Olfactory Training
as a treatment option for Patients with Olfactory Dysfunction

Sama Mosaed AlOhali
KSU Medical Intern
28/12/2016
Outline

• Review of clinical olfaction

• Sniffin Sticks Test

• Olfactory Training

• Other medical treatment trials
Anatomy & Physiology

NEUROSCIENCE Se, Figure 15.1 (Part 1)
Before an odorant can activate a receptor it must first reach the olfactory cleft. The pathway of odorant exposure to the nasal cavity is usually thought to occur through an anterior pathway via the nares and anterior nasal cavity. It has become clear, however, that a retronasal stimulation of the olfactory epithelium is also important and probably plays a role in flavor appreciation during eating. This secondary pathway is important in cases of anterior nasal obstruction from polyp disease, in which odor identification appears to be more effective through a retronasal route.

Olfactory nerve is not alone

The trigeminal nerve, is a chemosensory system and can detect the presence of almost all odors at a high enough concentration. Therefore, anosmics will still have the ability to detect strong trigeminal-activating odors such as menthol and ammonia.

# Olfactory Disorders

<table>
<thead>
<tr>
<th>Disorders of detection</th>
<th>Disorders of identification (dysosmia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normosmia</td>
<td>Normal function</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>Decreased ability to detect odors</td>
</tr>
<tr>
<td>Anosmia</td>
<td>Inability to smell</td>
</tr>
<tr>
<td>Parosmia</td>
<td>Altered odor perception with odor present</td>
</tr>
<tr>
<td>Phantosmia</td>
<td>Perception of smell without odor present</td>
</tr>
</tbody>
</table>
Olfactory Dysfunction Classification

- **Conductive disorder** (tumors, nasal packing, stenosis, congenital, CRS with polyps)

- **Sensorineural disorders** (URTI, head trauma, Neurodegenerative disorders, congenital, CRS)

19% Of the general population have Olfactory Dysfunction

Etiology

Table 3 Result of data from smell testing at several research centers

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Cain</th>
<th>Miwa</th>
<th>Seiden</th>
<th>Temmel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasosinus disease</td>
<td>30.2 %</td>
<td>21.4 %</td>
<td>14 %</td>
<td>21 %</td>
</tr>
<tr>
<td>Post-URI</td>
<td>18.6 %</td>
<td>17.1 %</td>
<td>18 %</td>
<td>36 %</td>
</tr>
<tr>
<td>Head trauma</td>
<td>8.6 %</td>
<td>17.1 %</td>
<td>18 %</td>
<td>17 %</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>21.0 %</td>
<td>28.4 %</td>
<td>18 %</td>
<td>18 %</td>
</tr>
</tbody>
</table>


Sniffin’ Sticks test

- Developed by *Hummel* in 1997
- Objective assessment method of the olfactory system
- **Olfactory Testing** for odor *threshold*, odor *discrimination*, and odor *identification*
1) **Threshold**: Three pens are presented to the patient in a randomized order, two contains odorless solvent, and the third contains an odorant in a certain dilution or concentration. The patient’s task is to indicate the pen with the odorant. Concentration is increased if one of the blanks was chosen and decreased if the correct pen was identified.
2) **Discrimination:** three pens are used, two with identical odors and a different one. The patient’s is asked to indicate the pen which had a different smell.
3) **Identification**: 16 pens containing common odors are used. The patient has to identify each of the odorants.
Sniffin’ Sticks test

• Scores reported as TDI-score with a maximum of 48 points

>30.5: Normosmia

16.5-30: Hyposmia

<16.5: Anosmia
University of Pennsylvania Smell Identification Test

- It consists of four cards with 10 odors, one per page. Stimuli are contained in plastic microcapsules on a brown strip on the footnote. The examiner asks the patient to scrape the strip with a pencil, which releases the odor. The patient then marks the option that best describes the odor.

