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The intranasal trigeminal system: roles in rhinitis (allergic and non-allergic)

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Abstract. – The aim of this paper is to review intranasal trigeminal system and associated reflexes. The literature survey was performed on PubMed, ProQuest Central database of Kirikkale University and Google Scholar.

The intranasal trigeminal system and associated reflexes play an important role in humans in both health and disease, including in rhinitis of non-allergic and mixed type. The intranasal trigeminal nerve provides sensory perception to the lining of the nose, supplying information on how patent the nasal airway is and responding to various chemical signals. The reflexes known to exist within the intranasal trigeminal system are nasobronchial reflex, trigemino-cardiac reflex, nasogastric reflex, and nasal cycle.

The intranasal trigeminal system and its reflexes play a vital role in normal human physiology. Alterations in how this system operates may underlie multiple forms of rhinitis and more research is needed to fully understand the mechanisms involved.

Key Words:
Nasal, Trigeminal, Reflex, Physiology, Rhinitis.

Introduction

The intranasal trigeminal system and associated reflexes play an important role in humans in both health and disease, including in rhinitis of non-allergic and mixed type.

The intranasal trigeminal nerve provides sensory perception to the lining of the nose, supplying information on how patent the nasal airway is and responding to various chemical signals. It also plays a part in regulating inflammation within the nasal cavity[1]. A major function of this organ is to restrict or halt inspiration through the nose where a potentially harmful or lethal substance could be inhaled into the upper or lower respiratory tract.

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This function depends on the reflex circuitry of the trigeminal[2].

The intranasal trigeminal system also aids olfactory perception. For an odoriferous stimulus to be fully perceived, both the olfactory nerve and trigeminal nerve must be stimulated. The majority of molecules that produce a sensation of smell, activate receptors on both nerves, as long as they are present at a high concentration[3,4]. However, whereas the first cranial nerve mainly supplies information about how pleasant or edible a substance is and how familiar, the fifth cranial nerve is more targeted on detecting harmful stimuli and triggering protective reflexes. The olfactory system links to social and other behaviour, whilst the trigeminal system works to protect the individual from harm.

The fifth cranial nerve within the nose can also initiate neurogenic inflammation in response to chemical challenge, physical injury or allergenic exposure[5].

For this paper, the literature survey was performed from PubMed, ProQuest Central database of Kirikkale University and Google Scholar.

The Nervous Supply to the Nose

The ophthalmic and maxillary divisions of the fifth cranial nerve provide the nerve supply to the interior of the nose. The ethmoid nerve divides off the ophthalmic division of the fifth cranial nerve (CN V) to supply the nasal exterior and the anterior portion of the nasal lining. The posterior portion of the nasal lining receives its nerve supply from a branch of the maxillary division of CN V, the nasopalatine nerve.

The nasal surfaces, sinus cavities, cornea and blephara, as well as the mouth and surrounding skin are all well-supplied with sensory receptors. The sensory receptors of the intranasal trigeminal system are sensitive to pressure, temperature, and the flow of air through the nose caused by breathing. These fibres also contribute to the overall perception of smell.

There are both chemosensory and mechanosensory neurones within the CN V. Mechanical perception is conveyed *via* Aδ fibres, which have a myelin sheath and conduct the signal rapidly. The sensation of warmth or cold (i.e., thermoception) and pain (which may be due to harmful chemical substances or mechanical in nature) are transmitted by C-fibres. These slender fibres lack a myelin sheath and transmit signals less rapidly than the Aδ type. Stimulation of the CN V produces perceptions of burning, stinging, itching or tickling, as well as warmth or cold. The slower, uninsulated C-fibres carry the perception of burning, whereas stinging sensations are conveyed by the rapidly conductive, insulated Aδ fibres. An alternative term used to denote the fifth cranial nerve supplying the nasal mucosal lining is the non-adrenergic, non-cholinergic (NANC) system[1].

A number of altered parameters can be detected by sensory receptors on the fifth cranial nerve, such as altered temperature, humidity, air pressure, and the presence of noxious substances. The trigeminal neurones express calcitonin gene-related peptide (CGRP) and Substance P, in addition to similar neuropeptides[6]. Chemosensation is mediated through fibres of the fifth cranial nerve located in the vicinity of isolated, specialist chemosensory cells in the lining of the nose[7].

There are cholinergic sensory receptors of nicotinic subtype located on trigeminal fibres. There are also numerous different transient receptor potential (TRP) channel proteins located on the sensory neurones. These operate by permitting various cationic species to cross the outer cell membrane, thereby generating an action potential. The channels are termed polymodal because of their ability to open in response to several different stimuli, both mechanical and chemical. Various molecules can cause the channel to allow cationic flow. There are six subtypes of these channel proteins, and they are listed as follows:

- Purinergic receptor (P2X)
- Vanilloid receptor (TRPV1)
- Acid-sensitive ion channels (ASIC/DRASIC)
- Channel responsive to thermal increase and eugenol (TRPV3) (senses increased heat)
- Channel responsive to menthol (TRPM8) (perception of cold)
- Channel responsive to the presence of isothiocyanate (TRPA1). Isothiocyanate is the main functional group found in mustard oil[8].

In addition to sensory nervous input from the nose, the normal functioning of this organ also depends on autonomic nervous control, both sympathetic and parasympathetic. The principal neurotransmitter of the parasympathetic division is acetylcholine, which attaches to cholinergic receptors of muscarinic type, leading to increased glandular activity or dilatation of blood vessels. Another neurotransmitter of importance in parasympathetic fibres is vasointestinal peptide (VIP). In the sympathetic division, the principal neurotransmitters are noradrenaline and neuropeptide Y. Both act on adrenoceptors to cause constriction of blood vessels and widening of the airway within the nasal cavity[1].

Nasal symptoms may arise as a result of imbalances affecting the physiological reflexes within the nose.

Activation of Trigeminal Receptors

When the receptors of the fifth cranial nerve are stimulated, a sensory perception of potential harm may be produced, or a smell may be more fully appreciated. This then activates a number of different reflexes within the nose. The degree to which the nasal lining is sensitive to stimuli activating the trigeminal fibres varies from location to location. The anterior portion has the greatest sensitivity for chemoception, whereas mechanical stimuli are most easily perceived in the posterior portion of the cavity[9-11].

