increasing the inflammatory response [2, 7].

Basophils are a type of white blood cell mediating allergic reactions. Substance P can bind to NK-1R and stimulate basophils to release histamine, interleukin-4 (IL-4) and other inflammatory mediators [13]. Itchy histamine is a kind of important medium that can combine with histamine receptors on sensory neurons and activate itchy signaling pathways. IL-4 can adjust the function of the immune system, promote the proliferation and differentiation of Th2 cells, and further aggravate allergic reactions and

itching. In allergic disease, the activation of basophils and release of inflammatory medium is one of the important reasons for causing itching and inflammation; substance P plays a key part in regulating the process [13].

Substance P can also activate macrophages, T cells, neutrophils and other immune cells. Substance P binds to NK-1R on T cells and mediates the activation, multiplication and cytokine secretion of T cells. In the inflammatory state, substance P can promote T cells to differentiate into Th1 and Th17 cells, and secrete inflammatory cytokines such as interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) [2, 8]. SP can also activate macrophages, promote their phagocytic function and the secretion of inflammatory mediators [11].

4.1.2. Promote immune cell proliferation and migration

Substance P enhances inflammatory responses by regulating the proliferation of bone marrow cells, lymphocytes, and vascular endothelial cells. Studies have shown that substance P can stimulate human T cells in vitro into proliferating, and this process may be achieved by promoting the expression of interleukin-2 (IL-2) [2]. Substance P also promotes angiogenesis by targeting immune cells. Substance P can induce nitric oxide production by endothelial cells to directly regulate angiogenesis and indirectly regulate angiogenesis by interacting with mast cells and granulocytes [3]. Substance P migration, adhesion, and can also enhance granulocytes angiogenic gene expression to promote the formation of blood vessels [11].

Substance P binds to the MrgprX1 receptor on CD301b + DCS, activates downstream pathways and promotes cytoskeletal reorganization and migration-related protein expression by regulating the expression of adhesion molecules and chemokine receptors, and finally triggers the migration of DCS to lymph nodes [8, 11]. Dendritic cells are one of the key cells mediating non-specific and specific immunity, whose migration is the basis of immune response. Substance P binds to the NK-1R on immune cells such as T cells and mast cells, and activates the G protein-coupled signaling pathway to stimulate the migration of immune cells [2]. In addition, substance P can also interact with NK-1R, upregulating the expression of chemokines such as macrophage inflammatory protein (MIP-1 β or CCL4, MIP-2 or CXCL2), monocyte chemotactic protein-1 (MCP-1 or CCL2), chemokine ligand 5 (CCL5) and interleukin-8 (IL-8) through ERK1/2 and p38 signaling pathways, and indirectly enhance the recruitment of leukocytes [11].

4.2. Promoting effect of inflammatory response on Substance P release

Substance P activates mast cells via MrgprX2 (human) or MrgprB2 (mouse), triggering histamine and tryptase release. In certain patients with chronic pruritus, MrgprX2 is overexpressed on cutaneous mast cells, thereby exacerbating the vicious itch-scratching cycle [3]. Factors regulated in part by substance P participate in the conduction of itch sensation, further promoting the release of substance P and the progression of scratching behavior. For example, when eosinophils, mast cells and T cells are stimulated by substance P, they increase the release of pruritus-inducing factors such as IL-4, IL-13 and IL-31 proteins; reduce the expression of proteins involved in keratinocyte differentiation; and promote inflammatory response through IL-4Rα/IL-13Rα1 axis [11]. The activation of immune cells like mast cells and eosinophils can promote the secretion of histamine. Histamine receptors and G protein-coupled receptors such as PAR2 can sense the source of pruritus, and then activate downstream TRP channels such as TRPV1 and TRPV4, which promote the depolarization of sensory cells and produce action potentials, and activate vesicles to release substance P [11].

5. Possible role of Substance P in pruritus sensitivity

Pruritus sensitivity means an enhanced reaction of itch-sensing neurons to their normal or subthreshold afferent inputs. Clinically, pruritus sensitivity is mainly divided into persistent pruritus, alloknesis (itching caused by innocuous touch stimulation), and hyperknesis (increased itching response to normal itchy objects) [3].

