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Finja Thiermann

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Abstract

Although olfaction plays a significant role in our everyday lives, in the past, science has given little attention to this field of research. A well-functioning sense of smell is essential not only for human well-being and the quality of life, it is also important to protect the organism from harmful influences it is exposed to, such as gas, toxic agents or rotten food. Various drugs interfere with human olfaction and are able to elicit olfactory dysfunction, but little is known about the underlying mechanisms. To date, a wide range of drugs have not been sufficiently investigated with respect to their impact on olfaction. This review provides an overview of drugs that have been identified as inducing olfactory disorders and discusses underlying causes and mechanisms. The second part of this work deals with drugs that are applied in the treatment of olfactory dysfunction. It offers possible treatment options, taking into account different etiologies and mechanisms of drug action.

Zusammenfassung

Obwohl das Riechen in unserem alltäglichen Leben eine bedeutende Rolle spielt, hat die Wissenschaft diesem Forschungsfeld in der Vergangenheit nur geringe Bedeutung beigemessen. Eine gut funktionierende Riechfähigkeit ist nicht nur für das menschliche Wohlbefinden und die Lebensqualität von Bedeutung, sondern ist ebenso wichtig, um den Organismus vor schädlichen Einflüssen, denen er ausgesetzt ist, wie z.B. Gas, toxischen Substanzen oder verdorbener Nahrung zu schützen. Zahlreiche Arzneistoffe können den Riechsinn beeinträchtigen und Riechstörungen hervorrufen, jedoch ist wenig über die zugrunde liegenden Mechanismen bekannt. Bisher wurde eine Vielzahl an Arzneistoffen nicht ausreichend auf ihren Einfluss auf das Riechvermögen untersucht. Diese Diplomarbeit gibt einen Überblick über Arzneistoffe, die Riechstörungen hervorrufen können, und diskutiert die zugrunde liegenden Ursachen und Mechanismen. Der zweite Teil dieser Arbeit beschäftigt sich mit Arzneistoffen, die in der Therapie von Riechstörungen eingesetzt werden, und zeigt mögliche Behandlungsoptionen unter Berücksichtigung verschiedener Krankheitsursachen und Wirkungsmechanismen von Arzneistoffen auf.

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1. Introduction

Thanks to evolution, humans are less dependent on their sense of smell than animals. Nevertheless, the importance of human olfaction is often underestimated. Detection of hazards in our environment, such as spoiled food, smoke or toxic agents requires a well-working olfactory function in order to protect the organism from harmful influences. Decrease in olfactory function further diminishes the capability to distinguish between different flavors. This can result in a decline of pleasure in eating, and can therefore affect nutrition and food intake. The sense of smell further affects human behavior, cognition, mood and sexuality. It is essential for human well-being and quality of life.[1] Ultimately, alteration or decrease in olfactory function often indicates neurodegenerative diseases such as Parkinson's disease or Alzheimer's disease.[2] Although the sense of smell is of great importance, research has attached little value in the past. Still today, little is known about the impact of drugs on human olfaction. In 1993, Buchbauer et al. reviewed the literature concerning drugs with influence on olfactory function.[3] This review provides an update on this topic analyzing both agents with harmful influence on the sense of smell and agents that are applied in the treatment of olfactory dysfunction.

1.1. The olfactory epithelium

The olfactory epithelium is located in the nasal cavity. It consists of three different cell types: olfactory sensory neurons, supporting or sustentacular cells and basal cells. Basal cells are stem cells, which are responsible for regeneration of olfactory neurons throughout one's whole life.[4] The olfactory epithelium contains about 10 to 20 million olfactory neurons, which are responsible for transduction of odor information from the nose to the brain.[1] Olfactory neurons have a bipolar structure. At the apical part of the cell body dendrites have an enlarged ending, the olfactory knob. Nonmotile cilia, which arise from the olfactory knob, cover the surface of the olfactory epithelium. The epithelium lies in a mucus layer.[5,1] In the membrane of the cilia, odors are able to bind to the olfactory receptor.[1] Mucus that covers the olfactory epithelium is a secretion of so-called Bowman's glands, specialized exocrine glands within the olfactory epithelium.[6] The proximal part of the cell body ends up in an axon. This axon joins with other axons generating

nerve bundles which cross the cribriform plate, where nerves end within glomeruli in the olfactory bulb.[5,1] From this, they synapse with mitral cells,[5] and finally project to subcortical and cortical brain regions.[4]

Detection of an odor begins with a sniff that carries odorant molecules into the mucus of the olfactory epithelium. From there, chaperones, which are also termed odorant-binding proteins, transport the odorant molecules to the olfactory receptors. These are localized in the membrane of the cilia of the olfactory neurons.[1] Usually, odorants bind to a variety of different olfactory receptors. This generates a pattern which is characteristic for each odorant, and which enables identification and distinction between different odors.[7]