Protective reflexes – such as an increase in secretions (i.e., saliva, tears, and nasal mucus), decreased inspiration, initiation of sweating, and reduction in nasal patency caused by congestion of the nasal turbinates – occur when trigeminal neurones bearing TRP channels are activated. The characteristic feature of TRP channels is polymodal activation, which means they become active in response to thermal, mechanical, or chemical stimulation. TRPV1 can be activated by a chemical stimulus, such as capsaicin, and by physical stimuli, such as heat application. Agents which can block TRP channels are under pharmaceutical investigation. Potentially useful agents include both existing drug molecules, such as amiloride or gentamycin, which can blockade TRPA1, and newer compounds. In investigations of the upper airway, the key TRP channels under research evaluation are those from the TRPV, TRPM, and TRPA families. TRPV1 possesses high affinity for capsaicin, the principal active vanilloid compound found within chilli peppers. Camphor and eugenol mostly activate the TRPV2 channel. The cold sensor TRPM8 is activated by both menthol and eucalyptol. TRPA1 has maximum affinity for cinnamaldehyde and mustard oil. Neurogenic inflammation can be triggered by release of neuropeptides by neuroendocrine cells within the respiratory mucosa following activation of sensory fibres. This mechanism may account for certain types of rhinitis without an allergic component[12]. There are raised levels of particular neuropeptides, namely substance P, CGRP, neuropeptide K (NPK) and neurokinin A (NKA), in the airways of some patients whose airways are inflamed[13,14].

Research findings strongly support the hypothesis that inflammation is promoted through the interaction of pro-inflammatory immune cells, sensory neurons, and neuroendocrine cells. This inflammation leads to airway hyperreactivity. Neurogenic inflammation has also been shown to be associated with altered neurotrophin expression, especially neurotrophins-3 and -4 and nerve growth factor (NGF).

In mammals, when the dendrites of the intranasal trigeminal nerve are stimulated, action potentials propagate in an antidromic direction, referred to as the axon reflex. This causes increased expression of inflammatory neuropeptides and the formation of neuronal varicosities. Furthermore, vascular permeability increases, and mucous gland activity rises. This series of events has also been demonstrated to occur in man. When the intranasal trigeminal nerve endings are stimulated, the nose becomes congested and obstructed, there is watery rhinorrhoea and sneezing occurs. It is highly probable that the axon reflex plays a significant part in nasal hyperreactivity and idiopathic (non-allergic, non-infectious) rhinitis (NINAR). It may also be of importance in the pathogenesis of allergic rhinitis, since substance P is involved in eosinophil recruitment.

When the nasal cavity is exposed to cold, dry air, persistent pain and increased secretions may occur[15,16]. The probable explanation for this phenomenon is that fibres of capsaicin-sensitive type are activated. Alternatively, the drying effect may cause nociceptors to be activated. These mechanisms may feature in nasal hyperreactivity and NINAR, which is the rationale for employing repeated applications of topical capsaicin as a means of desensitising the mucosa in such cases[12]. It has been shown that intranasal application of capsaicin offers symptomatic relief and decreases nasal hyperreactivity in cases of idiopathic rhinitis[17-19].

Both a single stimulus and repeated stimuli can elicit these responses. However, Aδ fibres and C-fibres react differently to repetitive chemical stimuli. In such situations, the painful burning sensation generated by C-fibres increases, whilst Aδ fibres generate a stinging sensation.

Trigeminal System Reflexes

An appreciation of how the various intranasal reflexes operate allows the pathophysiological mechanisms (mucosal, systemic, or central nervous) underlying the signs and symptoms of rhinitis to be clearly understood. Nonetheless, there

remains considerable controversy about how specific nasal syndromes not involving allergic mechanisms should be defined, which complicates discussions of this subject[20,21].

The function of chemoceptive fibres of the fifth cranial nerve can only be properly understood when the variety of different types of nociceptors and ion-transport channels (e.g., TRP) is appreciated. Trials involving anosmic patients in which the nose was exposed to numerous chemical substances within a cross-desensitisation experimental design indicate that there are large numbers of separate subtypes of nerve cells within the fifth cranial nerve capable of chemoception. Estimates range from 6 to 12 subtypes, with the possibility that not all subtypes have yet been identified[22].

The following are the reflexes known to exist within the intranasal trigeminal system.

The Nasobronchial Reflex

The nasobronchial reflex is one component of the diving reflex, in which breathing is immediately halted when the head enters cold water. This apnoeic response is accompanied by constriction of the bronchi and spasm of the larynx. Moreover, the heart slows, with a reduction in cardiac output and constriction of vessels in the skin and muscles, as well as gut and kidneys, a series of events collectively referred to as the nasocardiac portion of the diving reflex[23-25]. The diving reflex protects the lungs from filling with water and lowers the overall use of oxygen by the body and, at the same time, ensuring the brain continues to receive adequate oxygenated blood. The diving reflex is especially important in aquatic mammals whose lifestyle involves remaining underwater for lengthy periods[26].

The fifth cranial nerve supplies sensation to the nasal cavity, whilst the parasympathetic efferent supply flows *via* the vidian nerve. Both afferent and efferent nervous supply to the lower respiratory tract is carried in the tenth cranial nerve. Coughing, sneezing or constriction of the bronchi are actions which protect the respiratory tract and are under reflex control. There are mechano- and chemoreceptors located in the nasal cavity, trachea, and throughout the airways. An example of the respiratory reflexes in action is the triggering of an acute bronchoconstrictive response in asthmatic individuals who breathe in cold, dry air through the nose. The superior and inferior portions of the airways respond as a single unit due to their being connected by the nasobronchial reflex. The sensory arm involves nasal, sinusal and pharyngeal receptors. This sensory information passes *via* the fifth, seventh, and ninth cranial nerves to the medulla oblongata, where there is a connection to the effector arm of the reflex passing in the tenth cranial nerve. The result is a constrictive response by the bronchi[27]. If dust, smoke, components of fragrances (such as phenethyl acetate), SO_2, NH_3 or other hydrophilic molecules are inhaled through the nose, the bronchi lower in the tract immediately contract and apnoea occurs as the muscles of inspiration cease contracting.

