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Synaptic transmission molecules and their role in the pathogenesis of allergic rhinitis

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ABSTRACT

Immune cells and molecules, as well as synaptic transmission molecules play a regulatory role in the communication pathways of the entire body when it is necessary to engage all body resources in the fight against infections or tumor cells wherever they appear. In potential allergy, the neuroimmune network controls allergen tolerance maintenance at both local and systemic levels.

The review focuses on different neurotransmitters and our understanding of a balance and imbalance between the immune system and the nervous system in allergic inflammation, including allergic rhinitis. However, the pathogenesis of the two endotypes of rhinitis (conventional allergic rhinitis and local allergic rhinitis) and the impact of the neuroimmune network on it remain unresolved.

Key words: allergic rhinitis, neurotransmitters, neurohormones, neuropeptides, receptors for neuro molecules.

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Синаптические нейромолекулы и их роль в патогенезе аллергического ринита

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РЕЗЮМЕ

Иммунные клетки и молекулы, а также синаптические нейромолекулы играют регуляторную роль в путях коммуникации на уровне всего организма, когда возникает необходимость максимального вовлечения ресурсов для отражения инфекций и подавления опухолей. При потенциальной аллергии нейроиммунная сеть контролирует поддержание аллергенной толерантности и на системном, и на локальном уровнях.

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Данный обзор фокусируется на рассмотрении разных нейромолекул и нашем понимании баланса и дисбаланса иммунной и нервной систем при аллергическом воспалении, включая аллергический ринит. Однако все еще остается нерешенным вопрос о механизмах патогенеза двух эндотипов ринита, классического аллергического ринита и локального аллергического ринита, и степени влияния на него нейроиммунной сети.

Ключевые слова: аллергический ринит, нейротрансмиттеры, нейрогормоны, нейропептиды, рецепторы для нейромолекул.

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INTRODUCTION

Due to a narrow focus of disciplines, biology and biomedical sciences used to develop in isolation from each other in the past. In particular, immunology was isolated from neurobiology. Currently, there is clear evidence for production and use of immune factors by the central nervous system and production and use of neuroendocrine mediators by the immune system. Alterations in communication pathways between these two systems can account for many pathological conditions that used to be considered isolated diseases of certain organs [1]. The role of neurotransmitters in the pathogenesis of allergic inflammation, including different endotypes of allergic rhinitis [2], made this problem very relevant.

INNERVATION OF TARGET ORGANS IN ALLERGIC INFLAMMATION

Target organs in allergic inflammation are innervated differently and, consequently, are exposed to effects of a distinct set of synaptic transmission molecules [3] (Table). The skin is innervated with somatosensory neurons with their cell bodies located in the trigeminal ganglion and dorsal root ganglion, which have central brainstem and spinal cord projections. The gastrointestinal tract is innervated with:

(1) extrinsic sensory neurons originating in the dorsal root ganglia;

(2) vegetative neurons which are divided into parasympathetic neurons (vagus nerve), whose cell bodies reside in the nodose and jugular ganglia and brainstem, and sympathetic neurons, whose cell bodies reside in the paravertebral ganglia;

(3) self-contained autonomic nervous system called the enteric nervous system, which consists of intrinsic primary afferent neurons, interneurons, and myenteric and submucosal plexuses. The enteric nervous system can accept vegetative signals, regulate gut microbiota, mucus production, and peristalsis, and respond to food consumption. This system appears to maintain allergen tolerance in the intestine.

In contrast to the skin and gastrointestinal tract, innervation of the unified airway is characterized by distinctive features. These organs are innervated by (1) somatosensory neurons with their cell bodies located in the thoracic dorsal root ganglia, and (2) autonomic nervous system via parasympathetic and sympathetic fibers. However, the unified airway has no self-contained nervous system [3] that can matter for the development of local forms of allergy, such as asthma [4, 5], local allergic rhinitis (LAR) [6, 7], dual allergic rhinitis [8, 9], and local allergic conjunctivitis [10].

Neurons of all types produce different neuromolecules (Table), which act on the neurons and target organs and cells, including cells of the immune system [11]. Within the neuroimmune network, cells of the immune system acquire more functional plasticity. On the other hand, all types of neuronal activity are modulated by cells of the immune system and modified depending on receptors expressed on the target cells [12].

