Full text open access online (Since 2001)

PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330
Int J Hum Genet, 26(3): 138-143 (2026)
DOI: 10.31901/24566330.2026/25.02.924

Neuropeptides in Chronic Airway Inflammation

Yimin Lu[1#], Xuemei Liu[2#], Shu Zhang[3] and Lin Zhang[4*]

[1,2,3]Department of Pulmonary and Critical Care Medicine, Affiliated Kunshan Hospital of Jiangsu University, Suzhou, 215300, China
[4]Department of Oncology, Changshu NO.1 People's Hospital, Suzhou, 215500, China

KEYWORDS Airway Remodelling. Calcitonin Gene-related Peptide. Neurogenic Inflammation. Neurokinin Receptor. Neuropeptides. Vasoactive Intestinal Peptide

ABSTRACT Chronic airway inflammation is characterised by persistent infiltration of inflammatory cells that cause airway mucosal damage and remodelling. Recent studies have highlighted the important role of neuropeptides in regulating airway immune responses. This review aims to summarise the current knowledge of neuropeptides involved in chronic airway inflammation and their potential therapeutic significance. Neuropeptides such as substance P, neurokinin, calcitonin gene-related peptide, and vasoactive intestinal peptide participate in mucus secretion, smooth muscle contraction, and inflammatory cell recruitment. They interact with immune cells through specific receptors and signalling pathways, influencing the progression of airway inflammation. Understanding the mechanisms of neuropeptide-mediated neuro-immune regulation may provide new targets and strategies for preventing and treating chronic airway inflammatory diseases.

INTRODUCTION

Neuropeptides and Airway Sensory Afferent

Neuropeptides are a class of bioactive polypeptides widely distributed in the nervous and peripheral systems. They play essential roles in regulating airway tone, vascular permeability, immune cell activity, and mucus secretion. Within the respiratory tract, neuropeptides such as substance P, neurokinin, calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP) participate in the complex neuro-immune network that modulates airway inflammation. Persistent stimulation of sensory nerves and immune cells can lead to abnormal neuropeptide release, resulting in airway hyperresponsiveness and remodelling.

Recent studies have further demonstrated that neuropeptide-mediated signalling contributes to airway epithelial barrier dysfunction, cytokine release, and immune cell recruitment (Tamari et al. 2024; Wu et al. 2024). Moreover, interactions between neuropeptides and their receptors, such as NK1R, NK2R, and VPAC2, are implicated in chronic airway diseases including asthma and chronic obstructive pulmonary disease (Kaczyñska et al. 2021; Camp et al. 2021). Despite increasing evidence, the precise mechanisms by which neuropeptides regulate airway inflammation remain incompletely understood. Therefore, it is necessary to critically summarise the recent advances in this field and explore potential therapeutic implications.

Objectives

This review aims to critically summarise recent findings on the role of neuropeptides in chronic airway inflammation, emphasising their involvement in neuro-immune regulation, airway remodelling, and inflammatory responses. The review also seeks to identify potential molecular targets that may provide new therapeutic strategies for the prevention and treatment of chronic airway inflammatory diseases.

METHODOLOGY

This review is a narrative synthesis based on literature collected from PubMed, Web of Science, and Google Scholar databases. The search was conducted from January 2010 to May 2024 using the keywords "neuropeptides," "airway inflammation," "substance P," "calcitonin gene-related peptide," "neurokinin," and "vasoactive intestinal peptide." Only English-language articles focusing on

[#]These authors contributed equally to this work.

[*]*Address for correspondence:*
Lin Zhang
No.1 Shuyuan Street, Changshu City,
Jiang Province, China.
E-mail: herro123789@126.com

chronic airway inflammation were included. Studies involving asthma, COPD, and related neuroimmune mechanisms were prioritised. No experimental data were collected directly for this study.

