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Hypothesis

Autonomous Breakdown of the Allergen Tolerance in the Nose: A Hypothesis

Vladimir Klimov*, Andrew Klimov and Natalia Koshkarova

Immunology & Allergy Department, Siberian State Medical University, 2 Moscowsky tr, Tomsk, Russian Federation

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Abstract

The prevalence of conventional and new pathogenic types of allergies is increasing. For the last few years, new atopic disorders – local allergic rhinitis (LAR), local allergic asthma, "dual" allergic rhinitis, and local allergic conjunctivitis – have been described. In particular, LAR was identified a decade ago, whereas its immunopathogenesis is still unclear. Nevertheless, the network of immune cells and neurons determining the maintenance or breakdown of allergen tolerance has partially been studied. Therefore, this field of research is currently at the cutting edge. However, there is still not any definitive answer as to why local disorders take place. Specifically, the nasal cavity is characterized by the following prevalent neuro molecules: acetylcholine, norepinephrine, substance P, neuromedin U, vasoactive intestinal peptide, and calcitonin-gene-related peptide; some of which are pro-immunogenic and a slightly smaller part is protolerogenic. In the spotlight, the hypothesis of an autonomous breakdown of tolerance to allergens in LAR is presented. The article describes immune tolerance as the antipode of the active immune response, which does not lead to producing effector cells and molecules, and vice versa is based on active immunosuppressive processes. In addition, this article focuses on the mechanisms of the maintenance and breakdown of allergen tolerance, a form of immune tolerance, at the nasal level and throughout the body, and the essential role of various cells and molecules, including neuro molecules, in the pathogenesis of LAR.

Introduction

In humans, allergen tolerance is the consequence of many tolerogenic responses to many environmental allergens.[1] Allergens can be dangerous only for selected humans, or so-called atopic individuals; therefore, the breakdown of allergen tolerance is always a pathologic condition for those people. The atopy displays a strong hereditary component and seems to be an evolutionary vestige.[2] Nowadays, atopy is determined as a group of polygenous inherited diseases. In the unified airway, perennial and seasonal allergic rhinites are atopic phenotypes in the nose,[3–5] whereas allergic asthma is one more atopic phenotype in the bronchi.[6] In contrast, endotypes of atopy in the unified airway, e.g., local atopic entities,[7] provide our clinical understanding with a deeper knowledge on pathogenesis, therapy response, and prognosis of the diseases.[8,9]

Furthermore, the presence or absence of allergic inflammation depends on tolerance forwarding, maintenance, or breakdown. Currently, many mechanisms, which control tolerance, have become a field of research interest and are considered from not only an immunologic viewpoint, but also according to the effects of neurotransmitters and neuropeptides.[10] In addition, the difference in allergen tolerance breakdown at the systemic and regional levels remains unclear.

Conventional allergic rhinitis and local allergic rhinitis (LAR) pathogenesis shares almost all the features of the allergic inflammation in the nose but differs in the mechanisms and level of the allergen tolerance breakdown. At the systemic level, allergen toler-

Keywords: Allergen tolerance breakdown; Local allergic rhinitis; Tolerogenic cells; Neuro molecules; Local neuroimmune imbalance.

Abbreviations: AIT, allergen-specific immunotherapy; ARC, antigen-recognizing cell; B7/CD28, costimulatory molecules for T cells; BCR, B-cell antigen-recognizing receptor; CD40/CD40L, costimulatory molecules for B cells; CGRP, calcitonin-gene-related peptide; CTLA-4/PD-1/PD-L1/BTLA/LAG-3, coinhibitory molecules for T cells and B cells; FasL/Fas, apoptosis mediated molecules; FDC, follicular dendritic cell; FoxP3, transcription factor; GABA, γ-aminobutyric acid; HDM, house dust mite; HLA, human histocompatibility complex; ILC2, group 2 innate lymphoid cells; LAR, local allergic rhinitis; M2/M2a, type 2 macrophages; MALT, mucosae-associated lymphoid tissue; NEC, neuroendocrine cell; PAMP, pathogen-associated molecular patterns; PRR, pattern recognition receptors; TCR, T-cell antigen-recognizing receptor; TDC, tolerogenic dendritic cells; Tfh, follicular helper T cell; Th2, type 2 helper T cells; TLR, toll-like receptors; Treg/pTreg, regulatory T cells, peripheral regulatory T cells; TSLP, thymic stromal lymphopoietin; VIP, vasoactive intestinal peptide.