- The test is scored out of 40 items

University of Pennsylvania Smell Identification Test

Use of Olfactory Training in Post-Traumatic and Postinfectious Olfactory Dysfunction

Iordanis Konstantinidis, MD, PhD; Evangelia Tsakiropoulou, MSc, MD; Paschalia Bekiaridou, MD; Chrysa Kazantzidou, MD; Jannis Constanttinidis, MD, PhD

Objectives/Hypothesis: There is evidence that the olfactory system can be modulated by repeated exposure to odors, a procedure called olfactory training. The aim of this study was to assess the effectiveness of olfactory training in patients with postinfectious and post-traumatic olfactory dysfunction.

Study Design: Prospective study of 119 patients with postinfectious and post-traumatic olfactory dysfunction.

Methods: Two groups of patients (postinfectious and post-traumatic) performed the olfactory training (n = 49 and n = 23, respectively) over a period of 16 weeks and were compared with two control groups of the same etiology (n = 32 and n = 15). Patients with sinonasal, neurologic, or idiopathic disease were excluded. Training was performed twice daily with the use of four odors (phenyl ethyl alcohol [rose], eucalyptol [eucalyptus], citronellal [lemon], and eugenol [cloves]). Olfactory testing was performed by means of the Sniffin’ Sticks test battery (threshold, discrimination, identification) at the time of diagnosis, and 8 and 16 weeks later. All patients evaluated their olfactory function by means of a visual analogue scale (0–100).

Results: Compared to controls, training patients in both groups presented significantly higher scores of olfactory function as measured by the Sniffin’ Sticks test. This increase was measured in 67.8% of postinfectious and 33.2% of post-traumatic patients. Subjective ratings were in accordance with the olfactory test results. Subset analysis showed that main olfactory function mainly increased olfactory identification followed by discrimination in both training groups.

Conclusions: The present study suggests that a 16-week short-term exposure to specific odors may increase olfactory sensitivity in patients with postinfectious and post-traumatic olfactory dysfunction.

Key Words: Anosmia, post-traumatic, postinfectious, olfactory training.

Level of Evidence: 3b.

Laryngoscope, 123:EB5–E90, 2013
Results at end of 16 weeks

Fig. 1. Percentages of individual improvement, no change, or worsening within the study groups (change in the threshold/discrimination/identification score of olfactory function of ≥6). URTI = upper respiratory tract infection.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>URTI Group, n = 81</th>
<th>Post-Traumatic Group, n = 38</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Training, n = 49</td>
<td>Control, n = 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>51.5 ± 5.2</td>
<td>53.1 ± 4.4</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Gender, No.</td>
<td>15 M/34 F</td>
<td>11 M/21 F</td>
<td>.1/03</td>
<td></td>
</tr>
<tr>
<td>Duration of disease, mo</td>
<td>9.2 ± 3</td>
<td>8.7 ± 2.5</td>
<td>.87</td>
<td></td>
</tr>
<tr>
<td>Patients with imaging findings, No.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>TDI, baseline</td>
<td>18.95 ± 2</td>
<td>19 ± 2.3</td>
<td>.9</td>
<td></td>
</tr>
<tr>
<td>TDI, 16 weeks</td>
<td>25.2 ± 1.8</td>
<td>20.5 ± 2</td>
<td>&gt;.001</td>
<td></td>
</tr>
<tr>
<td>Identification baseline</td>
<td>8.6 ± 1.4</td>
<td>8.8 ± 1.7</td>
<td>.77</td>
<td></td>
</tr>
<tr>
<td>Identification, 16 weeks</td>
<td>12.2 ± 1.3</td>
<td>9.6 ± 1.2</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Threshold, baseline</td>
<td>2.4 ± 1.4</td>
<td>2.3 ± 1.6</td>
<td>.91</td>
<td></td>
</tr>
<tr>
<td>Threshold, 16 weeks</td>
<td>2.5 ± 1.3</td>
<td>2.6 ± 1.8</td>
<td>.9</td>
<td></td>
</tr>
<tr>
<td>Discrimination, baseline</td>
<td>7.8 ± 1.8</td>
<td>7.9 ± 1.6</td>
<td>.95</td>
<td></td>
</tr>
<tr>
<td>Discrimination, 16 weeks</td>
<td>10.4 ± 1.1</td>
<td>8.3 ± 1.3</td>
<td>.065</td>
<td></td>
</tr>
</tbody>
</table>