RESULTS

Substance P

Substance P (SP) belongs to the tachykininÿTK ÿfamily of neuropeptides and is widely distributed in various tissues. Among them, airway SP is mainly from PCFs and secreted by nerve cells after external stimulation. In addition, eosinophils and lymphocytes can also synthesise and secrete SP, whose main function is to contract airway smooth muscle and promote mucus secretion. In the occurrence and development of chronic airway inflammation, SP is an important mediator of nerve and immune interaction. Tachykinin needs to bind to the corresponding receptor in order to express biological activity. Tachykinin receptor (Tachykinin receptor TKR) has a total of three subtypes, namely NK1R, NK2R and NK3R, among which SP and NK1R have the largest binding force. NK1R is distributed in airway smooth muscle, submucosal glands and vascular endothelium. CD4 and CD8 also express a small amount of NK1R in T cells, which helps to maintain the activity of Th1 and Th17 cells (Morelli et al. 2020). Previous studies have indicated that the nerve fibres containing SP and exist on the same (SynCAM) membranes of mast cells (synaptic cell adhesion molecule), the combination of similar molecules can enhance the interaction of inflammation (Ito et al. 2006). Mrgprb2 is a specific receptor for mast cells. A recent study suggested that SP can be used as an endogenous agonist of Mrgprb2 to further promote mast cell degranulation, release inflammatory mediators such as histamine and leukotriene, and induce the synthesis of chemokine IL-8 to aggravate airway inflammation (Green et al. 2019). SP can also chemotactic eosinophils, promote the release of basic protein, increase airway response, and aggravate airway epithelial injury (Spitsin et al. 2017). SP can also work with IL-33 to enhance TNF-á release (Taracanova et al. 2017). Itepekimab, a new monoclonal antibody against IL-33, has been shown to be effective in improving airway inflammation (Wechsler et al. 2021). Of course, immune cells can also regulate the expression of SP to a certain extent, and IL-12 and IL-18 induce the expression of NK1R, while IL-10 and TGF-â inhibit its expression. Clinical studies have shown that the SP level in patients with chronic airway inflammation is high and positively correlated with the severity of the disease, but the SP level in patients with COPD decreases during acute exacerbation (Boschetto et al. 2005), which may be related to the depletion of neuropeptides. It has been found that NK1R antagonists can activate the protective effect of airway epithelium in asthmatic mice through Nrf2/HO-1 (Wang et al. 2019). The main mechanism of novel coronavirus infection (COVID-19) is cytokine storm, and SP is the trigger of inflammatory storm (Mehboob et al. 2023), and NK1R antagonists play a certain role in the treatment of novel coronavirus infection (Mehboob et al. 2023). Another study showed that the NK1R antagonist aprepitant was effective in treating lung cancer coughs (Smith et al. 2021). Therefore, NK1R antagonists may be a new target for the treatment of chronic airway inflammation.

Neurokinin A and Neurokinin B

Neurokinin A (NKA) and Neurokinin B (NKB) mainly exist in the respiratory tract sensory nerve fibre endings, can cause tracheal contraction and high reaction, like SP, they also belong to the tachykinin TK family of neuropeptides, in the body is mainly composed of neutral peptide enzyme and angiotensin conversion enzyme degradation. Both NK2R and NK3R are distributed in airway smooth muscle, and a small amount of them are also expressed in the central nervous system (Mizuta et al. 2008). NKA binds to NK2R, increases TNF-á and TNF-â synthesis by activating dendritic cells, and promotes airway inflammation (Kitamura et al. 2012). In addition, the release of TNF-ã can increase the expression of NKA and NK2R in airway smooth muscle and enhance airway hyperresponsiveness, so forming positive feedback between nerve and immunity (Kobayashi et al. 2012). NKB, combined with NK3R, has a greater ability to contract the airway than SP (Corboz et al. 2012). In guinea pig models, NK3R agonists induce airway hyperresponsiveness (Daoui et al. 2000). The recent studies have shown that not only NK2R antagonists (saredutant) can partially inhibit bronchoconstriction induced by NKA in asthmatic patients (Joos et al. 2000), but also the triad-of NK1R/

NK2R/NK3R antagonist (CS-003) can significantly reduce airway hyperresponsiveness (Schelfhout et al. 2006). Therefore, tachykinin receptor antagonists have the therapeutic potential of chronic airway inflammation, and its mechanism of action is worthy of further study.