1.2. Pathway of olfactory signal transduction

The binding of an odorant molecule to the receptor leads to a conformational change in the receptor. A G_{olf}-protein is activated. Consequently, the G-protein activates the enzyme adenylate cyclase (AC), which generates cyclic adenosine monophosphate (cAMP) from adenosinetriphosphate (ATP) as a second messenger. cAMP mediates the opening of cyclic nucleotide-gated ion channels (CNG), which causes an influx of sodium and calcium into the cell. Thus, the potential of the membrane gets less negative and a depolarisation of the cell membrane leads to an action potential, which conveys the signal into the brain.[5]

In 1991, Linda Buck and Richard Axel discovered in rat experiments that odorant receptors belong to the family of 7-transmembrane-G-protein-coupled receptors. Buck and Axel also identified the large gene family that encodes the odorant receptor proteins.[4] This gene family is the largest family in the human genome and includes almost 850 genes. However, not all of these receptor genes are functional. About half of them are pseudogenes and thus not able to encode receptors. In humans, only approximately 390 genes are functional.[8] This leads to the assumption that the significance of sense of smell decreased in history of evolution.[5]

1.3. Trigeminal chemosensation

Also the trigeminal system plays an important key role in chemosensation. The trigeminal system is composed of polymodal nociceptive neurons and axons in the cranial nerve V (trigeminal nerve) and, to a lesser extent, of nociceptive neurons

whose axons join the cranial nerve IX (glossopharyngeal nerve) and the cranial nerve X (vagus nerve). Branches of the trigeminal nerve's neurons innervate the whole face region including the nasal, oral and ocular cavities. Neurons of the trigeminal system are activated when the organism is exposed to irritant stimuli like air pollutants, ethanol, ammonia, menthol, acetic acid, carbon dioxide or capsaicin. Afferent axons of the trigeminal nerve run into the trigeminal nucleus, from where information is transmitted to ventral posterior medial nucleus of the thalamus. From there, the information is passed on to the somatic sensory cortex and other brain areas responsible for processing pain and facial irritation. In comparison to olfaction, much higher threshold concentrations are necessary to elicit trigeminal activation. Physiological reactions towards trigeminal chemosensory stimuli comprise nasal secretion, increased salivation, vasodilatation, tearing, sweating, bronchoconstriction and a decreased respiratory rate.[9]

1.4. Classification of olfactory disorders

Olfactory disorder (dysosmia)		
Quantitative	Hyperosmia	Oversensibility
	Normosmia	Normal sensibility
	Hyposmia	Reduced sensibility
	Anosmia	**Complete anosmia:** complete loss of sense of smell **Functional anosmia:** distinct restriction of sense of smell; comprises complete loss of smell as well as marginal perception of odors **Partial anosmia:** marked diminished sensibility towards a certain fragrance/group of fragrances compared to general population, not considered as pathological
Qualitative	Parosmia	Alteration of perception of odors with a stimulus present
	Phantosmia	Perception of odors without an odor present

Table 1- Classification of olfactory disorders (adapted and newly drawn [10])

1.5. Etiologies of olfactory dysfunction

Not only drugs play a decisive role in the development of smelling disorders. Various other reasons can induce alterations in smelling function.[11] In a large number of patients, upper respiratory tract infection, nasal and paranasal sinus disease, or head trauma cause smelling disorders.[12] Besides this, various other causes can evoke alterations in smelling capacity, such as tumors, endocrine or metabolic disorders, or toxin exposure.[11] Aging is another important factor for the occurrence of olfactory dysfunction.[13] Further, impaired smelling ability is often an early symptom of neurodegenerative diseases as for instance Parkinson`s disease or Alzheimer`s disease.[2]

1.6. Assessment of olfactory function

Different methods of measurement for identification and classification of olfactory dysfunctions are available. Psychophysical tests comprise assessment of the odor threshold, odor identification, and odor discrimination. The *odor threshold* test measures the lowest concentration of an odorant that can be perceived by a subject. The *odor identification* test demands to identify or associate an odorant from subject. The *odor discrimination* test allows to detect, if the subject is capable of differentiating between different smells. Besides, electrophysiological measurements which include electro-olfactograms and electroencephalographic-derived olfactory event-related potentials allow the assessment of smelling ability. Eventually, functional magnetic resonance imaging offers a new strategy for the extensive exploration of the functional topography of the human sense of smell.[14]

2. Drugs which exert negative impact on olfaction

Chemotherapeutic agents

Patients undergoing cancer chemotherapy are affected by a multitude of side effects such as tiredness, hair loss, nausea, sleep disturbances, anxieties, anorexia and changes in smell and taste capacity.[15] In general, most attention is given to vomiting and nausea issues, disregarding that normal taste and smelling performance is also essential for sufficient food intake and maintenance of patients' quality of life.[15,16] Reduced capability of taste and smell can result in weight loss and malnutrition. This, in turn, can eventually lead to greater adverse effects of chemotherapeutic agents, less therapy response and poor compliance.[16]

