Nasal hyperreactivity*

R. Gerth van Wijk[1], C. de Graaf - in 't Veld[1], I.M. Garrelds[2]

[1] Dept. of Allergology, University Hospital Rotterdam,
[2] Institute of Pharmacology, Erasmus University, Rotterdam, the Netherlands

SUMMARY

Nasal hyperreactivity is an important feature of allergic and non-allergic rhinitis. This paper reviews the possible mechanisms behind hyperreactivity. Distinct mechanisms may play a role in allergic rhinitis -an inflammatory disease- and non-allergic rhininitis, mainly a non-inflammatory disease. In allergic rhinitis, particularly in perennial allergic rhinitis, there is a close connection between allergic response and non-specific hyperreactivity. In non-allergic rhinitis, a pathological entity comprising a heterogeneous series of diseases, understanding and measuring nasal hyperreactivity is much more difficult.

A variety of methods to assess nasal hyperreactivity are available. Given the heterogeneity of mechanisms, the various patients groups and the lack of standardization in tests, it is not surprising that measurement of nasal hyperreactivity is not included in the diagnostic arsenal of the clinician.

Key words: allergy, nasal hyperreactivity, rhinitis

INTRODUCTION

The notion that non-specific stimuli may precipitate nasal symptoms in-patients with rhinitis is well established. The concept of nasal hyperreactivity, however, has a shorter history than its counterpart in the lower airways.

While investigating the systemic effects of histamine (Weiss et al. 1932) and acetylcholine (Dale 1914) in man, it was noted that these agents precipitated asthmatic attacks in asthma patients. By comparison with healthy subjects and by determination of the dose required to induce a bronchial reaction, a dose-dependent hyperresponsiveness to histamine and acetylcholine could be demonstrated in asthmatic patients (Curry, 1946; Curry, 1947).

It was in the sixties that Dutch investigators explored the field of nasal hyperreactivity. In 1960 van Lier found that veratrine (a mixture of alkaloids) induced a sneeze response in patients with grass pollen allergy (van Lier, 1960). The response to veratrine appeared to increase during the pollen season. Grobler (1966) demonstrated an increased responsiveness to histamine comparing healthy subjects and patients with rhinitis.

In 1968 Connell performed already classical experiments showing that repeated exposure to ragweed pollen increased the nasal sensitivity to pollen. After allergen exposure less pollen was required to induce a nasal response. This phenomenon - also called nasal priming - appeared to be a temporary effect, as normal responsiveness was observed a few days after the last allergen exposure (Connell, 1968). Nowadays it is recognized that this priming effect is based on a generally increased responsiveness to stimuli after allergen exposure.

Patients with rhinitis and asthma may show a striking resemblance with respect to hyperreactivity of the airways. However, mere extrapolation of hypotheses formulated for patients with asthma to rhinitis patients is not justified. Fundamental differences between the end-organs (i.e. nose and lungs) may explain the differences between rhinitis and asthma.

THE CONCEPT OF NASAL HYPERREACTIVITY

One of the characteristics of rhinitis is the ability to react on exposure to non-specific stimuli such as tobacco smoke, perfume, dust and paint. In addition, many investigators have demonstrated that patients with rhinitis may have an exaggerated response to agents such as histamine, methacholine, capsaicin and other substances. Partial correlation between histamine responsiveness and the ability to respond to non-specific stimuli encountered in daily life has been established (Gerth van Wijk, 1989). This overall hyperresponsiveness to non-specific stimuli in daily life or non-specific agents applied in the nose is called nasal hyperreactivity. By this definition nasal hyperreactivity is a feature of nasal disease and not a disease of its own. Sometimes, the term "non-specific hyperreactivity" is used as a synonym of non-allergic rhinitis. Although patients with non-allergic rhinitis -but not all- may experience nasal symptoms

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provoked by non-specific stimuli, nasal hyperreactivity is also seen in patients with allergic rhinitis.
Nasal hyperreactivity is complex, as different tissues in the nose may be involved. Not only different types of nasal tissue (vascular, glandular) but also different neuroregulatory systems (adrenergic, cholinergic, peptidergic) may determine the type of reaction to nasal stimulation.
In the past several possible mechanisms have been proposed to explain nasal hyperreactivity.

