Introduction

The research on gustatory and olfactory senses have not been fully developed as compared to those on visual and auditory functions. Yet these senses contribute significantly to one’s QOL in everyday life. Due to hearing difficulty, aged people tend to be isolated from their communities and also from participating in social activities. Considering these aspects, gustatory and olfactory disturbances among them may interfere with their desire to live and enjoy...
their lives.

At the beginning of the 21st century, our aging society continues to be complex and faces further problems to be solved. The pathophysiological elucidation of various olfactory disturbances and the development of new therapeutic methodology are much desired. The current situation is presented in this literature.

**Chronic Paranasal Sinusitis**

Paranasal sinusitis is the most frequent cause of olfactory disturbances in Japan.\(^1\) It is true that sequential changes that occur at the olfactory mucosa caused by paranasal sinusitis have not been investigated sufficiently. Nor have appropriate animal models been found that are suitable for such studies. Therefore, we prepared a model for experimental paranasal sinusitis by using rats to elucidate the mechanism by which olfactory disturbances develop and to conduct histological observations of the olfactory epithelium and olfactory bulb.\(^2\)

I. Pathophysiology

(1) Olfactory disturbance

**(direct effects of sinusitis)**

A foreign material (polyvinyl acetal) coated with *Staphylococcus aureus* was inserted into one of the nasal cavities of rats and 3, 7, 14, 21, and 28 days later, samples from the nasal cavity and olfactory bulb were collected (from 10 animals at each experiment) to prepare coronal sections. HE stain was applied to the samples from the nasal cavity to examine the maxillary sinus and ascertain the onset of paranasal sinusitis.

The HE-stained nasal sinus section obtained from the rats affected by paranasal sinusitis was used to measure the thickness of the olfactory epithelium. The sections from the nasal cavity of the rats with paranasal sinusitis were used for immunohistological observation of the olfactory epithelium by using the following antibodies: anti-protein gene product 9.5 (PGP9.5) antibody, anti-proliferating cell nuclear antigen (PCNA) antibody, anti-single-stranded DNA (ssDNA) antibody, and anti-inducible nitric oxide synthase (iNOS) antibody. To ascertain the presence (or absence) of changes to the central olfactory system, an immunohistological study was conducted on the olfactory bulb samples of the rats affected by paranasal sinusitis by using an anti-tyrosine hydroxylase (TH) antibody.

The results of these observations may be summarized as follows: The onset of paranasal sinusitis was confirmed in 6 animals after 3 days, 7 animals after 7 days, 6 animals after 14 days, 6 animals after 21 days, and 7 animals after 28 days following exposure to *Staphylococcus aureus*. Inflammation developed in the olfactory epithelium that was affected by paranasal sinusitis within 3 days and the inflammatory condition persisted even after 28 days. The thickness of the olfactory epithelium, the number of olfactory cell layers, and the count of the olfactory cells per 100\(\mu\)m\(^2\) of the olfactory epithelium continued to be markedly reduced until after 21 days. The olfactory neurofibril bundles became elongated and scarce in proportion to the time (i.e., number of days) that the foreign body was retained in the nasal cavity. The olfactory cell regenerating activity was markedly reduced for the initial 7 days and hardly recognized on the 21st or 28th day. Apoptosis of the olfactory cells was most pronounced on the 3rd and 7th days, after which the activity was reduced and became barely recognizable on the 21st or 28th day. The iNOS expression in the olfactory epithelium was hardly noted in the normal olfactory epithelium. The enzyme expression was abundant around the basal cells of the samples obtained from the animals with paranasal sinusitis; but it was somewhat reduced where the olfactory epithelium had undergone marked degeneration. In the olfactory bulb, the TH expression of the juxtaglomerular cells began to be reduced on the 7th day and became much reduced on the 21st and 28th days.

It has been shown for the first time that in
addition to the olfactory epithelium, histological changes develop in the olfactory bulb and central olfactory disturbances may occur in chronic paranasal sinusitis.