The afferent limb of the nasobronchial reflex was discovered through studying patients undergoing unilateral surgical transection of the maxillary nerve to provide relief from intractable trigeminal neuralgia[28]. When these patients were examined after surgery, it was noted that applying very fine sand to the nose on the side where the operation was performed did not trigger either a localised intranasal, nor a bronchial, response. However, when the sand was applied to the nose on the intact side, the subjects reported a burning sensation in the nasal lining, the nasolacrimal response was triggered and there was narrowing of the airway lower in the respiratory tract. It was then later shown that the maxillary nerve constituted the afferent limb. Stimulation of either the olfactory or ethmoid nerve failed to elicit the reflex[29]. There have been studies[30,31] examining how the superior and inferior portions of the respiratory tract interact in patients with rhinitis (both allergic and non-allergic), in addition to asthma. These studies focused on neural reflexes, including the nasobronchial reflex, and on plasticity in the nervous system. It is known that stimulation of the afferent portion of reflexes in the nose produces severe constriction of the bronchi[32] as well as bradycardia. The nasobronchial reflex can also be activated when mechanoreceptors in the nose are stimulated. A study involving healthy non-smokers ascertained that, when the middle meatus or inferior turbinate were mechanically stimulated, FEV1 fell[33]. A different study looked at the effect of applying histamine to the nasal cavity. This action caused the bronchi to contract in 8 out of 12 individuals, all of whom had both allergic rhinitis and asthma[34].

The Trigemino-Cardiac Reflex

Another component of the diving reflex is the trigemino-cardiac reflex (TCR)[35]. This reflex causes bradycardia, hypotension, cessation of

breathing and rapid emptying of the stomach. The TCR may be triggered prior to surgery or may become activated during eye surgery or procedures involving the eyes. Moreover, neurosurgical operations in the region of the cerebellopontine angle may trigger the reflex, since these result in the mid portion of the fifth cranial nerve being stimulated. One study examined the nasocardiac reflex in 80 healthy individuals. A 25% ammonia solution was applied to the mucosal lining of the middle turbinate[36]. Every subject had a bradycardic episode, and 11 subjects became apnoeic before the heart rate slowed. Pre-treating the nasal mucosa with 2% lidocaine prevented the reflex occurring. On the other hand, electrically stimulating the fifth cranial nerve can trigger the trigemino-cardiac reflex[23]. If the maxillary nerve is transacted or systemic atropine is administered, slowing of the heart and cessation of breathing do not occur when the usual trigger is applied. Patients who misuse glue, paint stripper or petrol for glue-sniffing have died from the abrupt cessation of respiration and bradycardia. Furthermore, there is a potential for bradycardia and even cardiac arrest to occur when a nasogastric tube is inserted or water is inhaled into the nose[37]. Some 10% of patients who undergo trans-sphenoidal surgery to remove a pituitary adenoma exhibit the trigemino-cardiac reflex[38], experiencing a 43% decrease in cardiac rate and 54% drop in blood pressure. The degree of hypotension and bradycardia correlates positively with the severity of the tumour in histopathological terms. The molecular biology of the trigemino-cardiac reflex still awaits elucidation. It does appear likely, however, that activation of mechanosensitive trigeminal or sympathetic afferent fibres and recruitment of brainstem cholinergic parasympathetic output may be involved.

Definition and Pathophysiological Basis of the Trigemino-Cardiac Reflex (TCR)[39]

The afferent portion of the TCR is believed to consist of sensory fibres of the fifth cranial nerve. These fibres relay information to the trigeminal sensory nucleus *via* the Gasserian ganglion[40,41]. The afferent portion then continues as interneurons within the reticular formation, which synapse with the efferent portion of the reflex at the vagal motor nucleus. Studies[42-44] in other animals reveal that the various reflexes affecting the heart that involve the fifth cranial nerve can be triggered by applying stimulation to various parts of the central nervous system. These triggering areas include the spinal fifth cranial nerve nucleus, the paratrigeminal nucleus, the superior ventrolateral medulla oblongata, parabrachial complex, and the dorsal reticular nucleus within the medulla.

The TCR can be triggered by applying stimulation at any point along the fifth cranial nerve, whether within or outside the cranium[45,46], in the peripheral or central nervous system. The first description of the TCR in the literature dates from 1999 and is by Schaller et al[40] They described its occurrence during neurosurgical procedures and in operations affecting the base of the skull. In these cases, the cardiac rate and arterial tension were recorded. The TCR was defined as a "heart rate less than 60 beats per minute and mean arterial blood pressure (MABP) 20% lower than the baseline". Amongst the cases studied, 3 individuals went into asystole for between 30 and 70 seconds[40]. The TCR is also observed during ophthalmic surgery or interventions, when it is known as the oculo-cardiac reflex (OCR)[45-47]. The OCR is believed to involve the fifth cranial nerve in its intracranial (i.e., central) portion[41].

TCR occurs with a frequency of between 10% and 18%[40,48-51]. The OCR is noted to occur in up to 67% of patients undergoing surgical procedures for strabismus[48]. However, this reported incidence may be considerably over-estimated, given that the majority of the authors quoted were prepared to accept a reduction of at least 10% in cardiac rate as evidence that the OCR had been activated.

The incidence of activated TCR was 11% in a series of 125 patients undergoing neurosurgical procedures for tumours within the cerebello-pontine angle or in whom microvascular decompression was undertaken to relieve trigeminal neuralgia, according to Schaller et al[51,5].

Risk Factors for Activation of a TCR

There are several situations in which the risk of activating a TCR is raised, such as low arterial oxygen tension, hypercapnia, light general anaesthesia, strong or long-lasting stimulation to the sensory portion of the reflex and young patient age (children are especially at risk). Additionally, some medications also raise the risk, notably narcotics, e.g., sufentanil or alfentanil, calcium channel blockers and beta adrenoceptor antagonists[53-55].

Nasogastric Reflex

The nasogastric reflex has its afferent portion within the fifth cranial nerve, the efferent portion travelling within the tenth cranial nerve. The two limbs of the reflex synapse within the central nervous system at the pontomedullary junction. There are sensory fibres with receptors in the lining of the nose. These project to the trigeminal nuclei within the pons and medulla, in the region of the brainstem devoted to general somatic afferent input. Sensory information may then be shared with the solitary tract nucleus located in the same vicinity. The neurotransmitters involved are glutamine and non-NMDA (non-*N*-methyl-d-aspartate). Activation of the reflex results in sensations of nausea and anorexia. Gastric acidity rises and the stomach relaxes. Furthermore, the tenth cranial nerve efferent also controls the tone of the lower oesophageal sphincter[56]. This mechanism helps to explain how irritation to the nasal lining can trigger symptoms affecting the stomach and proximal portion of the gut[56-58]. Since gastric contents may subsequently be refluxed and cause irritation to the nasal mucosa, a vicious cycle may be set up through activation of the reflex.