Increase in epithelial permeability
One hypothesis is that epithelial damage with concomitant increased epithelial permeability leads to increased accessibility for stimuli to sensory nerve endings, vessels and nasal glands. Although Buckle and Cohen found that 125I-albumine penetrated better in nasal mucosa of patients with rhinitis than healthy subjects (Buckle, 1975), recent studies do not support this. Inflammatory processes after allergen challenge (Svensson, 1995) or during natural exposure (Svensson, 1990) lead to plasma exudation. Outward exudation of plasma proteins is not accompanied by an increased inward absorption of ^{51}Cr-EDTA. It appeared that nasal mucosa absorption permeability was decreased during seasonal allergic rhinitis (Greiff, 1993) or unchanged during common cold (Greiff, 1994). In fact, it has been suggested that plasma exudation will tighten the nasal mucosa (Svensson, 1998). If this holds true, nasal responses in hyperreactive individuals are elicited in spite of a diminished accessibility of stimuli.

Altered neuromodulation
Increased sensitivity of sensory nerve endings would induce an exaggerated response to normal stimuli. Some mediators such as prostaglandins and peptidoleukotrienes modulate sensory nerve function, making it easier to stimulate nerves (Baraniuk, 1998). Changed modulation of afferent impulses in the central nervous system has been put forward in explanation. It has been hypothesized that in animals stress may result in loss of hypothalamic control over sympathetic innervation, resulting in a relative dominance of the parasympathetic system (Eccles, 1981). Confirmatory data are lacking, however.
It has been shown that patients with non-allergic rhinitis react differently from healthy controls in nasal resistance changes when exposed to autonomic stimuli (isotonic or isometric exercise, cold applied to the face, axillary pressure etc.)(Jones, 1997). It has been suggested that non-allergic rhinitis is a condition of autonomic imbalance and nasal hyperreactivity in non-allergic patients might be explained by autonomic imbalance. Evidence, however, is only circumstantial.

End-organ hyperresponsiveness
Alterations in responsiveness of glands or vasculature to stimuli may be the basis of hyperreactivity. It has been shown that allergic subjects react to methacholine with an increased secretory response (Druce, 1985). Patients with non-allergic rhinitis may also react to methacholine (Stjarne, 1989). However, this response is seen only in subjects predominantly bothered by a runny nose. Methacholine stimulates nasal glands without involvement of neural reflexes, pointing to an increased affinity or density of muscarinic receptors (van Megen, 1989).
Control in vascular tone is regulated by the non-adrenergic non-cholinergic neurotransmitters VIP and NP-Y, while stimulation of -adrenergic receptors causes vasoconstriction and stimulation of -adrenergic receptors has little effect (Jones, 1997). Changes in α- or β-receptors were not found in allergic rhinitis (van Megen, 1989), however VIP staining nerve fibers responsible for vasodilatation have been demonstrated in allergic rhinitis at a higher level than seen in healthy subjects or non-allergic patients (Fang, 1997).
In vivo increased responsiveness of nasal vessels resulting in vasodilatation may be demonstrated by directly acting substances such as histamine. Both in allergic and non-allergic rhinitis patients histamine hyperresponsiveness in terms of changes in nasal airway resistance or nasal dimensions has been shown by some investigators (Corrado, 1986; Hilberg, 1995), but not by others (Gerth van Wijk, 1987, 1991).
Microvascular exudative hyperresponsiveness described by Svensson has been shown in seasonal allergic rhinitis during the birch pollen season (Svensson, 1998). Histamine, 40μg and 400μg/ml, induced a dose-dependent increase of plasma proteins such as α^2-macroglobulin and albumin in nasal lavage fluid at a significantly increased level during the season compared to the challenge outside the season. Increased responsiveness of endothelial cells of the postcapillary venules, loss of endogenous factors with stabilizing effects on the endothelial cells and inhibition of nitrogen oxide have been suggested as possible causes of this form of hyperresponsiveness.
In recent years our knowledge about the pathophysiological backgrounds of nasal hyperreactivity has increased. However, it appears that an overall theory covering all aspects of nasal hyperreactivity is too simplistic taking into account the different aspects of hyperreactivity, the different nasal tissues involved and the different ways patients express their symptoms.