NEUROTRANSMITTERS, NEUROHORMONES, AND NEUROPEPTIDES

For a neuromolecule to belong to neurotransmitters, it must meet some criteria:

(1) it must be produced by neurons;

(2) it should be present in the presynaptic membrane of the first neuron and released in amounts sufficient to exert a defined action on the postsynaptic membrane of the second neuron or target cells in effector organs;

(3) exogenous administration should mimic the effect of an endogenously synthesized neurotransmitter;

(4) intrinsic mechanisms must exist to remove neurotransmitters from their site of action [13, 14].

Neurotransmitters are stored in small synaptic vesicles, but also found in the blood and target organs. On the one hand, neurotransmitters influence innate and adaptive immune responses. On the other hand, immune cells send signals to the brain through cytokines and are present in the brain to influence neuronal processes [12]. Some neuromolecules, including dopamine, L-glutamate, serotonin, and substance P, are crucial in the classical neuroimmune network [15]. The neuroimmune network is closely associated with the hypothalamic-pituitary-adrenal (HPA) axis, vagus nerve, sympathetic nervous system, and synapse from the vagus nerve to the spleen [15]. Depending on their defined action, all neurotransmitters may be categorized as excitatory (*proimmunogenic*), inhibitory (*protolerogenic*), and modulatory (*immunomodulatory*). Destroyed bidirectional communication between the nervous and immune systems is a prerequisite in immunopathological disorders [15, 16] (Table).

Table

Types of synaptic transmission molecules

Category	Characterization of signal transmission	Impact on immune system in the context of allergic inflammation	Molecules
Excitatory neuro-transmitters	For a short time, they've managed to increase the electrical excitability on the postsynaptic membrane due to ion flow that leads to the facilitation of signal transmission	Proimmunogenic, proinflammatory (except for norepinephrine)	Acetylcholine* Norepinephrine* Dopamine* L-glutamate* Histamine
Inhibitory neuro-transmitters	For a short time, they've managed to decrease the electrical excitability on the postsynaptic membrane due to ion flow that results in the reduction of signal transmission	Protolerogenic, anti-inflammatory	Serotonin* γ aminobutyric acid (GABA) Dopamine* Glycine
Modulatory neurotransmitters	They spend for a long time in the cerebrospinal fluid that affects the activity of other neurons, and target cells	Immunomodulatory	Acetylcholine Norepinephrine Dopamine L-glutamate Serotonin
Neurohormones	They act in the whole body	Immunomodulatory	Oxytocin Vasopressin Melatonin
Neuropeptides	They are slow-onset long-lasting modulatory synaptic neuro molecules packaged in large granular vesicles	Immunomodulatory	Substance P Calcitonin gene-related peptide (CGRP) Neuromedin U Vasoactive intestinal peptide
Atypical neuro-transmitters (neurochemicals)	They are synthesized «on- demand» and released from the postsynaptic membrane	Immunomodulatory	Nitric oxide Carbon monoxide Hydrogen sulfide Lipid mediators Adenosine ~~Angiotensin-converting enzyme (ACE)~~ Endocannabinoids

* also immunomodulatory effects.

Adenosine triphosphate

The brain also synthesizes molecules, neurochemicals, neurohormones, and neuropeptides, which act on various receptors of immune cells but do not meet the criteria for neurotransmitters [17–20]. So far, only 12 small molecule neurotransmitters and over 100 neuropeptides have been identified [11]. During crosstalk between the nervous system and the immune system, most neuromolecules exploit membrane vesicles,

ligand- and voltage-gated ion channels, transporters for extracellular transport and entry into cells, as well as G protein-coupled receptors for signaling [15].

IMPACT OF NEUROMOLECULES ON CELLS OF THE IMMUNE SYSTEM

In response to environmental allergens (Figure), nasal epitheliocytes produce alarmins, IL(interleukin)-25, IL-33, and thymic stromal lymphopoietin (TSLP), which, together with neuromedin U [21], upregulate group 2 innate lymphoid cells (ILC2) [22], dendritic cells (DCs), and type 2 helper T (Th2) cells. These cytokines are essential regulators of type 2 immunity, as they lead to the production of IL-13 and IL-5.