F = female; M = male; TDI = threshold/discrimination/identification score; URTI = upper respiratory tract infection.
This study suggests that a **16-week short-term exposure to specific odors may increase olfactory sensitivity in patients with postinfectious and post-traumatic olfactory dysfunction**
What if we extended the training period and used more odors?
Modified Olfactory Training in Patients With Postinfectious Olfactory Loss

Aytug Altundag, MD; Melih Cayonu, MD; Gurkan Kayabasoglu, MD; Murat Salihoglu, MD; Hakan Tekeli, MD; Omer Saglam, MD; Thomas Hummel, MD

Objectives/Hypothesis: Patients with olfactory dysfunction benefit from repeated exposure to odors, so-called olfactory training (OT). This does not mean occasional smelling but the structured sniffing of a defined set of odors, twice daily, for a period of 4 months or longer. In this prospective study, we investigated whether the effect of OT might increase through the use of more odors and extension of the training period.

Study Design and Methods: This study shows OT results when performed with four or 12 odors for 36 weeks in patients with postinfectious olfactory dysfunction. A total of 85 subjects participated (mean age 45.6 ± 10.5 years, range 24-68 years). Three groups were formed: 1) In the modified olfactory training (MOT) group, patients used three sets of four different odors sequentially. 2) Participants in the classical odor training (COT) group used four odors. 3) Participants in the control group did not perform OT. All groups were matched for age and sex distribution of participants.

Results: Both participants in the COT and MOT groups reached better scores than controls in terms of odor discrimination and odor identification. Continuing OT with four different odors after the 12th and 24th weeks produced better results in terms of odor discrimination and odor identification scores as compared to using the same four odors throughout the entire study.

Conclusion: This study confirmed the effectiveness of OT. Increasing the duration of OT and changing the odors enhances the success rate of this therapy.

Key Words: Olfaction, anosmia, smell, regeneration.

Level of Evidence: 2b.
Results

<table>
<thead>
<tr>
<th>TABLE II. Number of Participants With Clinically Significant Improvement of Olfactory Function in Relation to Baseline.*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>12th Week</td>
</tr>
<tr>
<td>MOT (n = 37)</td>
</tr>
<tr>
<td>COT (n = 33)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>(n = 15)</td>
</tr>
</tbody>
</table>

*Difference in TDI score of 6 and more points.
COT = classical olfactory training; MOT = modified olfactory training.
Results

Fig. 1. Means and standard errors of means of changes of threshold-discrimination-identification score over time (beginning of the study and at weeks 12, 24, and 36) separately for the three groups. Note that the y-axis starts at 10. Control group = no training; COT = classical olfactory training; MOT = modified olfactory training. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]
Conclusion

This study confirmed the effectiveness of Olfactory Training. It also concluded that the duration of Olfactory Training and changing the odors enhances the success rate of this therapy.

-One remaining issue whether or not the OT-induced improvement produces lasting results or is it only temporary?
Other Treatment Trials
Treatment of Olfactory Dysfunction, II: Studies With Minocycline