The Nasal Cycle

The nasal cycle refers to a process whereby most airflow occurs first through one side, then the other, of the nose, depending on which side exhibits most resistance to airflow. In approximately 4 out of 5 adults, this cyclical change in nasal resistance has a periodicity of between 50 minutes and 4 hours[59]. Vasodilation of one side occurs alongside vasoconstriction of the contralateral passage, with the result that most flow shifts to one nostril or the other, but the total resistance remains unvaried[60]. Whilst individuals are exercising and breathing more rapidly or deeply than usual, the resistance to airflow in the nose falls, probably due to the vessels becoming decongested. Recently, studies examining the crutch reflex, in which there occurs ipsilateral congestion of the nose when the axilla is stimulated, have produced findings indicating that one-sided reflexes affecting the nasal cavity exist[58].

The circadian control of the nasal cycle is still not properly understood. The autonomic system is likely to play a key role. Some medications have been observed to affect the cycle. Furthermore, conditions which result in dilation of nasal vessels, a thickened nasal lining and altered levels of nasal secretion, such as allergic, non-allergic or infectious rhinitis, also affect how the cycle occurs.

Diagnostic Testing of Intranasal Trigeminal Function

There are a number of different techniques which may be employed to assess the function of the intranasal trigeminal system, directly or indirectly. Direct methods include psychophysical or electrophysiological tests, as well as imaging. Indirect techniques measure how reactive the nasal mucosa is.

Psychophysical Tests

Psychophysical evaluation assesses various parameters, in particular the nasal threshold, perception of stimuli above the threshold, the ability to discriminate between stimuli and being able to determine which side a stimulus has been presented to[61-63]. These tests indicate an age-related reduction in the level of sensitivity of the nose[64].

Psychophysical research[65] suggests that the human intranasal trigeminal system is capable of qualitative specificity, although, for the majority of odoriferous substances, its sensitivity falls below that of the olfactory system. In terms of nociception, substances which activate the trigeminal are more rapidly perceived as painful and the pain is more intense that when a substance activates the olfactory system. The same stimulus can produce different perceptions by the two nasal perceptory systems. In normosmic individuals, trigeminal stimuli accompanied by an olfactory stimulus are perceived more intensely, but perception of stimuli that activate olfaction is unaffected by additional stimulation of the trigeminal system[65].

Repeated presentation of the same stimulus to the olfactory system leads to desensitisation, but this is not the case with the trigeminal system, in which nociception actually increases if the same stimulus is applied in rapid succession. However, trigeminal habituation can occur where there is a long period in between presentation of the same stimulus[65]. Studies of trigeminal nociception, where the painful stimulus used was capsaicin, reveal that increased sensitisation occurs with presentation intervals of less than 1 minute, but desensitisation if the interval is 4 minutes. The possi-

bility of utilising the habituation effect for patients suffering with nasal hyperalgia or NINAR has led to studies[8] where a repeated painful stimulus is applied to the nose. Some molecules appear to increase nasal sensitivity, whereas others decrease it.

Patients' sense of how clear and open their nasal passages are depends on the trigeminal system. Application of menthol to the mucosa creates a feeling of greater nasal patency by stimulating cold receptors, but the nasal airway remains the same diameter as before[66]. On the other hand, when the nasal lining is anaesthetised, the airway feels closed, but again this does not correlate with any actual alteration in nasal airway dimensions. The thresholds of the trigeminal system are raised in patients with anosmia, research has found[61]. Currently, no method for measuring intranasal trigeminal function has been developed that is of sufficient validity and standardisation to be used in routine clinical practice. Such a test would also need to exhibit cost-effectiveness, be efficient in terms of time taken and fit in with other nasal testing, such as those for allergy or olfactory function. Stimulation of trigeminal fibres could involve an olfactometric device or using vials or sticks impregnated with particular substances. For psychophysical testing of the intranasal trigeminal system, there are usually three components: threshold quantification, discrimination and identification. The threshold is quantified by gradually increasing the concentration of the stimulus to the point where a response is noted. Discrimination testing may involve presenting three substances to the nose, two of which are perceived as smells, the other stimulating only a trigeminal sensation. The patient then needs to identify the trigeminal stimulating substance. The last phase is identification, wherein the patient must make a forced choice to identify a substance that activates the trigeminal response. In addition to the tests described above, patients may be asked to say which side a stimulus has been applied to. It is not possible for a blindfolded subject to accurately lateralise an olfactory or mixed stimulus, but a substance that only evokes a trigeminal response can be lateralised in this way[62]. This is an important difference between olfactory and trigeminal stimulation.

Electrophysiological Testing

Two potential differences are measured during electrophysiological studies of the intranasal trigeminal system, namely the negative mucosal potential (NMP) and the trigeminal event related potential (Trigeminal ERP). The former is peripheral, the latter central.

Measurement of the peripheral value i.e., NMP, is taken from the nasal lining. This potential probably represents the sum of all the potentials generated by cells sensitive to chemical induced pain[67]. In humans, when pain perception scores are compared with the NMP for subjects exposed to carbon dioxide inhalation, there is a correlation[62]. An NMP is also generated when polymodal nociceptors (TRPA1, TRPV1 and TRPV2) are activated. Different substances, such as carbon dioxide, menthol, or ethanol produce different values of NMP. When the stimulus is repeated, the NMP decreases, indicating habituation[62].

The trigeminal ERP, on the other hand, correlates with activation of cortical areas after the intranasal trigeminal system is stimulated multiple times, such as through carbon dioxide inhalation. The level of carbon dioxide required is between 30% and 60% of the total volume and should be presented at intervals of between 20 and 40 seconds. This can be achieved with an olfactometric device[9,62,68,69] or alongside nicotine[70]. It is important to take precautions to ensure that mechanoreceptor stimulation does not occur from altered flow rates or thermal gradients, so that only chemoception is represented in the trigeminal ERP. Flow should be maintained at a steady $8L.min^{-1}$, and the temperature should not deviate from between 36 and 37 Celsius. A thermometer is used to ensure the latter. Notably, the response recorded as stimulus strength (i.e., concentration) is raised exhibits a more rapid rise when the trigeminal system is activated than occurs with the olfactory system[68].

Measurement of the trigeminal ERP may also be of value in assessing patients with abnormal olfactory function. In such cases, the trigeminal ERPs are generally preserved, unlike those arising from olfactory perception. Neither the latency nor amplitude of the potentials is usually affected[9,69,71,72].

Electrophysiology is beneficial to understand the effect of increasing age, sex, dysosmia, and medications, both on the peripheral portion of the trigeminal system (as represented by NMP) and the central events (as seen by ERP).