Different chemotherapeutic agents in combination

Bernhardson et al.[15] highlighted the chemosensory problems of patients undergoing treatment with chemotherapeutic agents. In order to examine the prevalence of self-reported alterations in taste and smell, he conducted a study in which 518 patients who received cancer chemotherapy participated. 387 of 518 patients (75 %) reported alterations in taste and smell. 40 of 387 patients reported smell disturbances alone, 134 taste disturbances alone. Additionally, younger patients and women complained more about smell and taste changes.[15]

From January to September 2007, a prospective study was carried out by Steinbach et al.[16] to evaluate the smell and taste alterations in 87 patients receiving chemotherapeutic agents, due to gynecologic malignancies or breast cancer. Using the 'Sniffin' Sticks' test as method of measurement to assess patients' olfactory function, it became obvious that chemotherapeutic agents exerted impact on both olfactory and gustatory function. A significant decrease in smelling capacity was observed during chemotherapy affecting odor thresholds more than odor discrimination and odor identification. Interestingly, the choice of the chemotherapeutic agent made no difference. All chemotherapeutic agents led to reduced smelling performance during chemotherapy, no matter which one was chosen. A comparison revealed no differences among them: *"(eg, cisplatin v carboplatin; fluorouracil, epirubicin, and cyclophosphamide [FEC] v docetaxel v docetaxel, doxorubi-*

cin, and cyclophosphamide [TAC])".[16] Olfactory measurements three months after chemotherapy revealed an almost complete recovery of sense of smell. Besides, chemotherapy led to greater smelling impairment in older than in younger patients.[16]

Olfactory impairment in old age is well known. Changes in the anatomy of the olfactory system such as loss of olfactory receptor cells, or decline and changes in composition of nasal mucus contribute to alterations in smelling performance with advancing age, as does a greater vulnerability of the olfactory mucosa towards neurotoxic agents. Also, changes in expression and function of specific receptor proteins or signaling cascades alter odor processing.[17] Thus, the finding of the study, that older patients experienced greater adverse effects concerning sense of smell, is not surprising. Furthermore, it is well established that the olfactory system undergoes neurogenesis throughout life.[18] This might be an explanation for the discovery that the olfactory epithelium had almost completely recovered three months after chemotherapy.

Another trial analyzed the short-term effects of different chemotherapeutic agents on the olfactory function. Forty-four patients were allocated to one of three groups. The patients received either *"oxaliplatin and antimetabolites (5-FU/capecitabine or gemcitabine; O+A group), taxanes and platinum analogues (cisplatin and carboplatin; T+P group) or taxanes and anthracyclines (doxorubicin or liposomal doxorubicin; T+A group)"*[19] in combination. In addition, the patients were divided into different age groups: 39-50, 51-62 and 63-73 years. Olfactory threshold, olfactory identification, olfactory discrimination and the composite threshold-discrimination-identification score (TDI) were assessed by using the 'Sniffin' Sticks' test at diagnosis, and before receiving the last of three to four cycles of chemotherapy. Riga et al.[19] revealed a significant impairment of olfactory threshold, olfactory identification, olfactory discrimination scores and the composite threshold-discrimination-identification score in every chemotherapeutic group. Significant differences in olfactory threshold and threshold-discrimination-identification scores were found between the T+P and the O+A group. Patients of all age groups exhibited a significant lower TDI score after chemotherapeutic therapy. At baseline, 10 subjects were diagnosed as hyposmic whereas at the end of chemotherapy, 42 of the 44 patients were hyposmic or anosmic. Additionally, a higher vulnerability to olfactory toxicity was found in

patients older than 50 years.[19] This might be related to changes in the olfactory epithelium in old age, such as decline of olfactory receptor cell regeneration capability, changes in epithelial thickness or decrease in mucus secretion as mentioned before.[13]

A single case of chemotherapy-induced parosmia was reported by Müller et al..[20] After a chemotherapeutic treatment, a 63-year-old woman complained about parosmia which resulted in severe lack of appetite and insufficient food intake. Her consequent weight loss was life-threatening. A nose clip brought relief and led to increased ingestion. Within 9 months parosmia disappeared and the olfactory sensitivity was enhanced. Ultimately, the woman was able to regain appetite and weight.[20]

Platin compounds

Cisplatin

Cisplatin is an alkylating agent which is used in the treatment of several solid malignancies. Anti-tumor properties of cisplatin contain toxic effects on both DNA and non-DNA. Cisplatin interacts with DNA by binding to the DNA inducing interstrand and intrastrand cross-links. Replication is inhibited and consequently apoptosis is provoked.[21] A study performed by Joussain et al.[22] analyzed the impact of cisplatin on odor perception in 15 male lung cancer patients compared to 15 control subjects. It became obvious that cisplatin chemotherapy resulted in a reduced pleasantness for food odors without affecting odor detection or odor identification. A decrease in pleasantness for non-food odors could not be detected. The observed effects might be related to side effects of chemotherapeutic agents, such as nausea or malaise, which often induce aversion to food odors.[22]