***Correspondence to:** Vladimir Klimov, Immunology & Allergy Department, Siberian State Medical University, 2 Moscowsky tr, Tomsk 634050, Russian Federation. ORCID: http://orcid.org/0000-0001-6673-7556. Tel: +7 (3822) 556395. E-mail: klimov@mail.tomsknet.ru; vlklimov54@gmail.com

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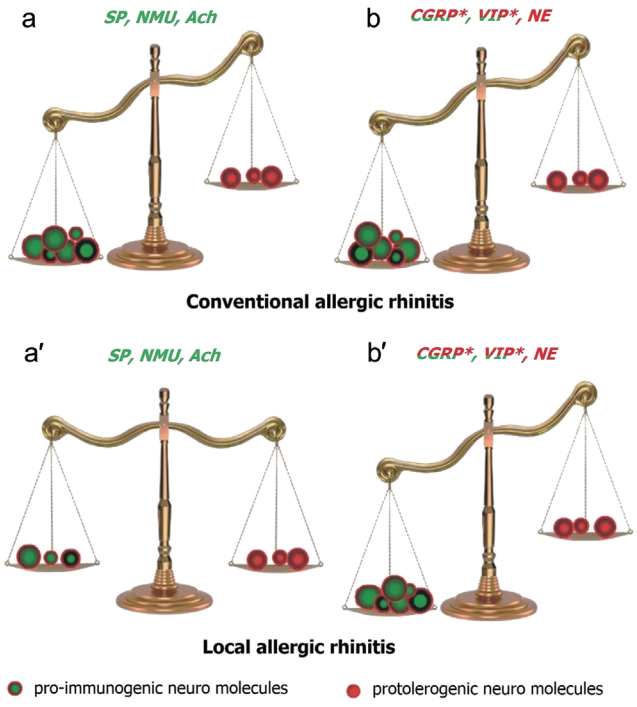

Fig. 1. Hypothesis of the autonomous breakdown of allergen tolerance in local allergic rhinitis. The figure symbolizes the two-level imbalances of neurotransmitters and neuropeptides in allergic rhinitis in an allegorical manner. Pro-immunogenic neuro molecules: substance P (SP), neuromedin U (NMU), and achetylcholine (ACh); protolerogenic neuro molecules: calcitonin-gene-related peptide (CGRP)#, vasoactive intestinal peptide (VIP)#, and norepinephrine (NE). #CGRP and VIP can also exert pro-immunogenic effects. (a, a′): systemic level; (b, b′): local level.

ance maintenance is associated with a well-known network of protolerogenic cells and biomolecules, such as peripheral regulatory T (pTreg) cells, tolerogenic dendritic (TDC) cells, interleukin (IL) -10, IL-35, transforming growth factor-β (TGF-β), protolerogenic neuro molecules, *etc.*[2] At the local (nasal) level, allergen tolerance also appears to depend on the peculiarities of the nose's innervation and the local set of neurotransmitters and neuropeptides.

The hypothesis of the autonomous breakdown of tolerance to allergens in the nose

The most important neurotransmitters and neuropeptides for the nose are acetylcholine, norepinephrine, substance P, neuromedin U, vasoactive intestinal peptide (VIP), and calcitonin-gene-related peptide (CGRP).[11–13] Among them, acetylcholine, substance P, and neuromedin U refer to a strong pro-immunogenic profile,[11,14–16] norepinephrine is a protolerogenic neurotransmitter,[15,17] whereas VIP and CGRP exert ambivalent properties, i.e., pro-immunogenic or protolerogenic depending on the micro-environment.[11,16,18] Therefore, pro-immunogenic neuromediators would predominate over protolerogenic neuro molecules. Hypothetically, when systemic allergen tolerance maintenance is still available, regional imbalances like pro-immunogenic polarization could lead to the activation of pro-immunogenic cells and neuro molecules in the nose. In this case, the vegetative nervous system may become responsible for autonomous allergen tolerance breakdown and atopic exacerbation only in this area (Fig. 1).

Rhinitis linked with the autonomic nervous system dysfunction has been described in humans, but there is no information on the type of this rhinitis: conventional allergic, local allergic, or non-allergic.[19] In a pilot study,[20] patients with allergic rhinitis were exposed to a standardized Trier Social Stress Test (TSST), followed by allergic skin tests. Stress responders were estimated based on the salivary cortisol concentrations, anxiety scale, and serum norepinephrine (noradrenaline), and oxytocin levels. Independent TSST baseline concentrations of norepinephrine and oxytocin were significantly higher in allergic persons. Hence, patients with allergic rhinitis were more stress-unresistant. Furthermore, mast cells and macrophages in the mucosa express oxytocin receptors under elevated oxytocin concentrations, which may interfere with local allergic responses, thus linking neuronal emotions and inflammation.[21] It has also been demonstrated that allergic rhinitis induced anxiety-like behavior in humans and altered social interaction in rodents parallelly by an increased expression of the type 2 helper T (Th2) cells.[22] Unfortunately, similar clinical studies in selected groups of conventional allergic rhinitis and LAR in humans and experiments in rodents have not yet been carried out.