Imaging Studies

PET studies of the central nervous system following intranasal trigeminal stimulation pro-

vide valuable information about the olfactory and trigeminal systems. This imaging modality reveals the trigeminal and olfactory systems have pathways in common. Stimulation with carbon dioxide leads to activation of the basal posterior central gyrus i.e., the primary and secondary somatosensory cortical areas, plus the pyriform cortex, especially on the right[62]. These PET findings are confirmed by functional MRI studies indicating involvement of the prefrontal cortex, the anterior caudate nucleus, the insula, and cerebellar regions.

Measurement of Nasal Hyperactivity

Nasal hyperreactivity (NHR) refers to the phenomenon whereby stimulation of the nasal lining produces nasal and bronchial hyperresponsiveness. Studies have examined NHR using various stimuli, such as hyperosmolar solutions[73,74], histamine[75], cold dry air (CDA)[76-79], and capsaicin[80]. CDA provocation tests are the most patient-friendly method in current diagnostic use. It stimulates a normal physiological response, has minimal potential for harm and is readily tolerated by patients. Furthermore, the superiority of CDA compared to topical intranasal histamine application has been demonstrated by Braat et al[77], since histamine failed to differentiate between cases of idiopathic rhinitis and healthy controls, whereas this was possible using CDA[77]. Histamine provocation testing is 100% sensitive, but not specific (0%), whereas CDA is less sensitive (87%), but adequately specific (71%). The study quoted employed a protocol that is too lengthy for routine clinical application, and there is a requirement for a swiftly administered, highly sensitive and specific diagnostic test showing the presence of NHR in cases of allergic or idiopathic rhinitis[81]. There is a growing consensus amongst clinicians that these types of tests should be performed routinely, since NHR typically remains unrecognised and is unassessed in studies evaluating the outcomes of medical treatment for rhinitis. The development of a time-efficient protocol and uniform design for a CDA delivery device is, therefore, a matter of priority.

The majority of cases where rhinitis has been diagnosed also involve some element of NHR, however, it is particularly important to verify the presence of NHR in the NINAR subgroup of patients suffering from idiopathic rhinitis[15,79].

The Relationship of the Intranasal Trigeminal System to Rhinitis

The evidence base strongly supports the hypothesis that the intranasal trigeminal system is of importance in rhinitis. The pathogenetic mechanism involves activation of the system, opening of TRP channels and a variety of neuromodulatory signalling molecules. In cases of allergic rhinitis, the neurone is stimulated in an antidromic direction, and this causes the expression and secretion of multiple neuromodulatory signals, which stimulate glandular hypersecretion and a vasodilatory response. Signals passing orthodromically then excite the central nervous system, resulting in pruritus, sneezing, ocular symptoms, and constriction of the bronchi. There is a limited literature concerned with trigeminal function in cases of allergic rhinitis. One study based on electrophysiology, which focused on trigeminal ERPs, noted that the ERP peak latencies P1 and N1 associated with somatoperception were significantly shorter than usual following an allergenic provocation test. The electrophysiological alterations mapped to symptoms described by the subjects during the course of the experiment. Moreover, the ERP peak latency was negatively associated with scores for general symptomatology, both prior to and following nasal challenge with the antigen. These findings indicate that intranasal trigeminal function is decreased in allergic rhinitis, both at baseline and following allergenic exposure.

The intranasal trigeminal system also appears play a major role in the pathogenesis of NINAR. There remain a substantial number of cases of idiopathic rhinitis classified as NINAR once the following aetiological factors have been excluded: allergic hypersensitivity, endocrine imbalance, and medication-related effects. For patients with NINAR, NHR is a fundamental feature. However, since the precise mechanism for NHR remains obscure, unsuspected environmental or microbial factors may be involved. Occupational or leisure-time exposure to noxious substances of low molecular mass potentially causes injury to the nasal epithelium, triggering mast cell activation, coupled with possible stimulation of the rich sensory nervous supply to the airways[82]. It has been shown that bacterial enterotoxins, such as those produced by *Staphylococcus aureus*, can stimulate a response by cells of the nasal lining, as well as passing through the epithelium to the submucosa[83]. A murine model produced the in-

teresting finding that hyperactivity of the bronchi occurs in response to environmental and microbial triggers, but without provoking an inflammatory response[84]. A recent study noted an alteration in how the nasal epithelium functions in cases of persistent inflammation affecting the nose and sinuses. The epithelial barrier became more porous in response to elevated interleukin-4 and interferon-gamma[85]. Histological studies have noted how NHR occurring within cases of idiopathic rhinitis is associated with raised levels of nerve fibres within the nasal mucosa. The periglandular nerve fibres exhibited increased expression of specific neuropeptides, in particular Substance P and CGRP, which may be considered markers of neuronal hyperactivity[86]. It is noteworthy that patients with allergic or idiopathic rhinitis demonstrate a similar degree of mucosal hyperinnervation, indicating neuroinflammation occurs in both disorders. According to Heppt et al[87], moreover, sensory nerves containing Substance P are over-abundant in nasal mucosal specimens taken from patients with idiopathic rhinitis[87]. However, it is not yet clear what factors trigger or contribute to this hyperinnervation.

Despite the fact that NHR frequently occurs in a variety of nasal disorders, including rhinitis, there is no single consensus about how this complication should be managed. In most clinics, the ARIA guidelines are followed by clinicians treating allergic rhinitis patients who exhibit NHR. On the other hand, cases of idiopathic rhinitis in which NHR is diagnosed are frequently managed by topical (intranasal) corticosteroid application. These treatments vary in their level of success. To complicate matters, there is only a single trial reported (an RCT with placebo control) where NHR featured as a primary outcome measure[88]. One potential explanation for this situation is that no gold standard diagnostic method exists for assessment of NHR, so that it could become a valid outcome measure. Capsaicin has been demonstrated to lower NHR in cases of idiopathic rhinitis, in a study by van Rijswijk et al[89]. The pathogenetic mechanisms underlying idiopathic rhinitis and how capsaicin functions to produce clinical benefit are now becoming clearer[90]. In idiopathic rhinitis, TRPV1 levels in the nasal lining are abnormally raised and nasal secretions also contain a raised concentration of Substance P. The mode of action of capsaicin appears to involve interference with the nasal mucosal perception of pain occurring through the action of Substance P on TRPV1[91].

Although there is strong evidence that capsaicin can be used to manage NHR, this strategy is rarely employed (Gevorgyan et al[92] – Cochrane review). The principal explanation for this strange situation is likely to be the length of time needed for capsaicin treatment to be effective, coupled with the lack of financial incentives to follow this path, both for the pharmaceutical manufacturers and for otorhinolaryngologists.