R. C. Kern, MD; D. B. Conley, MD; G. K. Haines III, MD; A. M. Robinson, PhD

Objectives/Hypothesis: The treatment of anosmia has changed minimally since the early 1970s, despite dramatic advances in the understanding of the molecular biology of olfaction. Recent studies from the authors' laboratory have suggested that most common causes of clinical olfactory dysfunction, including rhinosinusitis, appear to be associated with increased apoptotic death of olfactory sensory neurons. This appears to result in a decline in the number of functioning mature olfactory sensory neurons, despite the capacity of the olfactory epithelium for regeneration. The current study evaluated the ability of the antibiotic minocycline to inhibit olfactory sensory neuron apoptosis. This drug is known to inhibit apoptosis separate from its anti-infective properties. Olfactory sensory neuron apoptosis was triggered by surgical deafferentation ("bullectomy"), the standard experimental model. Earlier studies have indicated that bullectomy and sinusitis invoke similar proteolytic enzyme cascades in olfactory sensory neurons. Study Design: Histological analysis of animal olfactory tissue. Methods: Mice underwent unilateral olfactory bullectomy to induce apoptotic olfactory sensory neuron death, with and without 45 mg/kg intraperitoneal minocycline given 12 hours before surgery and every 12 hours until death. Mice were killed at 2 and 4 days after bullectomy and assessed for activation of caspase-3 and olfactory sensory neuron survival by immunohistochemical analysis. Results: Minocycline resulted in partial suppression of cell death at 2 days after surgery when compared with untreated animals. Conclusion: Minocycline inhibits olfactory sensory neuron death in the face of a potent pro-apoptotic stimulus. This drug is well tolerated and is currently undergoing human trials for the management of peripheral olfactory loss as well. Key Words: Minocycline, hyposmia, anosmia, olfactory neuron, apoptosis.

Laryngoscope, 114:2200–2204, 2004

INTRODUCTION

The period since the early 1980s has witnessed tremendous growth in our understanding of the basic science of olfaction. However, these strides have not translated into any significant improvements in the management of clinical olfactory dysfunction, which arguably has not changed since the advent of oral steroids decades ago. Despite advances in the molecular basis of olfactory transduction, axonal guidance, regeneration, and neuron turnover, effective treatments for most common causes of olfactory loss remain elusive. Broad gaps exist in our understanding of the basic pathophysiology of most causes of olfactory loss including aging, viral infection, trauma, and chronic rhinosinusitis. The relative indifference on the part of most otolaryngologists and neurologists who treat these problems, coupled with the paucity of any significant translational research on the topic, is responsible for the current stagnant state of affairs. The issue is compounded by the absence of animal models of smell loss relevant to the human condition. In overview, most clinical cases of anosmia and hyposmia appear to be associated with a significant component of peripheral (intranasal) disease in the olfactory mucosa. In age-related smell loss, postural anosmia, and olfactory deficits from rhinosinusitis, the net loss of mature olfactory sensory neurons (OSNs) in the nose appears to be the dominant pathological process in the epithelium. Therefore, most...
Treatment of Postinfectious Olfactory Disorders With Minocycline: A Double-Blind, Placebo-Controlled Study

Jens Reden, MD; Birgit Herting, MD; Katja Lill, MD; Robert Kern, MD; Thomas Hummel, MD

**Objectives/Hypothesis:** Infection of the upper respiratory tract is one of the most common causes of olfactory loss. One of the possible underlying pathologic pathways is an increase of apoptosis of olfactory receptor neurons. Therefore, treatment with the antibiotic minocycline, which has been shown to act as an antipoptotic agent, is thought to accelerate improvement of olfactory function. To investigate this idea, 55 patients with postinfectious olfactory dysfunction were tested for their olfactory ability.

**Study Design:** Randomized, prospective, double-blind, placebo-controlled.

**Methods:** Olfactory function was examined by means of a standardized psychophysical method (Sniffin’ Sticks) before and 7 months after a 3-week treatment with either minocycline (2 × 50 mg/d) or a placebo.

**Results:** Statistical analyses did not reveal any influence of the treatment on the progress of olfactory function, possibly indicating that pathologic changes other than apoptosis contribute to postinfectious olfactory loss, either on a peripheral level (e.g., scarring/reorganization of the olfactory epithelium) or on a central nervous level.

**Conclusions:** In conclusion, the present results indicate that minocycline in the given dosage has little or no effect on the recovery of human olfactory function following postinfectious olfactory loss. However, spontaneous recovery is found in approximately 20% of the patients over an observation period of 7 months.