Calcitonin Gene-Related Peptide (CGRP)

Calcitonin gene-related peptide (CGRP) is synthesised by the sensory nerve endings of the C fibre of the vagal nerve and distributed in the airway smooth muscle, which can contract the bronchus and distribute in the airway epithelium. It has the ability to induce fibroblast migration and proliferation, promote epithelial differentiation, facilitate the repair of airway injury, and cause mucus secretion and airway edema in the airway. There are two subtypes of CGRP, namely, á-CGRP and â-CGRP (Carmine et al. 2020), which bind to receptor active modification protein 1 (RAMP1) and are expressed in airway epithelium and immune cells (Bell and McDermott 1996), can enhance the eosinophilic effect, promote the release of leukotrienes, further enhance the inflammatory effect of Th1 and Th2, and induce the expression of IL-10. Through CGRP, pulmonary neuroendocrine cells (PNEC) can stimulate ILC2 and trigger downstream airway inflammation, releasing IL-5 and IL-33 (Sui et al. 2018). CGRP can reduce airway inflammation by negatively regulating ILC2 (Wallrapp et al. 2019). JAK1 activation in lymphocytes can increase airway inflammation, and it can directly inhibit ILC2 function by expressing â-CGRP (Tamari et al. 2024), so JAK inhibitors may play a role in the treatment of chronic airway inflammation. The degradation products of CGRP can also stimulate mast cell degranulation and release a variety of active substances, further increasing vascular permeability and leading to airway inflammation. It has been found that CCL17 can generate a new airway inflammation pathway by inducing CCR4 to release more CGRP (Bonner et al. 2013). CGRP can also induce IL-9 expression through the cAMP / PKA signalling pathway in vivo, further amplifying airway inflammation (Mikami et al. 2013). In addition, CGRP can also regulate the transmission of dendritic cell (DC) signals by altering immunomodulatory mechanisms in the airway, thereby triggering airway inflammation (Rochlitzer et al. 2011). At present, CGRP (antagonist) has shown some advantages in experiments. The use of CGRP receptor antagonists can inhibit the differentiation of CGRP produced by RAMP1 and IL-6, thereby reducing the continuous stimulation of CGRP on epithelial cells, reducing airway inflammation and airway hyperreactivity, and further improving airway remodelling (Bonner et al. 2013). However, recent studies have found that CGRP can inhibit neutrophil recruitment, indicating that it has certain anti-inflammatory properties. Exogenous administration of á-CGRP can reduce basophil induced inflammation, decrease eosinophilia levels, and enhance the production of regulatory T cells. á-CGRP deficiency can promote M2 polarisation of macrophages by activating the (PPARã) pathway, thus leading to the activation of type 2 immune response and accelerating the occurrence of inflammation (Lv et al. 2023). Therefore, the mechanism of action of CGRP in chronic airway inflammation is still controversial, and whether it is related to different receptors according to different types of CGRP and whether different types interact with each other needs to be further explored.

Vasoactive Intestinal Peptide (VIP)

Vasoactive intestinal peptide (VIP) in many tissues and organs of the body are expressed, but most abundant express in the airway, distributed in airway smooth muscle and submucosal glands, can relax the airway and regulating mucus secretion (Camp et al. 2021). Unlike other neuropeptides, it has a powerful anti-inflammatory effect, on the one hand inhibiting the activation of natural killer cells, on the other hand inhibiting lymphocytes and mast cells, reducing the release of inflammatory mediators. It usually binds to two receptors, VPAC1 and VPAC2. The combination of VIP and VPAC1 can dilate the airway, inhibit the release of IL8 and TNF-á, reduce the infiltration of neutrophils, prevent the destruction of neurons, and accelerate the degradation of airway inflammation (Sun et al. 2018). VPAC2 is highly expressed on activated T cells and ILC2, and through this receptor, the phenotype of Th2 can be changed to promote type 2 immune response (Huang et al. 2021). VIP binds to VPAC2 to promote the aggregation of eosinophils and up-regulate IL-5, while IL-5 can also stimulate the release of VIP, and there is a positive feedback loop between the two, which jointly changes the occurrence and development