Conclusions

The intranasal trigeminal system and its reflexes play a vital role in normal human physiology. Alterations in how this system operates may underlie multiple forms of rhinitis and more research is needed to fully understand the mechanisms involved.

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References

1) Baraniuk JN. Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa. J Allergy Clin Immunol 1992; 90: 1045-1050.

2) Baraniuk JN, Kim D. Nasonasal reflexes, the nasal cycle and sneeze. Curr Allergy Asthma Rep 2007; 7; 105-111.

3) Doty RL, Brugger WPE, Jurs PC, Orndorff MA, Snyder PJ, Lowry LD. Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans. Physiol Behav 1978; 20: 175-185.

4) Doty RL. Intranasal trigeminal chemoreception. In: Doty, R.L. (Ed.), Handbook of Olfaction and Gustation. Marcel Dekker: New-York, 1995: 821-833.

5) Iannilli E, Del Gratta C, Gerber JC, Romani GL, Hummel T. Trigeminal activation using chemical, electrical and mechanical stimuli. Pain 2007; 139; 376-388.

6) Finger TE, StJeor VL, Kinnamon JC, Silver WL. Ultrastructure of substance P- and CGRP-immunoreactive nerve fibers in the nasal epithelium of rodents. J Comp Neurol 1990; 294: 293-305.

7) Finger TE. Evolution of taste and solitary chemoreceptor cell systems. Brain Behav Evol 1997; 50: 234-243.

8) Brand G, Jacquot L. Sensitization and desensitization to allyl isothiocyanate (mustard oil) in the nasal cavity. Chem Senses 2002; 27: 593-598.

9) Rombaux P, Guerit JM, Mouraux A. Lateralisation of intranasal trigeminal chemosensory event-related potentials. Neurophysiol Clin 2008; 38; 23-30.

10) Frasnelli J, Heilmann S, Hummel T. Responsiveness of human nasal mucosa to trigeminal stimuli depends on the site of stimulation. Neurosciences Letters 2004; 362: 322-328.

11) Meusel T, Negoias S, Scheibe M, Hummel T. Topographical differences in distribution and responsiveness of trigeminal sensitivity within the human nasal mucosa. Pain 2010; 151; 516-521.

12) Lacroix J, Buvelot J, Polla B, Lundberg J. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy 1991; 21: 595-700.

13) Baraniuk JN, Lundgren JD, Okayama M, Mullol J, Merida M, Shelhamer JH, Kaliner MA. Vasoactive intestinal peptide in human nasal mucosa. J Clin Invest 1990; 86: 825-831.

14) Shusterman D, Murphy MA, Balmes J. Differences in nasal irritant sensitivity by age, gender, and allergic rhinitis status. Int Arch Occup Environ Health 2003; 76: 577-583.

15) Van Gerven L, Boeckxstaens G, Jorissen M, Fokkens W, Hellings PW.mShort-time cold dry air exposure: a useful diagnostic tool for nasal hyperresponsiveness. Laryngoscope 2012; 122: 2615-2620.

16) Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y. Changes in airway resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. J Appl Physiol (1985) 1996; 81: 1739-1743.

17) Blom H, Severijnen A, Van Rijswijk J, Mulder P, Van Rijk R, Fokkens W. The long-effect of capsaicin aqueous spray on the nasal mucosa. Clin Exp Allergy 1998; 28: 1351-1358.

18) Van Rijswijk J, Boeke E, Keyzer J, Mulder P, Blom H, Fokkens W. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy 2003; 58: 754-761.

19) Van Gerven L, Alpizar YA, Wouters MM, Hox V, Hauben E, Jorissen M, Boeckxstaens G, Talavera K, Hellings PW. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis. J Allergy Clin Immunol 2014; 133: 1332-1339.

20) Raphael GD, Meredith SD, Baraniuk JN, Kaliner M. Nasal reflexes. Am J Rhinology 1988; 2: 8-12.

21) Eccles R. Pathophysiology of nasal symptoms. Am J Rhinol 2000; 14: 335-338.

22) Green BG, Mason JR, Kare MR (editors). Chemical Senses, Vol. 2, Irritation. Marcel Dekker. New York. 1990, pp. 141-170.

23) Patow CA, Kaliner M. Nasal and cardiopulmonary reflexes. Eur Nose Throat J 1984; 63: 78.

24) Widdicombe JG. Reflexes from the upper respiratory tract. In: Fishman AP, Cherniak NS, Widdicombe JG, Geiger SR (editors). Handbook of Physiology. Section 3. The Respiratory System. Volume II, Control of Breathing, Part 1. American Physiological Society. Washington DC. 1986, pp. 363-394.

25) Mygind N. Non-immunological factors. In: Mygind N. (editor) Nasal Allergy. Oxford. Blackwell Scientific. Oxford. 1978, pp. 140-154.

26) Widdicombe JG. Defensive mechanisms of the respiratory system. In: Widdicombe JG (editor). International Review of Physiology, Vol. 14, Respiratory Physiology II. University Park Press. Baltimore. 1977, pp. 291-315.

27) Cingi C, Muluk NB, Cobanoglu B, Çatli T, DikiciO.Nasobronchialinteraction. World J Clin Cases 2015; 3: 499-503.

28) Kaufman J. Chen JC, Wright GW. The effect of trigeminal resection on reflex bronchoconstriction after nasal and nasopharyngeal irritation in man.Am Rev Respir Dis 1970; 101: 768-769.

29) Allen WF. Effect of various inhaled vapors on respiration and blood pressure in anesthetized, unanesthetized, sleeping, and anosmic subjects. Am J Physiol 1929; 88: 620-632.

30) Togias A. Mechanisms of nose-lung interaction. Allergy 1999; 54 Suppl 57: 94-105.

31) Undem BJ, McAlexander M, Hunter DD. Neurobiology of the upper and lower airways. Allergy 1999; 54 (Suppl 57): 81-93.

32) Locke MM, Spiekermann BF, Rich GF. Trigemino vagal reflex during repair of a nasal fracture under general anesthesia.Anesth Analg 1999; 88: 1183-1184.

33) Milicic D, Mladina R, Djanic D, Prgomet D, Leovic D. Influence of nasal fontanel receptors on the regulation of tracheobronchal vagal tone. Croat Med J 1998; 39: 426-429.