Allergens that pass through the unified airway epithelial barriers are processed by DCs, which, in turn, migrate to draining lymph nodes, where they present allergen-derived peptides on HLA class II molecules to naïve T cells. The naïve T cells can differentiate into Th2 cells and follicular helper T (Tfh) cells. Th2 cells produce type 2 cytokines, such as IL-4, IL-5, IL-9, and IL-13 and function as effector cells that drive many aspects of allergic inflammation. Tfh cells produce IL-21, IL-4, and IL-13, which promote IgE class switch recombination in B cells, plasma cell maturation, and allergen-specific IgE production. Allergen-specific IgE antibodies bind to FcεRI molecules on mast cells and basophils, resulting in their degranulation and allergic inflammation development due to histamine and other mediators [23, 24]. In theory, proimmunogenic neuromediators must upregulate allergen tolerance breakdown, whereas protolerogenic neuromolecules should inhibit the process.

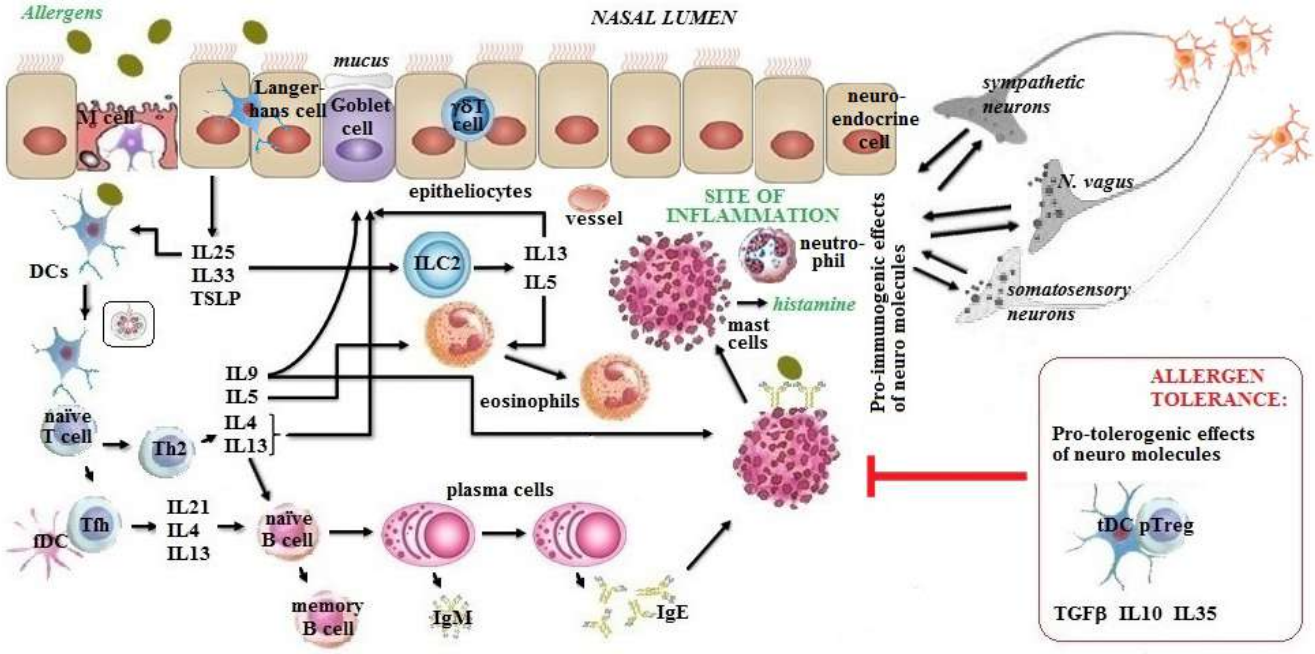

Fig. Allergen tolerance breakdown in allergic rhinitis in the context of the role of neuromolecules

Acetylcholine

Acetylcholine is the main neurotransmitter of the parasympathetic nervous system synthesized in neurons from choline and acetyl-coenzyme A by choline acetyltransferase. A deficit of acetylcholine in the cerebral cortex and hippocampus progressively leads to Alzheimer's disease [25]. Commonly, immune cells, such as T cells and monocytes, can interact with cholinergic nerves associated with lymphatic vessels or acetylcholine synthesized by immune cells themselves [13]. Functioning via muscarinic and nicotinic receptors, acetylcholine promotes differentiation of Th2 and degranulation of mast cells and basophils, but paradoxically downregulates ILC2 proliferation and upregulates T-regulatory (Treg) cells. Acetylcholine can bind to the muscarinic receptors M1AchR, M2AchR

and nicotinic receptor a7nAchR on the ciliated epithelial cells, resulting in mucus secretion [3, 12].