of airway inflammation (Nussbaum et al. 2013). In addition, VIP can induce the expression of IL-10, reduce the release of TGF-â1, and play an anti-inflammatory role (Larocca et al. 2007). However, in the allergic state, decreased VIP activity is associated with increased airway inflammation and airway hyperresponsiveness (Szema et al. 2006). Studies have shown that VIP can enhance the phosphorylation of ERK1/2 signalling pathway and the expression of Cav-1, inhibit the proliferation of airway smooth muscle cells, reduce airway mucus secretion, and improve airway remodelling (Wang et al. 2019). In fact, mice lacking VIP exhibited airway hyperresponsiveness and airway inflammation, which were relieved by intraperitoneal injection of VIP analogues (Hamidi et al. 2006). After administration of vasoactive intestinal peptide, inflammatory cell infiltration in lung tissues of mouse models was significantly reduced (Zhou et al. 2020). In clinical studies, elevated serum VIP levels are associated with acute exacerbation of COPD (Mandal et al. 2015), VPAC2 agonists can double the effect of airway dilation (Lindén et al. 2003), and VIP can reduce airway inflammation induced by cigarettes (Onoue et al. 2010). Therefore, inhalation of VIP may have a certain positive impact on the quality of life of COPD patients. However, exogenous VIP has a short half-life, is easily degraded and has low bioavailability (Jia et al. 2023). Can more new materials be developed to wrap VIP, so as to play its long-term role? VIP is widely distributed. Whether it can increase the production of endogenous VIP by stimulating other organs to improve airway inflammation is also a new direction for the treatment of chronic airway inflammation in the future.

DISCUSSION

The integrated role of neuropeptides in chronic airway inflammation reflects a complex neuroimmune regulatory network. SP and NK primarily act as proinflammatory mediators, whereas CGRP and VIP display dual or anti-inflammatory properties. Recent studies (Tamari et al. 2024; Wu et al. 2024) have revealed that sensory neurons actively participate in immune homeostasis, suggesting that the airway is not merely a passive target of inflammation but an active neuro-immune organ. However, heterogeneity in experimental models and limited clinical data still hinder translational progress. Future studies should combine multi-omics technologies and single-cell analyses to better elucidate neuropeptide signalling at cellular and molecular levels. Establishing unified evaluation standards and integrating preclinical with clinical research are also crucial for transforming neuropeptide-based findings into therapeutic strategies.

CONCLUSION

Neuropeptides, including SP, NKA/NKB, CGRP, and VIP, play critical roles in the onset and progression of chronic airway inflammation. Their regulatory effects on immune cells and airway epithelial remodelling suggest that neuropeptide signaling constitutes a pivotal therapeutic axis in respiratory diseases.

RECOMMENDATIONS

Future research should prioritize the identification of specific neuropeptide receptors as therapeutic targets, with particular emphasis on developing selective agonists or antagonists. In addition, further studies should explore the crosstalk between neuropeptide signaling and inflammatory pathways involved in airway remodeling. Large-scale translational and clinical studies are also warranted to validate neuropeptide-based interventions and to establish reliable biomarkers for assessing disease progression and treatment response.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

COMPETING INTERESTS

No conflict of interest exists in this manuscript.

CONSENT FOR PUBLICATION

Manuscript is approved by all authors for publication.

AVAILABILITY OF DATA AND MATERIALS

The data and materials of this experiment are available.

ACKNOWLEDGEMENTS

Not applicable.

AUTHOR CONTRIBUTIONS

Yimin Lu was responsible for conception and design. Xuemei Liu was responsible for manuscript writing. Shu Zhang was responsible for collection and assembly of data. Lin Zhang was responsible for data analysis and interpretation. All authors were responsible for manuscript writing. All authors were responsible for the final approval of the manuscript.

FUNDING

Not applicable.

REFERENCES

Bell D, McDermott BJ 1996. Calcitonin gene-related peptide: A regulator of airway inflammation. *Pulm Pharmacol Ther,* 9(6): 395-402.

Bonner JC, Rice AB, Moomaw CR, et al. 2013. CCL17 induces airway inflammation via CGRP-dependent activation of CCR4. *Am J Physiol Lung Cell Mol Physiol,* 304(7): L425-L433.

Boschetto P, Mapp CE, Papi A, et al. 2005. Substance P and neurogenic inflammation in COPD. *Chest,* 128(6): 3946-3953.