34) Yan K, Salome C. The response of the airways to nasal stimulation in asthmatics with rhinitis. Eur J Respir Dis 1983; 64 (Suppl 128): 105-108.

35) Kratschmer F. On reflexes from the nasal mucous membrane on respiration and circulation. Respir Physiol 2001; 127: 93-104.

36) Betlejewski S, Betlejewski A, Burduk D, Owczarek A. Nasal-cardiac reflex. Otolaryngol Pol 2003; 57: 613-618.

37) James JEA, Daly MdeB. Nasal reflexes. Proc Soc Med 1969; 62: 1287-1293.

38) Schaller B. Trigemino-cardiac reflex during transsphenoidal surgery for pituitary adenomas. Clin Neurol Neurosurg 2005; 107: 468-474.

39) Arasho B, Sandu N, Spiriev T, Prabhakar H, Schaller B. Management of the trigeminocardiac reflex: Facts and own experience. Neurology India 2009; 57: 375-380.

40) Schaller B, Probst R, Strebel S, Gratzl O. Trigeminocardiac reflex during surgery in the cerebellopontine angle. J Neurosurg 1999; 90: 215-220.

41) Schaller B. Trigeminocardiac reflex: A clinical phenomenon or a new physiological entity? J Neurol 2004; 251: 658-665.

42) Schaller B, Cornelius JF, Prabhakar H, Koerbel A, Gnanalingham K, Sandu N, Ottaviani G, Filis A, Buchfelder M; Trigemino-Cardiac Reflex Examination Group (TCREG). The trigemino-cardiacreflex: an update of the current knowledge. J Neurosurg Anesthesiol 2009; 21: 187-195.

43) Ohshita N, Nakajo N, Takemura M. Characteristics of the trigeminal depressor response in cats. J Neurosci Res 2004; 76: 891-901.

44) Schaller BJ, Buchfelder M. Trigemino-cardiac reflex in skull base surgery: From a better understanding to a better outcome? Acta Neurochir (Wien) 2006; 148: 1029-1031.

45) Aschner B. Über einen bisher noch nicht beschriebenen Reflex, vom Auge auf Kreislauf und Atmung. Verschwinden des Radialispulses bei Druck auf das Auge [About a not previously described reflection from the eye to circulation and respiration. Disappearance of radial pulse when pressure on the eye.] Wien Klin Wochenschr. 1908; 21: 1529-1530.

46) Dagnini G. Intorno ad un riflesso provocato in alcuni emiplegici collo stimolo della cornea e colla pressione sul bulbo ocular [Around a reflex caused in some hemiplegic neck stimulus of the cornea and pressure on the ocular bulb] Bull Sci Médicales 1908; 79: 380.

47) Alexander JP. Reflex disturbances of cardiac rhythm during ophthalmic surgery. Br J Ophthalmol 1975; 59: 518-524.

48) Apt L, Isenberg S, Gaffney WL. The oculocardiac reflex in strabismus surgery. Am J Ophthalmol 1973; 76: 533-536.

49) Gharabaghi A, Koerbel A, Samii A, Kaminsky J, vonGoesseln H, Tatagiba M, Samii M. The impact of hypotension due to the trigeminocardiac reflex on auditory function in vestibular schwannoma surgery. J Neurosurg 2006; 104: 369-375.

50) Schaller B. Trigemino-cardiac reflex during transsphenoidal surgery for pituitary adenomas. Clin Neurol Neurosurg 2005; 107: 468-474.

51) Schaller B. Trigeminocardiac reflex during microvascular trigeminal decompression in cases of trigeminal neuralgia. J Neurosurg Anesthesiol 2005; 17: 45-48.

52) Kratschmer F. About reflexes of the nasal mucous membrane on respiration and circulation. Sber Akad Wiss Vienna 1870; 62: 147-170.

53) Rivard JC, Lebowitz PW. Bradycardia after alfentanil-succinylcholine. Anaesth Analg 1988; 76: 907.

54) Starr NJ, Sethna DH, Estafanos FG. Bradycardia and asystole following rapid administration of sufentanil with vecuronium. Anesthesiology 1986; 64: 521-523.

55) Schmeling WT, Kampine JP, Warltier DC. Negative chronotropic actions of sufentanil and vecuronium in chronically instrumented dogs pretreated with propanolol and/or diltiazem. Anaesth Analg 1989; 66: 4- 14.

56) Hornby PJ, Abrahams TP. Central control of lower esophageal sphincter relaxation. Am J Med 2000; 108: 90S-98S.

57) Shoja MM, Tubbs RS, Ansarin K, Farahani RM. Proposal for the existence of a nasogastric reflex in humans, as a potential cause of upper gastrointestinal symptoms. Med Hypotheses 2007; 69: 346-348.

58) Widdicombe JG. The physiology of the nose. Clin Chest Med 1986; 7: 159-170.

59) Hasegawa M, Kern EB. The human nasal cycle. Mayo Clin Proc 1977; 52: 28.

60) Kennedy DW, Zinreich SJ, Kumar AJ, Rosenbaum AE, Johns ME. Physiologic mucosal changes within the nose and ethmoid sinus: imaging of the nasal cycle by MRI. Laryngoscope 1988; 98: 928-933.

61) Cometto-Muñiz JE, Cain WS. Trigeminal and olfactory sensitivity: comparison of modalities and methods of measurement. Int Arch Occup Environ Health 1998; 71: 105-110.

62) Hummel T. Assessment of intranasal trigeminal function. International Journal of Psychophysiology 2000; 36: 147-155.

63) Frasnelli J, Hummel T. Intranasal trigeminal thresholds in healthy subjects. Environ Toxicol Pharmacol 2005; 19: 575-580.

64) Frasnelli J, Hummel T. Age-related decline of intranasal trigeminal sensitivity: is it a peripheral event? Brain Research 2003; 987: 201-206.

65) Hummel T, Schiessl C, Wendler J, Kobal G. Peripheral electrophysiological responses de-

crease in response to repetitive painful stimulation of the human nasal mucosa. Neurosci Lett. 1996; 212: 37-40.

66) Eccles R, Jawad H, Morris S. Olfactory and trigeminal threshold and nasal resistance to airflow. Acta Otalaryngol 1989; 108: 268-283.

67) Thürauf N, Friedel I, Hummel C, Kobal G. The mucosal potential elicited by noxious chemical stimuli with CO2 in rats: is it a peripheral nociceptive event? Neurosci Lett. 1991; 128: 297-300.