On the whole, a decrease in acetylcholine in target organs leads to reduction of cholinergic modulation promoting allergic inflammation [26]. Neuromedin U secretion by cholinergic neurons triggers ILC2 proliferation and expression of Th2 cytokines, including IL-5 and IL-13 [27]. Solitary chemosensory cells in the nasal cavity can use cholinergic neurotransmission to induce the neurogenic inflammation pathway [28].

Norepinephrine

Norepinephrine (noradrenaline) is a sympathetic neurotransmitter of the catecholamine family that mediates the fight-or-flight response and is produced in the brain neurons, especially inside the pons, sympathetic ganglia near the spinal cord, and adrenal medulla [13, 24]. Adrenergic receptors are expressed on immune cells, including T cells, B cells, macrophages, and natural killer (NK) cells. This neurotransmitter has a modulatory effect on the immune system. Norepinephrine mainly exerts anti-inflammatory effects by interacting with the adrenoreceptors expressed on lymphocytes and macrophages and inhibiting the production of TNFα, IL1β, and IFNγ and migration of lymphocytes from the lymph nodes to inflamed tissues. Norepinephrine binds to the β_2-adrenergic receptor on Th2 cells to suppress T cell activation [3]. Additionally, norepinephrine upregulates the production of IL-10 [13], limits ILC2-dependent type 2 inflammation, and counterbalances the effects of neuromedin U to prevent overactivation of ILC2s [29]. However, it may lower the activity of Treg cells. Interestingly, norepinephrine can promote inflammation in the initial phase of immune responses, whereas it downregulates inflammation in later phases [30].

Dopamine

Dopamine is a critical neurotransmitter of the catecholamine family, associated with emotions, pleasure, reward system, and gamble. A decrease in dopamine in the substantia nigra promotes Parkinson's disease, whereas its excess in the frontal lobes may result in schizophrenic episodes [25]. Dopamine is synthesized in the brain from L-tyrosine by tyrosine hydroxylase. It was identified in cells of the immune system, such as Treg cells, macrophages, granulocytes, T cells, and B cells. It functions via D_1–D_5 receptors promoting Th2 cell differentiation through D_4 [15]. D_1 activation on DCs upregulates Th2 and Th17 polarization, whereas signaling via this receptor expressed on Treg cells slows down the above-mentioned effect.

The communication between dopamine and CD4+ T cells is provided by an age-related mechanism underlying susceptibility to Th2-mediated allergic inflammation at an early age [31]. During B cell-mediated responses, the activity of dopamine in the brain is markedly elevating. However, direct effects of dopamine on the immune cells are contradictory, as they may also be immunosuppressive. Dopamine signaling through D_4 is known to suppress lymphocyte function by inhibiting a set of tyrosine kinases and transcription factors. Activation of D_1 and D_5 on Treg cells reduces their protolerogenic activity. Moreover, dopamine released from T cells can enhance intracellular reactive oxygen species (ROS) production, leading to oxidative stress and apoptosis in peripheral lymphocytes. In T cell-dependent responses, dopamine simultaneously displays increased production of TNF and IL-10 by naïve T cells [13, 24].

L-glutamate

L-glutamate is a critical neurotransmitter synthesized from glutamine in the brain by glutaminase and from a-ketoglutaric acid in the citric acid cycle [15]. L-glutamate influences the ability of learning and memory functioning through two groups of receptors: metabotropic (mGluRs) and ionotropic (iGluRs) glutamate receptors. In the brain, this neurotransmitter can contribute to neurotoxicity in multiple sclerosis and amyotrophic lateral sclerosis [25]. L-glutamate prevents apoptosis in activated T cells, facilitates TCR signaling, and promotes Th1 differentiation. Conversely, in some situations, L-glutamate can contribute to immunosuppression and resolution of chronic inflammation [15].