The origin of neuronal sensitization in chronic pruritus remains uncertain, whether it is attributable to central, or peripheral mechanisms, or a combination of both. Some researchers have proposed that sensitization of normal skin to chemical and mechanical stimuli may be due to central mechanisms, while further sensitization of diseased skin may be due to peripheral sensitization associated with persistent inflammation, pruritus, and pain [3].

Peripheral sensitization may result from increased sensory neuronal excitability caused by hyperinnervation or loss of inhibitory neuronal innervation and receptors, including PAR-2, Mrgprs, TLR3, cytokine receptors, and TRP channels increase in expression, sensitivity, and responsiveness of sensory neurons to mediators such as NGF, BDNF, neurotrophins 3 and 4, SP, CGRP, endorphins, T and H2 cytokines (IL-4, IL-13, and IL-31), prostaglandin E2 and ET-1. Peripheral glial cells such as Schwann cells and satellite glial cells also participate in the overreaction to itch signals [3, 9].

Clinical studies have shown that inhibition of spinal cord neurons expressing NK-1R reduces behavioral signs of persistent pruritus, pruritus disarticulation, and excessive pruritus, as well as chemically induced scratching, suggesting that spinal cord neurons expressing NK-1R play an important part in pruritus signaling and sensitization. NK-1R is one of the important

receptors of substance P, which reveals the possible role of the neuropeptide in nerve sensitization. The substance P signaling pathway may be involved in pruritus sensitization. Thus, drugs targeting this pathway may be promising for the treatment of chronic pruritus [6].

Previous studies have shown that the secretion of substance P and glutamate reduces the pain threshold of dorsal horn projection Neurons derived from Wide Dynamic Range Neurons (WDR), while increasing its pain perception range. Located in the spinal cord, these neurons are responsible for transmitting pain signals. This suggests that substance P may be related to the body's perception of pain. This result may partially explain why pain caused by scratching inhibits the itch sensation [4, 14].

6. Relevant clinical findings

In mouse models, MrgprA1, MrgprB2, and TRPV1 mediate pruritus and inflammatory responses induced by substance P, including mast cell degranulation, dendritic cell migration, and enhanced vascular permeability [9, 10, 13, 16]. In the research on several patients suffering from psoriasis and atopic dermatitis, the number of nerve fibers expressing substance P in their skin was more than that in the control group. NK-1R was overexpressed in the entire epidermal layer of skin of patients with both non-itch and itch specific dermatitis. Some clinical trials for chronic pruritus have shown that aprepitant, a high-affinity NK-1R antagonist, can noticeably reduce the degree of pruritus in patients, but this effect is not significant in atopic dermatitis [6, 15]. The circulating serum substance P level of patients with chronic urticaria is remarkably higher than that of the control group, and the content of MrgprX2 in skin-derived mast cells is positive correlated with the severity of the symptoms. Substance P is also found to activate skin mast cells by activating MrgprX2, which is involved in the etiopathogenesis of chronic urticaria [2].

7. Conclusion

Substance P plays a significant part in signal transduction, inflammatory response and neural sensitization in the itch-scratch cycle. Substance P binds to its related receptors, such as NK-1R and Mrgprs, and triggers the downstream transduction of itch and pain signals. At the same time, substance P enhances the body's inflammatory response by promoting the migration and proliferation of immune cells, regulating the secretion of cytokines, and activating immune cells. Substance P may also cause pruritus sensitivity through nerve sensitization. The immunological effects of SP in mechanical pruritus and neurogenic pruritus are lacking in current studies. Future studies on the role of SP in mechanical pruritus and neurogenic pruritus, the role of SP in the upper pathway of itch-scratching behavior, and the interaction between SP and other neurotransmitters are needed to fill the gap in the research field.

References

[1] Stander, S., & Yosipovitch, G. (2019). Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus. *The British Journal of dermatology*, *181* (5), 932-938.

[2] Zhu, Z., & Bhatia, M. (2023). Inflammation and Organ Injury the Role of Substance P and Its Receptors. *International Journal of Molecular Sciences*, *24* (7), 6140.

[3] Misery, L., Pierre, O., Le Gall-Ianotto, C., Lebonvallet, N., Chernyshov, P. V., Le Garrec, R., & Talagas, M. (2023). Basic mechanisms of itch. *The Journal of allergy and clinical immunology*, *152*(1), 11-23.