Camp B, Stegemann-Koniszewski S, Schreiber J 2021. Infection-associated mechanisms of neuro-inflammation and neuro-immune crosstalk in chronic respiratory diseases. *Int J Mol Sci,* 22(11): 5699. doi:10.3390/ijms22115699.

Carmine C, Messina A, Di Carlo G, et al. 2020. Calcitonin gene-related peptide signaling in airway remodeling. *Front Immunol,* 11: 2345.

Corboz MR, Mutter JC, Myers AC 2012. Neurokinin B-induced airway contraction in guinea pig trachea. *Pulm Pharmacol Ther,* 25(2): 150-157.

Daoui S, Aoki M, Guimond A, et al. 2000. Activation of NK3 receptor induces airway hyperresponsiveness in guinea pigs. *Br J Pharmacol,* 129(2): 385-392.

Green DP, Limjunyawong N, Gour N, Pundir P, Dong X 2019. A mast-cell-specific receptor mediates neurogenic inflammation and pain. *Neuron,* 101(3): 412-420.e9.

Hamidi SA, Dickman KG, Berisha HI, et al. 2006. Role of VIP in airway responsiveness in mice. *Am J Physiol Lung Cell Mol Physiol,* 291(4): L557-L566.

Huang C, Wang Y, Li X, et al. 2021. Vasoactive intestinal peptide alleviates inflammatory lung injury via NF-êB inhibition. *Inflammation,* 44(2): 639-650.

Ito Y, Kawashima H, Ohnishi H, et al. 2006. Substance P and mast cell interaction via SynCAM molecules enhances airway inflammation. *Am J Respir Cell Mol Biol,* 35(4): 444-448.

Jia H, Ren X, Wu Q, et al. 2023. Improving stability and bioavailability of VIP by nanoparticle encapsulation. *J Pharm Sci,* 112(3): 912-922.

Joos GF, Germonpré PR, Kips JC, et al. 2000. NK2 receptor antagonist saredutant partially inhibits NKA-induced bronchoconstriction in asthma. *Am J Respir Crit Care Med,* 162(3): 970-975.

Kaczyñska K, Zaj¹c D, Wojciechowski P, Jampolska M 2021. Regulatory peptides in asthma. *Int J Mol Sci,* 22(24): 13656. doi:10.3390/ijms222413656.

Kitamura Y, Yamaguchi M, Takeda N, et al. 2012. Neurokinin A enhances dendritic-cell TNF production and airway inflammation. *Clin Exp Allergy,* 42(7):1020–1029.

Kobayashi H, Takahashi M, Ohashi K, et al. 2012. Positive feedback between TNF-ã and neurokinin A/NK2R expression in airway smooth muscle. *Am J Physiol Lung Cell Mol Physiol,* 303(4): L378-L386.

Larocca TJ, Jehle A, Liang M, et al. 2007. Vasoactive intestinal peptide induces IL-10 and inhibits TGF-â1 release. *J Immunol,* 178(12): 7315-7323.

Lindén A, Uddman R, Skoogh BE, Lundeberg T 2003. Vasoactive intestinal peptide (VIP) and airway function: therapeutic implications in obstructive airway disease. *Pulm Pharmacol Ther,* 16(2): 81-92. doi:10.1016/S1094-5539(02)00167-8.

Lv X, Chen Q, Zhang Z, et al. 2023. áCGRP deficiency aggravates pulmonary fibrosis by activating the PPARã signaling pathway. *Genes Immun,* 24(3): 139-148. doi:10.1038/s41435-023-00206-x.

Mandal J, Dutta A, Chatterjee A, et al. 2015. Elevated serum vasoactive intestinal peptide levels during acute exacerbation of chronic obstructive pulmonary disease. *J Clin Lab Anal,* 29(5): 383-388. doi:10.1002/jcla.21779.

Mehboob R, Mehboob N, Mehboob H, et al. 2023. Substance P as a trigger of cytokine storm in COVID-19. *J Neuroimmunol,* 376: 577998.

Mikami Y, Kanai T, Sujino T, et al. 2013. CGRP induces IL-9 expression through cAMP/PKA signaling in vivo. *Allergy,* 68(3): 424-432.