(2) Olfactory disturbance (indirect effects of sinusitis)

Inflammatory changes in the olfactory cleft, nasal polyps, especially those of the olfactory cleft, and excessive secretion that are caused by sinusitis have been pointed out. It is well known that these conditions are also accompanied by morphological deviations of the nasal cavity, such as accentuated curved nasal septum and nodules of the nasal septum. The pathophysiology of olfactory disturbances caused by chronic paranasal sinusitis may therefore be summed up as the so-called mixed olfactory dysfunctions, where the aforementioned olfactory epithelial changes and respiratory olfactory dysfunction — due to deviations in air flow within the nasal cavity — are involved.

2. Treatment

Needless to add, the treatment of chronic paranasal sinusitis, the cause of olfactory disturbances, also constitutes the basis of treatment of the latter.

(1) Surgical treatment

Surgical correction of morphological deviations of the nasal cavity — e.g., modification of the nasal septum, excision of the turbinate, and elimination of nasal polyps — and endoscopic surgery of the paranasal sinus are effective in improving respiratory or mixed olfactory disturbances. However, complete recovery from extensive and multiple polyps is difficult. It has been reported that the recovery rate is about 50%.3)

(2) Drug therapy

(i) Nasal instillation, nasal spraying, or local injection of adrenal cortex hormones

With the patient in the head-down (chin-up) position, 1 to 2 drops of a 0.1% solution of betamethasone sodium (Rinderon®) are instilled in the nasal cavity 3 to 4 times a day, during which time the patient is instructed to hold the position for about 5 minutes. If no improvement is seen within one month, the medication is discontinued. When the patient is unable to hold his head in the specified position or he has chronic sinusitis or has recently undergone surgery, the same preparation is sprayed from an atomizer twice a day. Topical application of 2 mg/0.5 mL of dexamethasone or 40 mg/1 mL of methylprednisolone to the olfactory mucosa is also recommended. Both are applied once every 2 weeks and repeated 4 to 6 times.

(ii) Oral medication

Recently, long-term application of a small amount of macrolide antibiotics has been recommended as a conservative or postoperative adjuvant therapy for chronic paranasal sinusitis. This medication is usually combined with ethyl L-cysteine hydrochloride (Cystanin®) or L-carbocysteine (Mucodyne®).

(iii) Therapeutic modalities projected in the near future

For the etiology of chronic paranasal sinusitis, it has been proven that inflammatory cytokines (e.g., IL-1β, TNF-α, GM-CSF, and IL-6) are involved. Therefore, much is expected from gene therapy to control the genes responsible for the expression of these cytokines at the genetic level or chemotherapy targeted at these genes.

Olfactory Disturbances Following a Common Cold

It is understood that olfactory disturbances complicating upper respiratory inflammation are caused by nasal occlusion, swelling of the nasal mucosa, or edema of the mucosa of the olfactory cleft. Most of these symptoms are transient, being eliminated in 2 to 3 days. However, in some instances they may develop after a cold and their prognosis is considered to be poor. The condition frequently affects women between 40 to 69 years of age.4) The question of the exaggerated susceptibility to infection by viruses from the olfactory nerve and the resistance to recovery from disturbances in this
age range, as well as the higher frequency of occurrence among women, have not been fully elucidated.

1. Pathophysiology

Excessive secretion or dryness of the olfactory mucosa and ciliary dysfunctions of the olfactory cells due to acute inflammation and subsequent secondary infection following viral diseases may explain the development of olfactory disturbances. Histopathological findings from the material obtained by a biopsy of the olfactory mucosa were presented by Tomlinson, who cited central nervous dysfunction via the olfactory nerve, and by Yamagishi, who called attention to a reduction in the number of olfactory cells.