Contrary to these findings, Yakirevitch et al.[23] could not reveal any negative influences on olfaction initiated by cisplatin. He and his co-workers studied the influence of high-dose cisplatin administration on olfaction in a single-blind study. The trial comprised 21 subjects who received 75 mg m^{-2} $cycle^{-1}$ cisplatin or more in combination with other chemotherapeutic agents for treatment of different types of primary tumors. Olfactory performance was measured using the 'Sniffin' Sticks' test before and after each cycle of chemotherapy. Final measurements were taken three weeks after the last cycle of chemotherapy. Moreover, serum

zinc levels were ascertained in 14 subjects, and standard audiometry was used in order to assess auditory ability. Hearing impairment is known to be an indicator for the neurotoxicity of cisplatin. All in all, only in one of 21 subjects was a decrease in smelling capability registered. This patient's smelling ability declined 60 % after the third cycle of chemotherapy. He received a cumulative dose of 225 mg m^{-2} cisplatin. After chemotherapy, serum zinc was at a normal level in this patient. Audiometry revealed that his hearing ability was normal. Interestingly, an improvement of olfactory function was found in 10 subjects. These findings were statistically significant. Further results revealed decreased zinc levels in 2 patients and decreased auditory ability in 9 patients. In summary, an impact of cisplatin on olfactory performance could not be detected. Improvement of olfaction which was seen in 10 subjects could probably be taken as a learning effect.[23]

In 1989, Sweeney et al.[24] ascertained that administration of cisplatin led to a decrease in plasma zinc levels and increased urinary zinc excretion.[24] Zinc has been discovered to influence human olfaction as discussed later in this overview. However, the only subject in which cisplatin led to a reduced smelling capability had normal zinc levels. Thus, low serum zinc levels can be excluded as a cause of olfactory impairment in this patient.[23]

The impact of cisplatin on olfactory function was also the focus of research by Zhou et al..[25] The neurotoxic effects of cisplatin became apparent in an animal experiment, involving 32 guinea pigs. Administration of cisplatin resulted in the destruction of olfactory nerves, the olfactory epithelium and the olfactory bulb.[25]

Carboplatin

The aim of the study by Steinbach et al.[26] was to investigate whether treatment with carboplatin plus taxol affects the chemosensory function in ovarian cancer patients. 12 patients participated in the study. In order to determine the degree of olfactory function, the ‘Sniffin’ Sticks’ test battery was applied before treatment, after 9 weeks, 18 weeks, and 30 weeks. In addition, patients were instructed to rate their smelling ability subjectively. Measurements revealed a significant decrease in olfactory function. Olfactory threshold was worst affected. By contrast, odor identification was only affected marginally. Also, patients’ self-evaluation revealed a decline in smelling ability immediately after treatment with carboplatin

and taxol. It turned out that the decrease in olfactory function was transient. Three months after chemotherapy, the sense of smell recovered almost completely.[26]
Findings of another study emphasize the effects of carboplatin on the olfactory function. 11 patients in whom ovarian cancer was diagnosed attended a study, in which they had to complete a 75-item self-report questionnaire. Patients evaluated side effects of carboplatin treatment, and the severity of the side effects they had experienced at each course of chemotherapy. Furthermore, patients had to determine which of the adverse effects had been the worst at each course. Of all side effects, alterations in sense of smell were also reported (mean incidence = 47.35 %). Although patients were more affected by other side effects with regard to incidence and severity, the results demonstrate that side effects concerning the sense of smell are not uncommon.[27]

Mikrotubule inhibitors

Vinblastine

Vinblastine is an antimitiotic drug that belongs to the vinca alkaloids. The mechanism of action is an intermittence of mitosis due to inhibition of polymerization of microtubules.[28] In 2012, Kavoi et al.[29] released a study that examined the influence of vinblastine on the olfactory mucosa of rabbits. 56 male adult rabbits were allocated to 7 verum groups and 1 control group. Each group comprised 7 animals. A single dose of 0.31 mg/kg, which corresponds to the dosage used in human cancer treatment, was then administered to the rabbits by way of the ear vein. The control group received a saline solution. Afterwards, the rabbits were euthanized on day 1, 2, 3, 5, 7, 10 and 15, using pentobarbital sodium. Animals of the control group were euthanized 1 day after saline administration. It turned out that the vinblastine administration induced morphological changes of the mucosa the first 3 to 5 days. Alterations implicated degeneration of axonal bundles with the occurrence of vasculature, cell death, degeneration of the Bowman's glands and *"disarrangement of the normal layering of nuclei of the epithelia."*[29] 7 to 15 days after vinblastine exposure, a regeneration of the olfactory mucosa was noticed. Mucosa recovered to normal morphology and blood vessels disappeared. Finally, the findings of the study suggest that alterations of the mucosa due to

vinblastine administration are impermanent. Eventually, the regeneration capacity of the olfactory mucosa leads to a recovery to normal morphological structure.[29]