**Key Words:** Smell, therapy, olfactory loss, hyposmia.

**Level of Evidence:** 1b.
Retinoic acid enhances the rate of olfactory recovery after olfactory nerve transection.

Yee KK*, Rawson NE.

Abstract
In the olfactory system, retinoic acid (RA) plays an important role in development and may affect growth in the adult animal. To explore the potential effects of RA on recovery after injuries, adult mice were trained in a buried food paradigm and were given a single oral supplement of RA after olfactory nerve transection. Results demonstrate that RA accelerates the recovery of olfactory functions after injury.

PMID: 11113521
[PubMed - indexed for MEDLINE]
Olfactory Function in Patients With Postinfectious and Posttraumatic Smell Disorders Before and After Treatment With Vitamin A: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

Jens Reden, MD; Katja Lill, MD; Thomas Zahnert, MD, PhD; Antje Haehner, MD, PhD; Thomas Hummel, MD, PhD

Objectives/Hypothesis: In this study we investigated the effectiveness of vitamin A in postinfectious and posttraumatic smell disorders. A possible effect of vitamin A is likely due to the stimulation of regeneration and repair of the peripheral olfactory system.

Study Design: Double-blind, randomized, placebo-controlled clinical trial.

Methods: A total of 52 patients (age range, 20–70 years; mean age, 52 years) participated, 26 of whom received placebo (7 male, 19 female) and another 26 verum (8 male, 18 female). A standardized history was obtained in each patient. Olfactory function was measured by means of the Sniffin’ Sticks test kit, a validated technique to investigate odor thresholds, odor discrimination, and odor identification. Vitamin A was prescribed at a dose of 10,000 IU per day for 3 months. Follow-up testing was performed on average 5 months after the first investigation.

Results: Forty-four percent of all patients reported recovery of their sense of smell; 29% of the participants exhibited significant improvement in measured olfactory function. However, there was no significant difference between the outcome of patients receiving verum or placebo.

Conclusions: The systemic application of vitamin A at a dose of 10,000 IU per day for 3 months does not appear to be useful in the treatment of postinfectious or posttraumatic olfactory loss.

Key Words: Anosmia, olfactory loss, nose, treatment.

Level of Evidence: 1b

Effects of Systemic Transplantation of Adipose Tissue-Derived Stem Cells on Olfactory Epithelium Regeneration

Yong Min Kim, MD; Young Seok Choi, MD, PhD; Jin Woong Choi, MD; Yong Ho Park, MD; Bon Seok Koo, MD; Hwan-Jung Roh, MD, PhD; Ki-Sang Rha, MD, PhD

**Objective/Hypothesis:** The purpose of the study was to investigate the effect of intravenous adipose tissue-derived stem cell (ADSC) transplantation on olfactory epithelium regeneration following transection of the olfactory nerve in rats.

**Study Design:** This was an experimental study using primary cultures of mesenchymal stem cells derived from animal adipose tissue with histological analysis of animal olfactory tissue.

**Methods:** All rats underwent unilateral transection of the olfactory nerve to induce degeneration of olfactory epithelium, and then were observed for regeneration according to time sequences. ADSCs were cultivated from neck adipose tissue of rats, and systemically injected into the experimental group. The control group was injected with phosphate buffered solution, instead of ADSCs. After 30 days, regeneration of olfactory epithelium was observed with olfactory marker protein (OMP) and proliferating cell nuclear antigen. To observe the characteristics of the transplanted ADSCs, olfactory epithelium was stained with von Willebrand factor and OMP.

**Results:** After olfactory nerve transection, mature olfactory cells disappeared in 5 days, but gradually regained their thickness with increased cell numbers at approximately 10 to 15 days. By 30 days post-transection, the thickness and cellular composition of epithelium was almost restored to baseline levels pretransection. However, OMP expression remained decreased compared with day 0 or 3. Systemically injected ADSCs were transplanted into the olfactory epithelium and survived beyond 4 weeks. The ADSCs promoted regeneration of olfactory epithelium in the animal model and differentiated into olfactory receptor neurons and endothelial cells.