We assumed that the autonomous allergen tolerance breakdown in the nose may be caused by the imbalance of immune-upregulating and immune-downregulating neurotransmitters and neuropeptides when the concentration of inhibitory molecules proved to be at the nasal level less. The paradigm of the neuro molecule imbalance seems to be one of more possible explanations for the LAR pathogenesis in the atopic predisposition but still requires further study and discussion.

Evaluation of the hypothesis

Tolerance at a glance

In the enlarged sense, immune tolerance could be considered as the opposite of any adaptive immune response, i.e., silence of the immune system despite antigen (allergen) entering the body.[23] In tolerance, an antigen is called the tolerogen. The dream of any allergist and all allergy patients worldwide is that at all times the allergens would convert into tolerogens.

Immune tolerance may be natural, artificial, and pathologic. For example, after transplantation, physicians induced artificial tolerance with the purpose of the graft to survive and not be rejected. In pathologic tolerance, e.g., in tumor growth and infections, which became chronic, immune responses and reactions of innate immunity were required, but they were suppressed. Hence, allergen tolerance is a form of natural tolerance that enables the body to avoid allergic diseases in most people, including some individuals even if they are atopic.[2]

In the 1950s, researchers[23] carried out experiments to study the factors which could influence the artificial immune tolerance to a large extent. They demonstrated that immune tolerance was able to be achieved depending on the immaturity of the immune system in fetal or newborn periods, extremely high or low doses of a particular antigen, exposure to such harm for the immune system factors like radiation and aggressive chemicals, and taken together corresponded to the lymphocyte "clonal deletion" model.[23]

Nowadays, immune tolerance is evaluated as an essential process for a health condition that downregulates adaptive immune responses at their termination phase, prevents the overactivation of the immune system, and decreases the risks of autoimmune and allergic inflammation. Tolerance as an active process is orches-

trated by a variety of protolerogenic cells, biomolecules, as well as tolerogenic microbiota using complex neuroimmune and metabolic mechanisms.[2] Taking into consideration immune tolerance, it is important to recognize the whole four processes: induction, maintenance, breakdown, and restoration of tolerance. In a healthy condition, the immune system must be tolerant to the following antigens:[2] (1) self-antigens of the own body, (2) antigens of beneficial microbiota and non-reactivated opportunistic microbiota, (3) peptide components of food, (4) environmental allergens, and (5) antigens of spermatozoa (in the female genital tract after coitus), and antigens of the fetus, which were acquired from the father.

Physiological processes for the maintenance of natural tolerance include[24,25] (1) mechanisms related to the primary organs, such as the thymus and bone marrow ("*clonal deletion"* of the T and B cells), (2) mechanisms in the periphery: activation-induced apoptosis, peripheral clonal anergy of the T and B cells, clonal ignorance, the peripheral system of natural tolerance maintenance, which consists of functioning cells, molecules of the immune and nervous systems, and tolerogenic microbiota.

Thymocytes are cells, which participate in T-cell lymphopoiesis in the thymus. In the last phase, single-positive thymocytes have to pass through selection when self-reactive cells undergo negative selection via apoptosis that results in "clonal deletion" of self-reactive clones.[26,27] Moreover, among the different agents, the *gene AIRE* (on 21q22.3) upregulates the process by the encoded transcription factor *AIRE*.[28] Non-self-reactive thymocytes survive (positive selection) and, enter the blood and lymph circulation as naïve cells and recent thymic emigrants. However, a small portion of self-reactive T cells with a low-affinity escape apoptosis in the thymus and along with another portion of T cells directed to the self-antigens not expressed within the thymus can occur in the periphery. Both groups represent the risk of autoimmune disorders.[29,30]

In the bone marrow, central B-cell tolerance is achieved by the clonal deletion of immature B cells, engaging apoptosis, and receptor editing.[31,32] Some self-reactive B-cells in the bone marrow get further chances to express alternative B-cell antigen-recognizing receptors (BCRs) through a gene rearrangement process known as receptor editing rather than undergoing apoptosis.[33]

A particular mechanism of tolerance induction and maintenance, activation-induced apoptosis, is mediated by the interaction Fas receptor (CD95) with FasL (CD178) in two self-reactive T cells previously activated via their T-cell antigen-recognizing receptors (TCRs) that result in triggering the CD95 pathway of apoptosis.[34,35] However, the co-stimulation of cells through a co-stimulatory molecule like CD28 cancels the process of apoptosis; therefore, the co-stimulation has to be unavailable. Activation-induced apoptosis is essential for maintaining natural tolerance and preventing autoimmune disorders in target organs.