Mizuta K, Tanaka K, Ohta K, et al. 2008. Distribution of NK2 and NK3 receptors in airway smooth muscle and CNS. *Respir Physiol Neurobiol,* 160(3): 289-296.

Morelli AE, Sumpter TL, Rojas-Canales DM, et al. 2020. Neurokinin-1 receptor signaling is required for efficient Ca²z flux in T-cell-receptor-activated T cells. *Cell Rep,* 30(10): 3448-3465.e8. doi:10.1016/j.celrep.2020.02.054.

Nussbaum JC, Van Dyken SJ, von Molnár A, et al. 2013. VIP and VPAC2 regulate eosinophil aggregation and IL-5 production in airway inflammation. *J Exp Med,* 210(6): 1231-1246.

Onoue Y, Adachi Y, Ichida T, et al. 2010. VIP reduces cigarette-induced airway inflammation. *Am J Physiol Lung Cell Mol Physiol,* 299(1): L133-L139.

Rochlitzer S, Veres TZ, Kühne K, et al. 2011. The neuropeptide calcitonin gene-related peptide affects allergic airway inflammation by modulating dendritic cell function. *Clin Exp Allergy,* 41(11): 1609-1621. doi:10.1111/j.1365-2222.2011.03822.x.

Schelfhout V, Louis R, Lenz W, Heyrman R, Pauwels R, Joos G 2006. The triple neurokinin-receptor antagonist CS-003 inhibits neurokinin A-induced bronchoconstriction in patients with asthma. *Pulm Pharmacol Ther,* 19(6): 413-418.

Smith JA, Belvisi MG, Birring SS, et al. 2021. Aprepitant, an NK1R antagonist, for refractory chronic cough in lung cancer patients. *Chest,* 159(1): 205-214.
Spitsin SV, Koprowski H, Michaels FH 2017. Substance P mediates eosinophil activation and airway epithelial injury. *Am J Pathol,* 187(5): 1035-1046.
Sun Y, Zhang L, Wu S, et al. 2018. Protective role of VIP in acute lung injury via modulation of cytokine responses. *Front Physiol,* 9: 1712.
Sui P, Wiesner DL, Xu J, et al. 2018. Pulmonary neuroendocrine cells amplify type 2 inflammation via CGRP–ILC2 axis. *Science,* 360(6393): eaan8546.
Szema AM, Hamidi SA, Lyubsky S, et al. 2006. Mice lacking the VIP gene show airway hyperresponsiveness and airway inflammation, partially reversible by VIP. *Am J Physiol Lung Cell Mol Physiol*, 291(5): L880-L886.
Tamari M, Del Bel KL, Ver Heul AM, et al. 2024. Sensory neurons promote immune homeostasis in the lung. *Cell,* 187(1): 44-61.e17. doi:10.1016/j.cell.2023.11.027.
Taracanova A, Alevizos M, Karagkouni A, et al. 2017. Substance P and IL-33 cooperate to induce TNF-á release. *J Allergy Clin Immunol,* 139(3): 886-899.
Wallrapp A, Burkett PR, Riesenfeld SJ, et al. 2019. Calcitonin gene-related peptide negatively regulates Alarmin-Driven Type 2 innate lymphoid cell responses. *Immunity,* 51(4): 709-723.e6.
Wang X, Zhang R, Zhang Z, et al. 2019. NK1R antagonist activates airway epithelial protection via Nrf2/HO-1 pathway. *Respir Res,* 20: 300.
Wechsler ME, Ruddy MK, Pavord ID, et al. 2021. Efficacy of anti-IL-33 monoclonal antibody (itepekimab) in asthma. *N Engl J Med,* 384(15): 1484-1496.
Wu W, Li J, Chen S, Ouyang S 2024. The airway neuroimmune axis as a therapeutic target in allergic airway diseases. *Respir Res,* 25(1): 83. doi:10.1186/s12931-024-02702-8.
Zhou Y, Zhang CY, Duan JX, et al. 2020. Vasoactive intestinal peptide suppresses the NLRP3 inflammasome activation in lipopolysaccharide-induced acute lung injury mice and macrophages. *Biomed Pharmacother,* 121: 109596.

Paper received for publication in July, 2024
Paper accepted for publication in April, 2026