HYPERREACTIVITY AND NASAL ALLERGY

It is well know that allergic rhinitis and bronchial asthma are basically inflammatory diseases. As nasal and bronchial hyperreactivity are regarded as hallmarks of these disorders it is attractive to adopt the concept that hyperreactivity is superimposed on an allergic inflammatory response and that inflammation and hyperreactivity are linked.
For many years it has been recognized that eosinophils and eosinophil activation are important in bronchial asthma. However, although presence and activation of eosinophils characterize allergic rhinitis, close connections between nasal function and eosinophils in nasal secretion are less clear. Klementsson (1991) found no correlation between nasal lavage eosinophils and allergen-induced hyperreactivity. Moreover, Andersson showed that nasal lavage eosinophils and ECP levels observed during an initial allergen challenge are not correlated with the degree of increase of nasal responsiveness to an allergen rechallenge. Although corticosteroids did abolish nasal hyperreactivity, in this study ECP-levels in nasal lavage fluid before the ini-

tial challenge and rechallenge were not affected (Andersson, 1989). This is in line with the observation that in some patients allergic to grass pollen allergen challenge did increase nasal responsiveness to histamine without any evidence of a late phase clinical or inflammatory reaction several hours after challenge (Gerth van Wijk, 1992).

These observations did give rise to the question whether perennial allergic rhinitis is more suitable to study nasal hyperreactivity and inflammation. Is it possible that chronic and continuous exposure to antigens creates a situation more comparable with bronchial asthma, a disease with a tighter connection between late phase reaction, airway inflammation and non-specific hyperreactivity? In contrast, the patient with a pollen allergy provides us with a model to monitor the allergic reaction from a resting state, as in pollen allergy experiments are virtually always investigated outside the pollen season.

In a series of studies several observations underline the connection between early and late phase nasal reaction on the one hand and nasal hyperreactivity on the other. In a study with patients allergic to house dust mites it was possible to predict the early and late phase allergic reaction after allergen challenge from both skin test reactivity to house dust mite extract and nasal hyperreactivity (Gerth van Wijk, 1993).

Vice versa, in another challenge study the nasal reaction to histamine 24 hours after allergen challenge appeared to be correlated with the early and late phase allergic reaction 24 hours before (de Graaf, 1997). It was possible to distinguish patients with an early allergic reaction from patients with a biphasic clinical response. The latter patient group was characterized by an increase in albumin efflux in nasal lavage during the late phase. Moreover, ECP release as an expression of eosinophil activation was also more prominent in late phase responders. Patients with a biphasic response showed stronger nasal responses to histamine application into the nose compared with subjects showing an isolated early response only. These results suggest that nasal hyperreactivity requires a certain level of inflammation.

Support for the connection between nasal hyperreactivity and airway inflammation could also be found in a study with 48 patients with perennial allergic rhinitis. In those patients a weak correlation ($r=0.31$; $p=0.035$) was seen between nasal responsiveness to histamine and the number of eosinophils in nasal secretion (de Graaf, 1996). The relatively low correlation between eosinophils and nasal hyperreactivity suggests that non-specific hyperreactivity and nasal symptoms in general cannot be attributed to the presence and activation of one type of cells.

The connection between nasal hyperreactivity and inflammation has been extensively investigated in a series of Japanese studies. Recently, Terada et al., (1998) confirmed our observation that patients with a late phase allergic reaction express a higher level of histamine sensitivity than patients with an isolated early response do. Earlier investigations showed that there is a significant inverse correlation between the eosinophil count and ECP concentration in nasal washings and the histamine threshold value (Terada, 1994). Moreover, the fact that repeated nasal application of eosinophil-derived mediators ECP, PAF and leukotrienes increases histamine reactivity (Terada, 1992; Konno, 1988) provides us with further evidence that nasal inflammation and in particular eosinophil activation is related with upper airway hyperresponsiveness.