[4] Zhang, Z., Zheng, H., Yu, Q., & Jing, X. (2024). Understanding of Spinal Wide Dynamic Range Neurons and Their Modulation on Pathological Pain. *Journal of pain Research*, 17, 441-457.

[5] Lotts, T., & Stander, S. (2014). Research in practice: substance P antagonism in chronic pruritus. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG*, *12* (7), 557-559.

[6] Stander, S., & Yosipovitch, G. (2019). Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus. *The British Journal of dermatology*, *181* (5), 932-938.

[7] Wang, N., Wang, J., Zhang, Y., Hu, S., Zhang, T., Wu, Y., Sun, X., Zhang, T., Yang, S., & He, L. (2022). Substance P-induced lung inflammation in mice is mast cell dependent. *Clinical and experimental allergy : Journal of the British Society for Allergy and Clinical Immunology*, *52* (1), 46-58.

[8] Perner, C., Flayer, C. H., Zhu, X., Aderhold, P. A., Dewan, Z. N. A., Voisin, T., Camire, R. B., Chow, O. A., Chiu, I. M., & Sokol, C. L. (2020). Substance P Release by Sensory Neurons Triggers Dendritic Cell Migration and Initiates the Type-2 Immune The Response to Allergens. *Immunity*, *53* (5), 1063-1077.

[9] Azimi, E., Reddy, V. B., Pereira, P. J. S., Talbot, S., Woolf, C. J., & Lerner, E. A. (2017). Substance P activates Mas-related G protein-coupled receptors to induce itch. *The Journal of allergy and Clinical immunology*, *140* (2), 447-453.

[10] Macphee, C. H., Dong, X., Peng, Q., Paone, D. V., Skov, P. S., Baumann, K., Roethke, T., Goldspink, D. A., Pearson, S. K., & Wu, Z. (2024). Pharmacological blockade of the mast cell MRGPRX2 receptor supports investigation of its relevance in skin Disorders. *The Frontiers in immunology*, 15, 1433982.

[11] Mashaghi, A., Marmalidou, A., Tehrani, M., Grace, P. M., Pothoulakis, C., & Dana, R. (2016). Neuropeptide substance P and the immune response. *Cellular and molecular life sciences: CMLS*, *73* (22), 4249-4264.

[12] Liu, A. W., Zhang, Y. R., Chen, C. S., Edwards, T. N., Ozyaman, S., Ramcke, T., McKendrick, L. M., Weiss, E. S., Gillis, J. E., Laughlin, C. R., Randhawa, S. K., Phelps, C. M., Kurihara, K., Kang, H. M., Nguyen, S. N., Kim, J., Sheahan, T. D., Ross, S. E., Meisel, M., Sumpter, T. L., … Kaplan, D. H. (2025). Scratching promotes allergic inflammation and host defense via neurogenic mast cell activation. *Science (New York, N.Y.)*, 387 (6733), eadn9390.

[13] Hashimoto, T., Rosen, J. D., Sanders, K. M., & Yosipovitch, G. (2019). Possible roles of basophils in chronic itch. *Experimental dermatology, 28*(12), 1373-1379.

[14] Zieglgansberger W. (2019). Substance P and pain chronicity. *Cell and tissue research, 375*(1), 227-241.

[15] Nattkemper, L. A., Tey, H. L., Valdes-Rodriguez, R., Lee, H., Mollanazar, N. K., Albornoz, C., Sanders, K. M., & Yosipovitch, G. (2018). The Genetics of Chronic Itch: Gene Expression in the Skin of Patients with Atopic Dermatitis and Psoriasis with Severe Itch. *The Journal of Investigative dermatology, 138* (6), 1311-1317.

[16] Nagamine, M., Kaitani, A., Izawa, K., Ando, T., Yoshikawa, A., Nakamura, M., Maehara, A., Yamamoto, R., Okamoto, Y., Wang, H., Yamada, H., Maeda, K., Nakano, N., Shimizu, T., Ogawa, H., Okumura, K., & Kitaura, J. (2024). Neuronal substance P-driven MRGPRX2-dependent mast cell degranulation products differentially promote Vascular permeability. *The Frontiers in immunology*, 15, 1477072.