In contrast with clonal deletion, clonal anergy represents the absence of the functioning of the survived cells. As mentioned above, despite the negative selection in the thymus, a portion of the self-reactive T cells characterized by a low-affinity along with another portion of T cells directed to the self-antigens not expressed in the thymus, but having a high-affinity, can appear in the periphery. Frequently, such self-reactive T cells become anergic due to losing the valuable TCR signaling and getting coinhibitory signals from the expressed coinhibitory molecules like PD-1 and CTLA-4.[36–38] Peripheral self-reactive B cells also transform into anergic non-functioning cells because they miss the BCR signaling, acquire coinhibitory signals from coinhibitory molecules, and do not receive aid from helper T cells.[39,40]

Clonal ignorance represents a mechanism of tolerance induction and maintenance caused by the absence of recognition of the so-called "sequestrated, or cryptic self-antigens",[41–43] which are normally separated by physiological barriers like the blood-brain barrier and unknown for the immune system. However, due to trauma or infection, these "hidden self" antigens may enter the circulation at a high value and trigger the active adaptive response leading to autoimmune disorder.

The physiological maintenance of tolerance to allergens in the nose

The development of tolerance reflects the regulatory networks that recruit multiple secreted mediators, such as IL-10, IL-35, TGF-β,[44–46] neuropeptides and neurotransmitters,[2] a group of regulatory cells including TDC,[47–49] pTreg,[50–53] regulatory B cells,[54,55] type 2 (M2) macrophages including M2a,[56,57] coinhibitory molecules,[58] tolerogenic microbiota,[59–61] etc. Taken together, those above-mentioned components form the peripheral system of natural tolerance maintenance. TDC and pTreg are the main tolerogenic cells of this system, which act on the target cells leading to suppressive effects as follows:[40,49,51,62] apoptosis in effector T cells and B cells; inhibition of helper T cells, group 2 innate lymphoid (ILC2), and memory cells; secretion of immunosuppressive cytokines, such as IL-10, IL-35, and TGF-β; production of enzymes, indoleamine-2,3-dioxygenase and heme oxygenase-1, toxic for T cells; competition with proliferating effector cells for IL-2, and stimulation of the expression of coinhibitory molecules, such as CTLA-4, PD-1, BTLA, and LAG-3.

Allergen tolerance is commonly dependent on many factors, including (1) dose, (2) age, and (3) level of maintenance. Some allergens at a high dose (for example, cat's Fel d 1) can promote an increase in the IgG_4 antibodies in the absence of detectable IgE antibodies and clinical symptoms.[1] In allergen-specific immunotherapy (AIT), allergens are first used at a low concentration, and a low-dose allergen tolerance is formed.[63] Both immune and allergen tolerance, as a particular form of immune tolerance, are age-dependent phenomena. The idea of the early introduction of allergenic food to achieve oral tolerance corresponding to the dual-allergen exposure concept enabled the unresponsiveness to some food allergens in predisposed babies when they became older.[64] Allergen tolerance displayed different mechanisms and distinct molecule and cell sets at the regional (e.g., nasal) and systemic levels.

There is the classical postulate by which the central nervous system is responsible for control at the level of the whole body, whereas the vegetative nervous system masters the local levels. On the other hand, irrespective of neuroregulation, including neuroimmune interactions, a critical role of the local immune environment was reported. This is according to the grafted organs in atopic and non-atopic people.[65] In addition, local allergic diseases like LAR[7] confirm the fact of distinct hierarchic mechanisms of allergen tolerance in a level-dependent manner. In "dual" allergic rhinitis, these two-level mechanisms even exist simultaneously and autonomously. Unfortunately, precise evidence, which could summarize the two-level functioning of the neuroimmune network and how it proceeds, is still unavailable. Allergen tolerance achieved by different routes of AIT, e.g., subcutaneous or sublingual, studied in both conventional and local respiratory forms of allergies, in terms of neuroimmunology, may be the best instrument to advance our understanding of two-level neuroimmune control of allergen tolerance.[2]