2. Treatment

For peripheral or central olfactory disturbances, vitamin B₁₂, vitamin A, and adenosine triphosphate (ATP) are commonly used. There is a report that extols the favorable effect of Oriental medicine (e.g., Toki-Shakuyaku-San and Keishi-Bukuryo-Gan). Sometimes the serum zinc content is reduced, with rapid loss of the gustatory and olfactory sensations and a resultant acute loss of taste for food. Whether the state is acute or chronic, it has been pointed out that reductions in the serum zinc level result in anorexia and gustatory and olfactory disturbances. It is not certain why a drop in the serum zinc level triggers these symptoms. In the brain, the zinc content is at the highest in the hippocampus, followed by the cortex, stria, and cerebellum. It is also known that zinc exists at a high concentration at the terminals of the mossy fibers of the cerebellum and hippocampus, suggesting that zinc is involved in the functioning of the central nervous system.

Parosmia

If a loss or reduction in the olfactory function represents quantitative deviations of olfactory functions, parosmia is typical of qualitative disturbances of the same function. In clinical patients, parosmia may be found in olfactory dysfunctions following a cold (mentioned earlier) and following trauma suggestive of disruption of the olfactory fibers. Characteristically, parosmia develops after some time has elapsed, instead of immediately after olfactory dysfunctions.

1. Pathophysiology

Instead of remaining viable throughout one’s life, the olfactory cells die after a certain time, repeating regeneration through division and proliferative processes. Specifically, the old cells are replaced by new olfactory cells that are generated by division of the stem cells of the basal layer so that the axons of new olfactory cells may constantly project to the olfactory bulb.

According to a recent finding, the site of the olfactory bulb to which the axons of olfactory cells project is well preserved in individuals and remains constant throughout one’s life. In other words, the axons that have newly developed accurately recognize the sites on the glomeruli: by projecting toward these sites, the “olfactory map” on the olfactory bulb is continually being recreated and maintained.

In parosmia, however, it is understood that axonal projection occurs at different sites on the olfactory bulb following regeneration. An olfactory stimulus may be detected by re-projection through neural regeneration but projection to a different site results in the perception of a different type of olfactory stimulus.

2. Treatment

The current therapeutic modalities are generally similar to those applied to the peripheral and central olfactory disturbances described above. In addition, administration of vitamin A, which is known to affect differentiation and proliferation of the olfactory epithelium, has been reported. Leopold, et al. ruled out the efficacy of vitamin A; instead they cited a case of parosmia in which unilateral excision of the
olfactory mucosa was found to be effective.\textsuperscript{13)} They attributed the improvement of the symptom to appropriate nerve projection pathway but this case is somewhat unique and follow-up studies are needed to prove the validity of the procedure.

3. Therapeutic procedures for the near future

Apoptotic death of the olfactory cells has been observed in the early stage following disruption of the olfactory fibers in experiments using mice and rats. It was proven that the number of olfactory cells and the thickness of the layer of these cells are reduced; but within 3 to 4 weeks, regeneration of these cells is completed, thus restoring the olfactory activities and functions. It is readily conceivable that similar processes take place in man. Prognosis is poor in those clinical patients who suggest disruption of their olfactory fibers: the olfactory function cannot be restored in most of these patients.

For the cause of parosmia, incomplete connection between olfactory fibers and the olfactory bulb — in spite of the regeneration of the olfactory cells — is considered. It is believed that the formation of granulation tissue around the lamina cribiform is the most significant disturbance. Therefore preventing the formation of granulation tissue at the site noted above or enabling the neural connection in spite of the presence of the granulation tissue will lead to the development of new therapeutic approaches.

In Closing

Recent pathophysiological findings on chronic paranasal sinusitis (a condition most often cited as the cause of olfactory disturbances in Japan), olfactory disorders consequent to the common cold, and parosmia were presented. Trends in the therapeutic modalities projected in the near future (including gene therapy) were also introduced.

REFERENCES

12) Costanzo, R.M.: Rewiring the olfactory bulb: changes in odor maps following recovery from...