Another method to elucidate a possible association between inflammation and hyperreactivity is to compare the effects of corticosteroids -effective anti-inflammatory agents and antihistamines- with no or with less pronounced effects on inflammation on allergen-induced hyperreactivity.

In a series of studies we investigated the effect of intranasal corticosteroids (de Graaf, 1995; Garrelds, 1994, 1995) and antihistamines (de Graaf, 1995; Garrelds, 1994) on the nasal allergic reaction.

Patients allergic to house dust mites and challenged with allergen showed a reduced immediate and late phase response after treatment with fluticasone propionate aqueous nasal spray. The nasal response to histamine was also diminished (de Graaf 1995). Not only clinical symptoms were affected; the influx of albumin, tryptase and ECP was also reduced in treated patients. Intranasal corticosteroid tended to decrease platelet activating factor and eicosanoid production (Garrelds, 1994) indicating the extensive mode of action of corticosteroids.

After allergen challenge dual responders showed increased levels of the cytokine interleukin-5, which levels were diminished after fluticasone administration (Garrelds, 1995). In a study with a similar design we looked at the properties of the H1 antagonist nasal spray levocabastine (de Graaf, 1995). In spite of the predominant effect on the early phase allergic reaction, no reduction of inflammatory mediators in nasal lavage fluid or diminution of nasal hyperreactivity in terms of methacholine responsiveness was seen. A good comparison was hampered by differences in patient groups studied. The patients participating in the fluticasone trial showed more pronounced late phase reactions, in spite of comparable immediate reactions. The absence of anti-inflammatory properties of levocabastine, however, was confirmed by its inability to inhibit allergen-induced histamine release in blood basophils (Garrelds 1996).

In conclusion nasal hyperreactivity and airway inflammation appear to be linked, in particular in perennial allergic rhinitis.

In addition to these observations we addressed the question how important nasal hyperreactivity is in nasal allergy. To this purpose we tried to predict the outcome of rhinitis-related quality of life questionnaires and symptom scores from nasal histamine challenge results. Although it was not possible to predict quality of life impairment very precisely, histamine challenge results correlated significantly with overall daily nasal symptoms ($r=0.43$) and overall quality of life ($r=0.59$) (de Graaf, 1996). These results suggest that assessment of nasal hyperreactivity provides us to some extent with an estimate of rhinitis severity and impairment in quality of life of rhinitis patients.

HYPERREACTIVITY AND NON-ALLERGIC RHINITIS

Nasal hyperreactivity as a feature of non-allergic rhinitis is less well studied and clarified. Increased methacholine and capsaicin responsiveness has been demonstrated in non-allergic patients

with sneezing and running nose as their main complaints (Gerth van Wijk, 1991; Stjarne, 1989). Patients characterized by nasal blockage or unselected rhinitis patients, however, are not characterized by histamine or methacholine hyperresponsiveness (Gerth van Wijk, 1991). With rhinostereometry, an optic method for detection of changes less than 1 mm in nasal congestion, it was possible to demonstrate histamine responsiveness in non-allergic patients with rhinitis (Graf, 1996).

Recently, it was shown that well selected patients with perennial non-allergic rhinitis did respond to cold dry air challenges (Braat, 1998). In this study cold dry air challenges appeared to be superior to histamine challenges. The precise mechanism behind cold dry air responsiveness is not known. Togias demonstrated that increased release of mast cell mediators in nasal tissue is responsible for this phenomenon (Togias, 1985). The patients in this study were selected -irrespective of their atopic state- by a history of nasal complaints after cold air exposure, whereas in the former study the absence of atopy and the presence of severe symptoms selected patients.

Studies with non-allergic rhinitis patients and comparison of data are hampered by the heterogeneity of patients.