Participation of the nervous system in the regulation of immune processes, tolerance and immunopathology is at the cutting edge of current research.[18,66] Somatosensory and viscerosensory neu-

rons as well as efferent neurons, endocrine glands, and cells and molecules of the immune system in their entirety have long been known as the mutual neuroimmune network,[67] which plays regulatory and effector roles at both the systemic and local levels to be ready to (1) fight against infection or cancer wherever they appear, or (2) provide allergen tolerance if allergens enter the body. However, the neuroimmune system is linked with the concept of "neurogenic" inflammation[68] by which neurons can damage the tissues they innervate. Neurons, neuroendocrine cells, non-neuronal cells, and microbiota produce different neuro molecules acting on the neurons themselves and target organs and cells of the immune system.[69,70] All neuro molecules, including neurotransmitters, neuropeptides, and neurohormones may be categorized as excitatory (pro-immunogenic), inhibitory (protolerogenic), and modulatory (immunomodulatory).[15,71] Predominant protolerogenic neuro molecules are norepinephrine, serotonin, γ-aminobutyric acid (GABA) (except for a small exclusion in relation to goblet cells), glycine, CGRP, VIP, endocannabinoids, and some others.[2,72] However, CGRP and VIP can display ambivalent effects. Destroyed communication between the nervous and immune systems and imbalance of pro-immunogenic and protolerogenic neuro molecules is a common feature in immunopathological disorders.[16,71]

The intriguing subject is the tolerance in the specific anatomic sites, e.g., the conjunctive and airway tract.[1] Approximately 30 years ago, it was demonstrated that following bone marrow transplantation, recipients with no atopic pathologies displayed biomarkers typical for their donors who suffered from atopies. After the lung transplantation from asthmatic donors to non-asthmatic recipients, they started to manifest asthmatic attacks, whereas, vice versa, the asthmatic persons whom healthy lungs were grafted did not suffer from asthma any longer.[65] This data could be considered as a critical role of the local immunological process illustration in atopy and phenomenon of entopy[73] and has to be taken into account in the AIT.

The nasal mucosa consists of (1) the mucociliary epithelial layer and (2) subepithelial region. The first layer, which is the primary barrier against the entry of aero-allergens, including substances from house dust mites (HDM), contains mucociliated epitheliocytes, in-built mucus-secreting goblet and club cells, chemosensory tuft cells, neuroendocrine (NEC) cells, basal (stem) cells, etc. The updated landscape of the nasal epithelium is currently described using a transcriptomic technology as single-cell RNA-sequencing.[74] In the subepithelial region, there are phagocyting macrophages, which serve as the second barrier against allergens if they overcame the epithelium and possible epithelial impairment, and passed through the M cells and DC. Some subepithelial DCs are allergen-presenting cells, while other DCs represent TDC, which are conversely immunosuppressive cells. Located here, Th2 cells upregulate the B-cell response leading to IgE end-production.[2,75] In addition, ILC2 cells are involved in the immune response via secreting some cytokines. Nasal epitheliocytes express pattern recognition receptors (PRR), including toll-like receptors (TLR) and C-type lectins[76] for recognizing not only molecular patterns, but also allergens. Upon activation of the PRR, epithelial cells[77,78] and resident macrophages produce alarmins, cytokines, chemokines, and other mediators that recruit a series of cells of the immune system to contribute to the inflammation and downregulation of allergen tolerance. However, (3) there is the third most essential mechanism of tolerance induction to allergens, which is associated with the peripheral system of natural tolerance maintenance. Atopic allergic responses develop in the context of the failure of tolerance toward specific allergens and lead to the production of allergen-specific IgE under the Th2 control.[79] Thymic nTreg cells possess a low diversity of TCR and hence have non-allergen specific suppression potency. Consequently, allergen-specific CD4+CD25+FoxP3 pTreg cells play a crucial role in the induction and maintenance of allergen tolerance.[80] They appear to originate from naïve T cells. The progression of allergen-specific Treg cells along with their subsets, type 1 regulatory T cells and type 3 helper T cells can limit the manifestation of allergic disorders and upregulate a state of sustained non-responsiveness to constantly invading allergens in healthy individuals. In addition, immature DC subsets due to their extensive functional plasticity and under the particular extracellular microenvironment, including cytokines and neurotransmitters, are able to be converted into the TDCs, which take part in the allergen tolerance maintenance.[44]

In a healthy nasal cavity, a local balance between protolerogenic and pro-immunogenic neuro molecules is slightly pro-immunogenically polarized. On the one hand, among most important neuro molecules in the nose, there are two pro-immunogenic neuropeptides, substance P and neuromedin U, and one neurotransmitter acetylcholine;[11,14–16] on the other hand, there are two preferable protolerogenic and simultaneously ambivalent neuropeptides, VIP and CGRP,[11,16,18] and one protolerogenic neurotransmitter norepinephrine.[15,17] In sensitization to aero-allergens and in the face of allergic inflammation in the nose, the balance deviated, but a general balance of all neuro molecule spectrums may be kept at the systemic level.