**Conclusions:** Our findings suggest the feasibility of ADSC transplantation as a treatment for head trauma-related olfactory dysfunction.

**Key Words:** Anosmia, mesenchymal stem cell, olfactory epithelium.

*Laryngoscope, 119:983-989, 2009*

**INTRODUCTION**

It has been well documented that the olfactory receptor neurons of the olfactory epithelium, which innervate the olfactory bulb of the brain, undergo a slow process of turnover and replacement by newly generated neurons throughout adult life.\textsuperscript{1} If there are any events disturbing this process, such as viral infection or transection of olfactory nerves, permanent loss of olfaction can occur.

Despite scientific advances in our understanding of olfaction, pathophysiology and effective treatments for common causes of olfactory loss, including aging, viral infection, trauma, and chronic rhinosinusitis, remain elusive.\textsuperscript{2} Oral steroids have been regarded as one treatment method to improve olfactory dysfunction for...
Lipoic Acid in the Treatment of Smell Dysfunction Following Viral Infection of the Upper Respiratory Tract

Thomas Hummel, MD; Stefan Heilmann MD; Karl-Bernd Hüttenbriuk, MD

Objectives/Hypothesis: The study aimed to investigate the potential therapeutic effects of lipoic acid in olfactory loss following infections of the upper respiratory tract. Possible mechanisms of action include the release of nerve growth factor and antioxidant effects, both of which may be helpful in the regeneration of olfactory receptor neurons. Study Design: Unblinded, prospective clinical trial. Methods: A total of 23 patients participated (13 women, 10 men; mean age 57 y, age range 22-79 y; mean duration of olfactory loss, 14 mo; range, 4 to 33 mo); 19 of them were hyposmic and 4 had functional anosmia. Alpha-lipoic acid was used orally at a dose of 600 mg/d; it was prescribed for an average period of 4.5 months. Olfactory function was assessed using olfactory tests for phenyl ethyl alcohol odor threshold, odor discrimination, and odor identification. Results: Seven patients (30%) showed no change in olfactory function. Two patients (9%) exhibited a moderate decrease in olfactory function; in contrast, six patients (26%) showed moderate and eight patients (35%) remarkable increase in olfactory function. Two of the 4 patients with functional anosmia reached hyposmia; 5 of 19 hyposmic patients became normosmic. Overall, this resulted in a significant improvement in olfactory function following treatment (P = .002). At the end of treatment parosmias were less frequent (22%) than at the beginning of treatment (46%).

Key Words: Olfaction, regeneration, therapy. Laryngoscope, 112:2076–2080, 2002

INTRODUCTION

Viral infections of the upper respiratory tract are among the most frequent causes associated with smell disorders.1-3 Although the pathogenesis of postviral olfactory dysfunction is unknown, histological studies have shown the destruction of the olfactory epithelium with an irregular arrangement of the mucosal layers including loss of olfactory receptor cells indicating the involvement of the peripheral olfactory system.4,6 Hence, postviral smell dysfunction seems to be due to an impairment of the olfactory neurons, both in function and in numbers. Although numerous treatments have been tried in postviral anosmia (e.g., corticosteroids, zinc, vitamin A), no pharmacological therapy has been established to date.2,6-8 This difficult situation is underlined by the fact that, when "parosmias" (distorted olfactory sensations elicited through odors) is present,9,10 in some patients surgical removal of the olfactory epithelium may be considered as a cure.11

When searching for potential candidates for the pharmacological treatment of olfactory dysfunction we came across lipoic acid (LA), which is used in the treatment of diabetes, cardiovascular disease, and peripheral neuropathy. The lipoic acid consumes free radicals and prevents cell damage. Lipoic acid also stimulate the release of nerve growth factor and protects against nerve damage. Therefore, we investigated whether lipoic acid had a positive effect on patients with postviral olfactory dysfunction.
Thank You!