68) Rombaux P, Mouraux A, Bertrand B, Guerit JM, Hummel T. Assessment of olfactory and trigeminal function using chemosensory event-related potentials. Neurophysiol Clin 2006; 36: 53-62.

69) Rombaux P, Mouraux A, Keller T, Hummel T. Trigeminal event-related potentials in patients with olfactory dysfunction. Rhinology 2008; 46: 170-174.

70) Hummel T, Livermore A, Hummel C, Kobal G. Chemosensory event-related potentials: relation to olfactory and painful sensations elicited by nicotine. Electroencephalography and Clinical Neurophysiology 1992; 84: 192-195.

71) Hummel T, Barz S, Lötsch S, Kettenmann B, Kobal G. Loss olfactory function leads to a decrease of trigeminal sensitivity. Chemical Senses 1996; 21: 75-79.

72) Frasnelli J, Schuster B, Zahnert T, Hummel T. Chemosensory specific reduction of trigeminal sensitivity in subjects with olfactory dysfunction. Neuroscience 2006; 142; 541-546.

73) Sanico AM, Koliatsos VE, Stanisz AM, Bienenstock J, Togias A. Neural hyperresponsiveness and nerve growth factor in allergic rhinitis. Int Arch Allergy Immunol. 1999; 118: 154-158.

74) Koskela H, Di Sciascio MB, Anderson SD, Andersson M, Chan HK, Gadalla S, Katelaris C. Nasal hyperosmolar challenge with a dry powder of mannitol in patients with allergic rhinitis.Evidence for epithelial cell involvement. Clin Exp Allergy 2000; 30: 1627-1636.

75) Gerth van Wijk R, Dieges PH. Nasal hyper-responsiveness to histamine, methacholine and phantolamine in patients with perennial non-allergic rhinitis and in patients with infectious rhinitis. Clin Otolaryngol Allied Sci 1991; 16: 133-137.

76) Togias AG, Naclerio RM, Proud D, Fish JE, Adkinson NF Jr, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Nasal challenge with cold, dry air results in release of inflammatory mediators. Possible mast cell involvement. J Clin Invest 1985; 76: 1375-1381.

77) Braat JP, Mulder PG, Fokkens WJ, van Wijk RG, Rijntjes E. Intranasal cold dry air is superior to histamine challenge in determining the presence and degree of nasal hyperreactivity in nonallergicnoninfectious perennial rhinitis. Am J RespirCrit Care Med 1998; 157 (6 Pt 1): 1748-1755.

78) Kim YH, Jang TY. Diagnostic criteria of nonspecific hyperreactivity using cold dry air provocation with acoustic rhinometry. Otolaryngol Head Neck Surg 2011; 144: 91-95.

79) Segboer CL, Holland CT, Reinartz SM, Terreehorst I, Gevorgyan A, Hellings PW, van Drunen CM, FokkensWJ. Nasal hyper-reactivity is a common feature in both allergic and nonallergic rhinitis. Allergy 2013; 68: 1427-1434.

80) Kowalski ML, Dietrich-Miłobedzki A, Majkowska-Wojciechowska B, JarzebskaM.Nasal reactivity to capsaicin in patients with seasonal allergic rhinitis during and after the pollen season. Allergy 1999; 54: 804-810.

81) Van Gerven L, Boeckxstaens G, Jorissen M, Fokkens W, Hellings PW. Short-time cold dry air exposure: a useful diagnostic tool for nasal hyperresponsiveness. Laryngoscope 2012; 122: 2615-2620.

82) Segboer CL, Holland CT, Reinartz SM, Terreehorst I, Gevorgyan A, Hellings PW, van Drunen CM, Fokkens WJ. Nasal hyper-reactivity is a common feature in both allergic and nonallergic rhinitis.Allergy 2013; 68: 1427-1434.

83) Xiao J, Zhang H. Comparative evaluation of Jatropha curcas L. seed meals obtained by different methods of defatting on toxic, antinutritional and nutritive factors. J Food Sci Technol 2014; 51: 1126-1132.

84) Huvenne W, Callebaut I, Reekmans K, Hens G, Bobic S, Jorissen M, Bullens DM, Ceuppens JL, Bachert C, Hellings PW.Staphylococcus aureus enterotoxin B augments granulocyte migration and survival via airway epithelial cell activation. Allergy 2010; 65: 1013-1020.

85) Hox V, Vanoirbeek JA, Alpizar YA, Voedisch S, Callebaut I, Bobic S, Sharify A, De Vooght V, Van Gerven L, Devos F, Liston A, Voets T, Vennekens R, Bullens DM, De Vries A, Hoet P, Braun A, Ceuppens JL, Talavera K, Nemery B, Hellings PW. Crucial role of transient receptor potential ankyrin 1 and mast cells in induction of nonallergic airway hyperreactivity in mice. Am J Respir Crit Care Med 2013; 187: 486-493.

86) Soyka MB, Wawrzyniak P, Eiwegger T, Holzmann D, Treis A, Wanke K, Kast JI, Akdis CA. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-γ and IL-4.J Allergy Clin Immunol 2012; 130: 1087-1096.e10.

87) Knipping S, Holzhausen HJ, Riederer A, SchromT. Allergic and idiopathic rhinitis: an ultrastructural study. Eur Arch Otorhinolaryngol 2009; 266: 1249-1256.

88) Heppt W, Peiser C, Cryer A, Dinh QT, Zweng M, Witt C, Fischer A, Groneberg DA. Innervation of human nasal mucosa in environmentally triggered hyperreflectoric rhinitis. JOccup Environ Med 2002; 44: 924-929.

89) KortekaasKrohn I, Callebaut I, Alpizar YA, Steelant B, Van Gerven L, Skov PS, Kasran A, Talavera K, Wouters MM, Ceuppens JL, Seys SF, Hellings PW. MP29-02 reducesnasalhyperreactivityandnasalmediators in patientswithhousedust mite-allergicrhinitis. Allergy 2018; 73: 1084-1093.

90) Van Rijswijk JB, Boeke EL, Keizer JM, Mulder PG, Blom HM, FokkensWJ.Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy 2003; 58: 754-761.

91) Van Gerven L, Alpizar YA, Wouters MM, Hox V, Hauben E, Jorissen M, Boeckxstaens G, Talavera K, Hellings PW. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis. J Allergy Clin Immunol 2014; 133: 1332-9, 1339. e1-3.

92) Gevorgyan A, Segboer C, Gorissen R, van Drunen CM, Fokkens W. Capsaicin for non-allergic rhinitis. Cochrane Database Syst Rev 2015; 7: CD010591.