Systemic breakdown of allergen tolerance in the body, including nose

In many cases, allergen tolerance maintenance does not last for a long time. Various factors can trigger allergen tolerance breakdown and reactivation of a Th2 cell-dependent adaptive response with IgE end-production. The gene expression and epigenetic modifications belong to one essential group of this subject.[81] Environmental factors, including excessive exposure to allergens by all entry routes, infection, negative stress, depression, endocrine imbalance, tolerogenic microbiota deficiency, occupational hazards, etc., constitute the other group.[1,75]

Allergic manifestation may consequently be divided into three phases: the early phase reaction, late phase reaction, and chronic inflammation.[82] The early phase commonly manifests within 10–20 minutes, after allergen exposure, mediated by presynthesized degranulated biomolecules from the mast cells. Among them, the main mediator is histamine, but there are also dopamine, serotonin, and chemotactic factors involving neutrophils and eosinophils, chymase, and tryptase.[83] In particular, histamine impacts the nerve endings leading to nasal itching, sneezing, capillary permeability (nasal obstruction and edema), mucus production by goblet and club cells (rhinorrhea), and, finally, the engagement of many inflammatory cells.

The late phase occurs within 4–6 hours and later by the generation of two groups of newly synthesized mediators, such as prostaglandins, cysteinyl leukotrienes, cytokines, chemokines, nitric oxide, and complement components, which promote allergic inflammation and make it progressive. To date, eosinophils have been considered as major cells of the allergic inflammatory process.[84] When activated, they produce a set of biomolecules, such as eosinophilic cationic protein, IL-5, galectin-10 (Charcot-Leyden's crystals), chemokines, cysteinyl leukotrienes, etc. In addition to eosinophils and neutrophils, monocytes, macrophages, DCs, ILC2, NEC, and Th2 cells also take part in allergic inflammation by the secretion of many biomolecules to a large extent.[2] There is accumulating evidence that pro-immunogenic neurotransmitters and