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a critical neurotransmitter synthesized from L-tryptophan in enterochromaffin cells of the gastrointestinal tract, epithelial neuroendocrine cells, and neurons of the central nervous system and taken up by platelets, basophils, and mast cells. On the one hand, serotonin transmission between neurons in the brain is responsible for mood, pleasure, sleep, and appetite. Serotonin may play an essential role in behavioral and psychological manifestations in depression, anxiety, obsessive-compulsive disorder, impulse control disorder, autism spectrum disorder, and attention deficit hyperactivity disorders [25].

On the other hand, it predominanly promotes the immunosuppressive effects and in some cases – immunostimulatory effects [32, 33]. Serotonin functions

through 5-HT1-5-HT7 receptors as a protolerogenic neurotransmitter inhibiting the production of proinflammatory cytokines, such as TNFα and IL-12, and canceling Th1 and Th17 polarization in immunopathology. Additionally, serotonin inhibits CXCL10 production, maturation of proinflammatory DCs, and promotes differentiation of tolerogenic DCs and synthesis of IL-10 [34]. During B cell-mediated responses, the activity of serotonin in the brain markedly decreases. However, only via the 5-HT2B receptor, serotonin has proimmunogenic effects in the context of Th1 and Th17 polarization [35].

GABA

Gamma aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system displaying anti-anxiety effects. Loss of GABA in the brain may be a prerequisite of an epileptic attack [13]. GABA is produced by glutamic acid decarboxylase from L-glutamate in the brain and spinal cord neurons and other cells (e.g., epithelial neuroendocrine cells) in many organs, including the unified airway. There are two main GABA receptors: $GABA_A$ and $GABA_B$, which mediate the activity of this neurotransmitter [36–38]. To date, GABAergic mechanisms have been demonstrated in many parts of the body, including synthesis in epithelial neuroendocrine cells [12]. In the immune system, GABA exhibits anti-inflammatory and immunosuppressive effects inhibiting Th1 and Th17 cells differentiation. However, the amount of GABA in the brain during inflammation in the body increases.

Oxytocin

Oxytocin is a neurohormone of the posterior pituitary mediating stress resilience, well-being, social interaction, growth, feeling of love, childbirth, and regeneration [39]. It is synthesized as an inactive precursor protein encoded by the *OXT* gene, undergoes a series of enzymes, and is released into the bloodstream. Oxytocin maintains immune homeostasis, allergen tolerance, and immune defense, acting via oxytocin receptors. Moreover, oxytocin downregulates allergic inflammation, autoimmune processes, and stress-associated immune disorders [40].

Melatonin

Melatonin, a hormone of the pineal gland (or epiphysis), has multiple effects. It acts as a biorhythmic regulator, modulates many of the immune processes related to stress responses, and regulates the level of glucose and cholesterol in the blood. Regarding the immune system, melatonin is exhibits proimmunogenic and anti-tumor effects. It has proinflammatory effect in asthma, leading to bronchoconstriction [41]. However, it disables inflammasome NLRP3 [42] and limits oxidative stress.

Substance P

Substance P is a critical neuropeptide of the neuroimmune network released from the terminals of specific somatosensory nerves in the brain, regulating emotions, as well as in most peripheral regions of the nervous system. It is synthesized in many immune cells [13, 15, 43]. Substance P exerts its biological effect through neurokinin receptors, which are found in close proximity to cells containing serotonin and norepinephrine. Substance P amplifies Th1- or Th17-mediated inflammatory responses, secretion of proinflammatory cytokines by T cells and macrophages, and production of immunoglobulins by plasma cells. However, CD8+T cells and NK cells show reduced activity in the presence of substance P [15].

Calcitonin gene-related peptide (CGRP)

Calcitonin gene-related peptide (CGRP) exists in two isoforms, α and β [13], encoded by separate genes and synthesized due to alternative splicing. α-CGRP is released from sensory neurons of the central nervous system, spinal cord, and trigeminal ganglion. In contrast, β-CGRP is mainly produced by organs of the immune system, immune cells, and epithelial neuroendocrine cells.