Although non-allergic patients may be characterized by eosinophilic infiltrate and responsiveness to intranasal corticosteroids, so-called NARES patients (Settipane, 1985), recent studies suggest that non-allergic rhinitis is basically a non-inflammatory disease with non-responsiveness to corticosteroids (Blom, 1995, 1997). It is plausible to assume that in these patients nasal hyperreactivity is based on other mechanisms than in patients with allergic rhinitis or NARES. Circumstantial evidence for this assumption can be found from the observation that repeated application of capsaicin diminishes nasal symptoms in non-allergic rhinitis patients (Blom, 1997), whereas capsaicin does not affect nasal responsiveness to allergen and histamine in patients allergic to house dust mites (Gerth van Wijk, personal communication).

ASSESSMENT OF HYPERREACTIVITY

Although assessment of bronchial hyperresponsiveness by determining PC_{20} histamine or methacholine is a standard procedure in the diagnosis and management of asthmatic patients, determination of nasal hyperreactivity is not commonly used in the diagnosis and treatment of patients with rhinitis. A striking lack of standardized methods is one of the causes. The main problem might be that the variety of agents used in challenge test have different functions and act on different compartments (vascular, glandular, neural) of the nose (Table 1). Given the heterogeneity of allergic and non-allergic patients encountered in research and daily practice it is not surprising that measurement of nasal hyperreactivity has not gained a position in the diagnostic arsenal of the clinician. Moreover, although differences in hyperreactivity can be found between study populations *at a group level*, valid tests to measure hyperreactivity in the individual patient are not available. Therefore, in a position paper from the Standardization Committee on Objective Assessment of the Nasal Airway (to be published) nasal challenges with non-specific stimuli will not be advocated for clinical practice, only for research.

CONCLUSIONS

Nasal hyperreactivity is an important feature of nasal disease. However, hyperreactivity cannot be described in terms of clear-cut mechanisms and methods of assessment. The ability to react to non-specific stimuli in an exaggerated way may be dominated by various nasal compartments in different patient groups. Possibly, data obtained from one patient group cannot be extrapolated to another. In particular, the pathophysiological mechanisms behind non-allergic rhinitis and its various phenotypes are not clarified very well, which makes it difficult to comprehend the role of nasal hyperreactivity in this heterogeneous disease. Therefore, it is understandable that we are far from measuring nasal hyperreactivity in daily nasal practice.

Table 1. Methods and agents in the assessment of nasal hyperreactivity.

Agent	Response	Target organ/ path way	Method of assessment	Hyperreactivity in allergy	Hyperreactivity in non-allergic rhinitis
Histamine	plasma exudate	nasal vasculature	weighing secretion and measuring plasma proteins	yes (Svensson 1998, Gerth van Wijk 1987)	trend (Gerth van Wijk, Togias 1993)
	glandular secretion	neuronal			
	nasal congestion	nasal vasculature	rhinomanometry	conflicting data	no (Gerth van Wijk, 1991) N.D.
			acoustic rhinometry	yes (Hilberg 1995)	
			rhinostereometry	N.D.	yes (Graf (1996)
	sneezes	neuronal		yes (Gerth van Wijk 1987)	trend in runners (Gerth van Wijk, 1991)
Methacholine	glandular secretion	nasal glands	weighing secretion	yes (Gerth van Wijk 1987, Druce 1985)	in runners (Gerth van Wijk 1991, Stjarne 1989)
Bradykinin	glandular secretion	neuronal	weighing secretion	yes (Riccio 1996)	not known
	sneezes				
Cold dry air	congestion	nasal vasculature	rhinomanometry	N.D.	yes (Togias 1985; Braat 1998)
	secretion	neuronal	weighing secretion		
Capsaicin	glandular secretion	neuronal	weighing secretion	yes (Sanico 1998)	in runners (Stjarne 1989)
	plasma exudate	nasal vasculature	plasma proteins		

Reviewing the literature, a lack of standardization in terminology and patient criteria becomes apparent. The efforts made in research to understand hyperreactivity in its different manifestations should include consensus and clear-cut definitions about terminology and characterization of patients studied.

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Dr. R. Gerth van Wijk
Dept. Allergology
University Hospital Rotterdam
Dr. Molewaterplein 40
3015 GD Rotterdam
The Netherlands