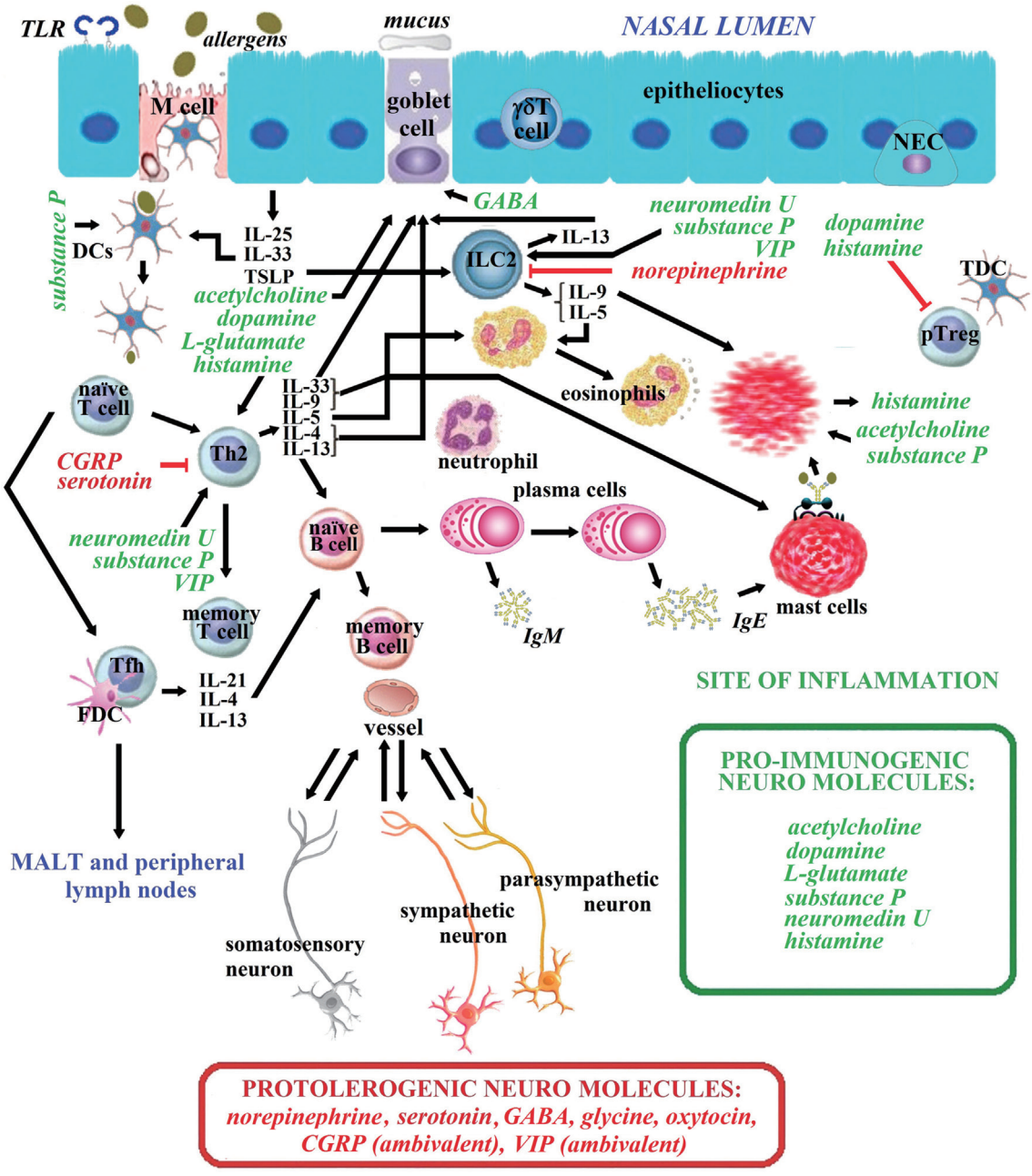

Fig. 2. Allergen tolerance breakdown in allergic rhinitis in terms of the neuroimmune system. Neurotransmitters and neuropeptides exhibit distinct effects upon allergen tolerance breakdown in allergic rhinitis. Acetylcholine and, paradoxically, GABA promote the goblet cells to produce mucus. Neuro molecules, achetylcholine, dopamine, L-glutamate, histamine, neuromedin U, substance P, and VIP stimulate the Th2-dependent response and allergic inflammatory process. Also, neuromedin U, substance P, and VIP upregulate ILC2, but norepinephrine cancels this effect. Acetylcholine and substance P activate the degranulation of mast cells, whereas dopamine and histamine inhibit TDC and pTregs. Therefore, in allergic rhinitis, pro-immunogenic neuro molecules are prevalent. Pro-immunogenic effects are noted in green, and protolerogenic are noted in red. CGRP, calcitonin-gene-related peptide; DC, dendritic cell; FDC, follicular dendritic cell; GABA, γ aminobutyric acid; ILC2, group 2 innate lymphoid cell; MALT, mucosae-associated lymphoid tissue; NEC, neuroendocrine cell; pTreg, peripheral regulatory T cell; TDC, tolerogenic dendritic cell; Tfh, follicular helper T cell; TLR, toll-like receptors; TSLP, thymic stromal lymphopoietin; VIP, vasoactive intestinal peptide.

neuropeptides are active participants of allergen tolerance breakdown contributing to the pathogenesis of allergic inflammation (Fig. 2). Finally, the early and late phases acquire a progressive potential and result in the third phase, chronic inflammation.[2,82]

In predisposed persons, such allergic inflammation is responsible for the manifestation of atopic diseases affecting the nose (allergic rhinitis), bronchi (asthma), skin (atopic dermatitis, or eczema), gut (food allergies), and genitourinary tract (particular forms of allergies, e.g., allergy to sperm). The most severe atopic condition is anaphylaxis.

Local allergic rhinitis

The unified airway is a specific anatomical site[85] that undergoes environmental aero-allergen attacks, preferentially by European HDM, *Dermatophagoides pteronissinus*, and American HDM, *Dermatophagoides farinae*.[86] Conventional allergic asthma and allergic rhinitis (rhinoconjunctivitis) have already been studied and, long ago, included in international position papers on diagnostics and therapy.[3,87,88] In the last decade, Rondón *et al*.[89] described a new atopic disorder, LAR, and later local allergic asthma; "dual" allergic rhinitis and local allergic conjunctivitis have recently been identified.[90,91] To date, "local respiratory allergy"[7] has become the whole spectrum of pathology.