CGRP receptors are found throughout the body, suggesting that this neuropeptide may modulate a wide range of physiological functions and pathological reactions, including neurogenic inflammation. CGRP is responsible for transmission of pain (migraine), decreased appetite, and increased heart rate. Additionally, CGRP inhibits activation of ILC2 [44] and differentiation of Th2 [45]. Therefore, CGRP acts as an anti-inflammatory mediator responsible for preventing tissue damage during allergic and other types of inflammation.

Neuroimmune regulation in allergic rhinitis

It was shown that allergic rhinitis induced anxiety-like behavior in humans and altered social interaction in rodents, along with the increased expression of Th2 cells [46]. Interestingly, the immunosuppressive effect of tryptophan, a precursor to the neurotransmitter serotonin, was demonstrated. Increased serum tryptophan concentrations were reported in patients with seasonal rhinitis and found only outside the pollen season and not during it. Besides, the association

of elevated tryptophan concentrations with a poor response to allergen-specific immunotherapy was demonstrated [47].

The well-studied GABAergic system exists not only in the brain but also in airway epithelial cells playing a protolerogenic role. In experiments, the protolerogenic neurotransmitter GABA inhibits overproduction of mucus and synthesis of IL-13 in mice with respiratory allergic reactions induced by ovalbumin [48]. It is known that the proimmunogenic neurotransmitter L-glutamate is a precursor of GABA. Interestingly, L-glutamate concentration in the nasal mucosa in patients with allergic rhinitis is significantly higher, whereas GABA corresponds to the control level [49].

In a pilot study [50], patients with allergic rhinitis were exposed to a standardized Trier Social Stress Test (TSST), followed by allergy skin tests. Stress responders were estimated based on salivary cortisol concentrations, anxiety scale, and serum norepinephrine and oxytocin levels. The baseline concentrations, independent of TSST, were significantly higher in allergic individuals. Therefore, it indicates that patients with allergic rhinitis are less resistant to stress. In another study, mast cells and macrophages in the mucosa expressed oxytocin receptors against the background of elevated oxytocin concentrations, which could indicate the presence of local allergic responses, linking neuron-mediated emotions and inflammation [51]. Unfortunately, similar clinical studies in selected groups with conventional allergic rhinitis and LAR in humans have not yet been carried out.

CONCLUSION

The accumulation of knowledge about synaptic transcription molecules led to the concept that neuronal signaling can produce neurogenic inflammation [52]. It has become clear that neuronal regulation of immunity plays an essential role in the context of allergic inflammation [3]. Mast cells, which take part in inflammation, are in close contact with nerves in the nasal mucosa [53]. Eosinophils, another key innate effector cell type in allergic reactions, were also found to be localized close to cholinergic nerves in allergic rhinitis [54]. Allergic inflammation in the respiratory tract involves a complex crosstalk between neurons and immune cells that could play a critical role in mediating disease progression. The nervous system could be a novel and exciting target in this process [3].

Neurons secrete mediators, including neurotransmitters and neuropeptides, which act on their cognate receptors on cells engaged in inflammation to drive or regulate immunity. These bidirectional neuroimmune interactions occur early and significantly influence the onset and development of allergic inflammation. On the whole, the molecular mechanisms of neurogenic inflammation are not completely understood. In the presence of nasal allergic inflammation, the neuronal function can also be chronically upregulated depending on stimulation of nociceptors and neurotrophins, such as nerve growth factor (NGF) [55].

In the context of allergic inflammation in allergic rhinitis associated with the neuroimmune network, we considered the neuromolecules with predominant proimmunogenic effects (such as acetylcholine, dopamine, L-glutamate, melatonin, and substance P) and protolerogenic effects (such as serotonin, GABA, norepinephrine, oxytocin, and CGRP). At the local (nasal) level, allergen tolerance is mainly associated with the peculiarities of the innervation and an appropriate set of neurotransmitters in the nasal cavity [3, 13]. When systemic allergen tolerance maintenance is still available, but the appropriate neurotransmitter imbalance occurs in the nose, the autonomic nervous system may be responsible for autonomous allergen tolerance breakdown that results in LAR.

We proposed a hypothesis to be tested that the autonomous allergen tolerance breakdown in the nose may be caused by an imbalance of proimmunogenic and protolerogenic neurotransmitters with a lower concentration of the latter [56]. The neurotransmitter imbalance paradigm seems to be among possible explanations of the pathogenesis of LAR in individuals with atopic predisposition, but requires further study and discussion.

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