Antimetabolites

Tegafur

The pyrimidine antimetabolite tegafur is applied in the treatment of different types of cancer. Tegafur is a prodrug, which is activated to 5-fluorouracil after administration and metabolic conversion.[30] Clinical studies were carried out in order to investigate the impact of tegafur on the olfactory performance. 5 Patients with an olfactory impairment after tegafur intake participated in the study. The drug intake averaged 22 months.[31] T&T olfactometry, an olfactory function test, which is most commonly applied in Japan,[32] revealed hyposmia in 1 patient and anosmia in 4 patients. Endoscopic examination of all patients was not able to determine any pathological changes of the olfactory mucosa. As opposed to these findings, histological examination of the olfactory mucosa of one patient revealed a severe degeneration of the olfactory epithelium, and a lack of olfactory receptor cells.[31]

Antibiotics

The discovery of penicillin by Alexander Fleming in 1929 revolutionized medicine. Nowadays, a wide range of different antibiotics are available, and their antimicrobial properties provide large fields of application for treatment of infectious diseases.[33] In the past, different case reports and investigations led to the assumption that intake of some antibiotic agents can provoke olfactory dysfunction.

Antituberculotic agents

Pyrazinamide

Pyrazinamide is an agent used in the treatment of tuberculosis. The current first-line therapy regimen for drug-susceptible tuberculosis comprises a combination of four different antituberculotic agents, including pyrazinamide, rifampicin, ethambutol and isoniazid. The treatment lasts for 6 months.[34] During a combination therapy consisting of pyrazinamide, rifampicin, ethambutol, isoniazide and streptomycin for treatment of pulmonary tuberculosis, a 63-year-old man com-

plained about cacosmia with an unpleasant perception of food odors. The treatment was discontinued and the smelling disorder improved. After another therapeutic attempt to introduce the same drugs again, it became obvious that pyrazinamide was responsible for the observed side effects. Consequently, pyrazinamide was left off. Nevertheless, the man recommenced pyrazinamide intake at a lower dosage after 10 days (500 mg/day instead of 1250 mg/day). The smelling disorder recurred, but the symptoms were not as severe as before. The man was able to cope with the adverse effects, and the dose of pyrazinamide was increased. In the present case report, it turned out that pyrazinamide altered smelling function and that the adverse effects caused were reversible as well as dose-dependent. By which mechanism pyrazinamide induced the olfactory dysfunction is still unclear.[35] Another case of olfactory disorder was reported by a 53-year-old woman. She underwent an antituberculotic treatment comprising isoniazid, rifampicin, pyrazinamide and streptomycin. Regularly, fifteen minutes after drug intake, the woman perceived a burning smell. This lasted about 4 to 5 hours, but disappeared completely after she discontinued use of pyrazinamide.[36]

Tetracyclines

Doxycycline

Also in the class of tetracyclines, adverse effects with respect to olfaction have been reported. There are several case reports of patients who developed an olfactory dysfunction after treatment with doxycycline. In one case, a man developed anosmia during doxycycline therapy of his skin disease. Two other cases of parosmia have been registered at *"the Adverse Drug Reactions Advisory Committee of the Commonwealth Department of Community Services and Health since 1972."*[37]

Macrolides

Telithromycin

Extensive review of the adverse effects of the macrolide telithromycin revealed specific side effects including smelling disorders.[38]

Aminoglycosides

Streptomycin, neomycin, tyrothricin, gentiamycin, kanamycin

Toxic effects on the olfactory function have also been reported after administration of different aminoglycosides. Persistent hyposmia and anosmia are able to occur and allergic rhinitis can also be induced.[3]

NSAIDs

Aspirin®

Aspirin® is one of the most popular and most widely sold drugs on the globe. In addition to its use as an analgesic, antipyretic and anti-inflammatoric for a multitude of different medical conditions, it is also effective, when used in low doses, in the secondary-prevention of myocardial infarction and to prevent transient ischemic attacks and thromboembolism, due to its capability to inhibit platelet aggregation.[39] The effective agent of Aspirin®, acetylsalicylic acid (ASA), was first synthesized in 1897 by Felix Hoffmann, a German chemist and pharmacist who wanted to ease his father's afflictions from arthritis.[40] ASA is a well-tolerated drug. Common side effects mainly concern the gastro-intestinal tract.[41] But salicylic acid is also able to induce adverse effects affecting the respiratory tract, and is therefore able to cause smelling impairments as well.