For the last decade, both experts in allergy and otorhinolaryngology have focused on the various aspects of LAR.[92] Most researchers[93–96] have substantiated that LAR was an endotype of allergic rhinitis, as it did not display all atopic biomarkers at the systemic level but exhibited them in the nasal mucosa.

In addition, patients with LAR had the same classic symptoms as those with conventional allergic rhinitis, such as nasal obstruction, rhinorrhea, and sneezing. A study comparing patients with allergic rhinitis and LAR also confirmed that both share a similar clinical phenotype. They were caused by sensitization to *Dermatophagoides* HDM, occurred preferentially in non-smokers, exhibited a certain persistent clinical picture often with conjunctival and asthma symptoms, and developed in children and adults.[94]

The confirmatory identification of LAR was based on the following criteria:[97,98] (1) absence of systemic atopic conditions, such as food allergies, insect allergies, or atopic dermatitis, (2) negative allergic skin tests, (3) absence of the elevated concentration of serum total IgE, and (4) evidence of IgE sensitization at the local level using a nasal allergen provocation test, which was recognized as the "gold standard" for the diagnosis of LAR.[95] Lack of systemic atopic diseases, increased serum total IgE, and negative allergic skin tests confirmed allergen tolerance maintenance at the systemic level in those patients. However, local atopic disorders in the unified airway, including the nose, may have been manifested in the form of LAR in some of the patients. Hence, the evidence of the IgE presence in the nose was an essential subject for the proper diagnosing and missing diagnostic errors.

There are no therapeutic approaches different from AIT, which could reinduce allergen tolerance in LAR. As a result of multicenter clinical trials in conventional allergic rhinitis, subcutaneous and sublingual AIT routes were confirmed by some international position papers and successfully introduced into healthcare practice.[3,88] However, there are no consensus documents in relation to AIT in local allergic atopies.

Future directions

New atopic entities, such as local allergic rhinitis, "dual" allergic rhinitis, local asthma, and local allergic conjunctivitis, occur only in the unified airway and develop due to allergen tolerance breakdown at the regional level. Furthermore, the neuroimmune network plays a significant role in the pathogenesis of not only conventional respiratory atopies but of local entities. Therefore, future research would enable the discovery of hidden mechanisms behind the local and systemic allergen tolerance breakdown in allergic rhinitis.

In the nasal cavity, prevalent neurotransmitters and neuropeptides originating from neurons, neuroendocrine cells, microbiota, and immune cells are acetylcholine, norepinephrine, substance P, neuromedin U, VIP, and CGRP. The study of neuronal-immune cell units, a novel neuroimmunology paradigm, with the use of new omics techniques, such as single-cell RNA-sequencing would be able to revise the cell landscape of the nasal mucociliated barrier affected by regulatory neuro molecules in all local allergic pathologies that would be potentially a significant contribution to the problem of the local allergen tolerance breakdown. Additionally, AIT with the subcutaneous or sublingual routes could become an ideal tool for studying allergen tolerance and its neuroimmune control at the systemic and local levels. This approach using AIT could also reveal the functioning of separate neuronal-immune cell units essential for such control.

Conclusions

Immune cells and molecules along with neurons and neuro molecules forming the neuroimmune network play a regulatory role in the communication pathways at the whole organism and local levels to recruit all body resources to fight against invaders or tumor cells wherever they appear. In atopic individuals, the neuroimmune network responds to environmental allergens leading to allergic inflammation. The local balance between pro-immunogenic and protolerogenic neuro molecules is important; however, this balance in the unified airway may be polarized due to the prevalence of pro-immunogenic neurotransmitters and neuropeptides over protolerogenic means. Moreover, the differences in the allergen tolerance breakdown in conventional allergic rhinitis and LAR still remain unclear. If allergen tolerance maintenance is available at the systemic level, but neuro molecule imbalances like pro-immunogenic polarization happen, this may make the vegetative nervous system become responsible for the activation of pro-immunogenic cells and neuro molecules in the unified airway, subsequent allergen tolerance breakdown, and atopic exacerbation only in this area.

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Author contributions

Klimov V. conceived the idea for the manuscript, participated in the drafting and preparation of the manuscript, including reference selection, interpretation of the findings from the cited sources, critical revising of the content, and performed the figures for the manuscript. Klimov A. took part in the drafting and preparation of the manuscript, including reference selection, interpretation of the findings from the cited sources, and critical revising of the content.

Koshkarova N. participated in the preparation of the manuscript, including interpretation of the findings from the cited sources, and critical revising of the content. All authors have made a significant contribution to this study and have approved the final manuscript.

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