Aspirin®-induced Asthma (AIA) is a hypersensitivity towards non-steroidal anti-inflammatory drugs (NSAIDs) including ASA. It was first described in 1922 by Widal et al..[42] Later, Samter and Beers[43] characterized a triad of symptoms including asthma, chronic rhinosinusitis with nasal polyps, and symptom evocation by Aspirin®. Therefore, the syndrome was also termed Samter's triad.[43] The disease is not only induced by acetylsalicylic acid. Cross-reactions between ASA and other NSAIDs with the same mechanism of action, an inhibition of cyclooxygenase (COX-1), are known to occur.[39]

Inhibitor Pathways	NSAIDs
Predominant COX-1 and COX-2 inhibitors	Piroxicam Indomethacin Sulindac Tolmetin Diclofenac Naproxen Naproxen sodium Ibuprofen Fenoprofen Ketoprofen Flurbiprofen Mefenamic acid Meclofenamate Ketorolac Etodolac Diflunisal Oxyphenbutazone Phenylbutazone
Poor COX-1 and COX-2 inhibitors	Acetaminophen Salsalate
Relative inhibitors of COX-2	Nimesulide Meloxicam
Selective COX-2 inhibitors	Celecoxib Rofecoxib

Table 2- NSAIDs which induce cross-reactions with Aspirin® (newly drawn according to Babu et al.[39])

Usually, the first clinical symptom of sensitivity towards ASA is rhinitis. Often, rhinitis appears after a viral respiratory tract infection. Later, patients develop nasal polyps, chronic nasal congestion, chronic rhinorrhea and asthma. Symptoms vary in severity, and are accompanied by smelling disorders like hyposmia. In the worst case, anaphylactic reactions can also be induced.[44]

The disease is not fully understood yet. Research concerning the pathophysiologic mechanisms revealed that cause of AIA is not an IgE-mediated reaction, but instead an excessive metabolism of cysteinyl-leukotrienes. Inhibition of COX after NSAID intake leads to an increased use of the lipoxygenase pathway accompanied by increased production of pro-inflammatory leukotrienes. Besides, COX inhibition results in a decline in the synthesis of anti-inflammatoric prostaglandines PGE_2.[39]

Therapy of the AIA entails avoiding ASA and agents which cross-react with ASA. Unfortunately, a great number of AIA patients suffer from thromboembolic diseases, or are dependent on ASA due to myocardial infarction. In these patients,

Aspirin® desensitization is another opportunity and the treatment of choice.[39] Initially, low doses ASA should be administered to the patient. Then, doses should be increased gradually, until it is possible to tolerate a daily maintenance-dose.[45]

Opioids

Opioids play an essential role as analgesics, especially in the treatment of severe acute pain, and in the management of pain in cancer patients. They act on different subtypes of opioid receptors: μ, κ, and δ.[46] Past investigations in animals revealed the expression of opioid receptor mRNA in the olfactory system.[47,48]

Remifentanil

Lötsch et al.[49] examined the influence of the opioid remifentanil on the sense of smell. For this purpose, remifentanil was administered to sixteen healthy subjects as an intravenous infusion adapted to specific target plasma concentrations. Respectively, one man and one woman were allocated to one of eight target plasma concentrations of remifentanil: 0, 1.2, 1.8, 2.4, 3, 3.6, 4.8 and 6 ng/ml. Subjects received remifentanil infusions within three hours. The olfactory function was measured before and at the finish of drug administration by testing olfactory threshold, odor discrimination, and odor identification performance with validated tests. In addition, visual analogue scales were applied, in order to assess remifentanil side effects like drowsiness, tiredness and sickness. The results of thirteen subjects were evaluated. It was found that remifentanil increased the olfactory thresholds. These findings were correlated with the concentrations of remifentanil in plasma. Compared to these results, the effects of remifentanil on odor identification and odor discrimination showed no statistical significance. Nevertheless, Lötsch et al. revealed a correlation between the target plasma concentrations of remifentanil and the subjects' self-assessment of drowsiness and tiredness. Drowsiness had a significant impact on odor thresholds, whereas sickness and drowsiness could not be significantly related to alteration in the subjects' smelling capacity.[49]

Cannabinoids

Δ^9-Tetrahydrocannabinol

Δ^9-Tetrahydrocannabinol (THC) is the major active compound found in *Cannabis sativa*.[50] It acts upon the cannabinoid receptors. Until now, two subtypes of cannabinoid receptors have been explored: Cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2). Both receptors are usually influenced by endocannabinoids, which are endogenous cannabinoid receptor ligands. Δ^9-Tetrahydrocannabinol is not only known for its psychoactive activity. The utility of THC becomes apparent in different medical conditions such as treatment of nausea and emesis of patients undergoing a chemotherapy, therapy of cachexia in AIDS patients or as spasmolytic agent in multiple sclerosis.[51]

In order to explore the influence of Δ^9-tetrahydrocannabinol on the olfactory function, Walter et al.[50] included 15 healthy subjects in a randomized, placebo-controlled, cross-over study. Subjects were divided into two groups. One group received two capsules with 10 mg of the effective ingredient THC daily, the other group received a placebo. Measurements of olfactory capability were taken at baseline, and two hours after drug administration using the 'Sniffin' Sticks' method. In addition, side effects including 'nausea', 'tiredness', 'drowsiness' and 'euphoria' were rated using visual analog scales. As a result, THC led to a significant increase in odor threshold. Besides, a significant influence on odor discrimination was detected. In comparison to the placebo, the correct discrimination of odors decreased under treatment with THC. Odor identification measurements revealed no differences between the THC- and placebo-group. The volunteers' gender did not affect the results. [50]

Past investigations revealed the expression of CB_1 receptors in rats' olfactory bulbs.[52] However, the expression of cannabinoid receptors in human olfactory bulbs has been refuted in different studies. A study in which the human olfactory bulb proteome was explored was not able to identify the expression of CB_1 receptors on proteomic level.[53] Further research is necessary to investigate the role of cannabinoids on the human sense of smell.

Divalent cation compounds

Zinc compounds

Zinc formulations are used intranasally in order to treat common cold.[54] In the past, the effect of zinc on olfactory capability led to controversial discussions. On the one hand, different researchers identified a correlation between zinc containing drugs and smelling dysfunction. On the other hand, zinc is assumed to be useful in treatment of olfactory disorders. It is believed that zinc ions and other divalent cations interfere with ion channels within the olfactory signal transduction pathway, by blocking these channels. This might induce smelling disorders as a consequence.[54]

Zinc gluconate

Alexander et al.[55] conducted a retrospective case series with seventeen patients who consulted the University of California San Diego Nasal Dysfunction Clinic between October 2002 und August 2005. Their complaint was a smelling dysfunction after intranasal zinc application. Odor threshold and odor identification in patients were tested using validated tests. Everyone included in the series applied an intranasal zinc gluconate gel. Fifteen of seventeen patients reported an unpleasant burning instantly after gel application, continuing from minutes to hours. Eventually, sixteen patients perceived a decrease in smelling capacity within 48 hours. One patient did not perceive burning and reduced smelling capacity over 2 weeks after zinc gluconate usage. Four patients developed parosmia. Ten of the seventeen patients used the gel for treatment of an upper respiratory tract infection. Six patients used the gel in order to treat a possible cold, without developing symptoms of an upper respiratory tract infection. One patient used the gel preventatively. Other reasons that might have triggered smelling dysfunction, such as toxin exposure or head trauma, were excluded. Two patients were diagnosed with allergic rhinitis, one of the patients had suffered from sinusitis in the past. For treatment of their olfactory disorder, 6 patients used nasal steroids. Three patients took systemic steroids without recovery. Physical examination of the patients did not reveal a neoplasm or an inflammatory disease. Tests which were performed in order to measure odor threshold and odor identification detected a loss of smell in all patients. Seven patients were classified as anosmic, ten patients as hyposmic.

In fifteen of the seventeen patients, zinc caused impaired olfactory function. Furthermore, mean composite scores on threshold and identification tests revealed lower values if the zinc gluconate gel had not been applied too long ago. Although these findings were not significant, they indicate that the olfactory function may recover gradually.[55]

Zinc gluconate, copper gluconate, magnesium gluconate

In order to evaluate the impact of different divalent cations on olfaction, Duncan-Lewis and co-workers[54] published a study, in which they tested the effects of zinc gluconate, copper gluconate and magnesium gluconate in an animal experiment. Mice had to pass a food-finding test. Afterwards, they were nasally irrigated with either zinc gluconate, copper gluconate or magnesium gluconate and then had to pass the food-finding test again. These mice were then compared to a control group. The comparison of mice to a control group revealed that the administration of zinc gluconate and copper gluconate led to a significant prolonged food-finding time, compared to the control mice. Magnesium gluconate had no negative impact upon the food-finding test. These findings suggest that intranasal application of zinc gluconate and copper gluconate impair smelling capacity. Smelling impairment was transient. One month later mice diagnosed as anosmic had regained normal smelling ability. The finding that magnesium did not induce anosmia in mice supports the idea that the magnesium ion is not able to block the ion channel because of its small molecular mass. In conclusion, it can be assumed that divalent cations larger than calcium can exert an negative impact on human olfaction.[54]

Phosphodiesterase 5 (PDE 5) inhibitors

Sildenafil, vardenafil, tadalafil, avanafil

Sildenafil, vardenafil, tadalafil and avanafil belong to the class of PDE 5 inhibitors. They inhibit phosphodiesterase 5 an enzyme responsible for degradation of cyclic guanosine monophosphat (cGMP). Therefore, PDE 5 inhibitors induce higher cyclic GMP levels. The indication of sildenafil is the treatment of erectile dysfunction.[56] The effects of sildenafil on olfactory capability were explored in a placebo-controlled, double-blinded crossover study. 20 healthy subjects participated in the study. Smelling performance was assessed using the ‘Sniffin’ Sticks’

test. It became apparent that a dose of 100 mg, but not a dose of 50 mg sildenafil led to decreased olfactory sensitivity in subjects.[57] Hellstrom et al.[58] investigated the safety and efficacy of vardenafil in a double-blind, placebo-controlled, randomized study. It turned out that rhinitis was one of the most commonly reported adverse effects during treatment with vardenafil.[58] Also, nasal congestion can occur after intake of all PDE 5 inhibitors.[59]

Antiarrhythmic agents

Amiodarone

Amiodarone is a class III antiarrhythmic agent. It is applied in all types of cardiac tachyarrhythmias. It can provoke various side effects affecting thyroid glands, lungs, eyes, liver, nerves and skin.[60] In the past, amiodarone was also associated with anosmia. A 66-year-old man reported on olfactory disturbances after amiodarone intake due to ventricular tachycardia. This was therapy-resistant to conventional antiarrhythmic drugs. Nearly three years after receiving 400 mg amiodarone daily, the man complained about olfactory dysfunction. Consequently, the maintenance dose of amiodarone was reduced from 200 mg 100 mg a day. As a result, the anosmia was partially improved. Other serious side effects like thyroid dysfunction, lung toxicity or corneal deposition were not observed. Computer tomography revealed no dysfunction of the central nervous system comprising the olfactory brain.[61]

Cardiac glycosides

Digoxin

Digoxin is a cardiac glycoside which is applied in the treatment of congestive heart failure and atrial fibrillation. Cardiac glycosides are known for their narrow therapeutic window.[62] Thus, they can lead to a multitude of adverse drug reactions. High digoxin levels are able to evoke typical side effects, e.g. cardiac arrhythmias, nausea, headache, emesis or visual disturbances like xanthopsia.[63]

A case report of a 62-year-old man also leads to the assumption that higher levels of cardiac glycosides can affect olfaction and taste and that they are able to provoke hyposmia, parosmia and hypogeusia. The man consulted an ophthalmology department because of xanthopsia. He received 0.25 mg digoxin a day for 10

years. He additionally received different other drugs including itraconazole. Digitalism of the eyes was suspected, and digoxin was omitted. Nevertheless, digoxin levels increased to 6.0 ng/ml. The man complained about parosmia since xanthopsia began. In order to assess olfactory threshold levels, T&T olfactometry was performed. Olfactometry revealed a loss of olfaction and a marginal increased detection olfactory threshold. The cognitive olfactory threshold increased considerably. Plasma digoxin levels declined to a normal value (1.9 ng/ml) 13 days after visiting the ophthalmology department and 23 days after the visit, detection and cognitive threshold recovered to normal values. Administration of itraconazole reduces the renal excretion of digoxin. This was probably responsible for increased digoxin plasma levels, and is an explanation for digoxin intoxication. Impact of cardiac glycosides on photoreceptor cells is well known. Because olfactory cells and photoreceptor cells have similar ways of signal transduction, interference of olfaction by digoxin might be the reason for the olfactory disturbances.[63] Additionally, existence of Na^+/K^+-ATPase is known on olfactory cells.[64] Hence, it is possible that loss of olfaction is a result of interaction of digoxin on olfactory cells.[63]

α_1-Agonists

Midodrine

Midodrine is an α_1-adrenoceptor agonist that induces an increase in vascular tone and a decline in blood volume by activating α-adrenergic receptors of vessels and subsequent vasoconstriction.[65] It is applied as an antihypotensive agent for orthostatic hypotension.[66] There are reasonable arguments to believe that midodrine also affects olfactory function. Young et al.[67] reported on a 64-year-old man with orthostatic hypotension, who developed smell disturbances after midodrine intake. Therapy started with the intake of 5 mg midodrine daily. Three months later, the dose was increased to 12.5 mg daily. Accordingly, the man observed impairment of smell and taste with weight loss as a consequence. The dose was reduced to 5 mg midodrine a day again, and consequently adverse effects disappeared. The patient was able to regain his previous body weight.[67]

α_1-Antagonists

Prazosin, terazosin, doxazosin, alfuzosin

Beside α_1-adrenoceptor agonists, selective α_1-antagonists are also noted for causing adverse drug reactions concerning the sense of smell. α_1-Antagonists are used as antihypertensives,[68] although they are not the first-line choice nowadays. Furthermore, they are applied in the treatment of benign prostatic hyperplasia.[68] Treatment with the candidates of class of α_1-adrenoceptor blockers such as prazosin, terazosin, doxazosin, tamsolusin, alfuzosin and silodosin can result in nasal congestion.[69]

Calcium channel blocker

Nifedipine, lacidipine, diltiazem

The calcium channel blockers nifedipine, lacidipine and diltiazem have also been suspected to cause olfactory disorders. For a 59-year-old man, the intake of nifedipine resulted in dysosmia.[70] These findings were previously observed by Levenson et al. in 1985.[71] A case report of a patient who suffered from drug-induced partial smell loss due to lacidipine treatment, underlines the effects of calcium channel blockers on the human sense of smell.[72] In future, studies will be necessary in order to confirm and explore the side effects of calcium channel blockers.

Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors are first-line agents in the treatment of hypertension.[73] Intake of ACE-inhibitors cannot only result in cough, but can also induce rhinitis, nasal blockage and postnasal drainage.[74]

Beta adrenergic receptor blockers

Pindolol

Adverse drug reactions of pindolol administration comprise, among other things, nasal congestion. But these side effects occur only rarely.[75]

Carbonic anhydrase inhibitor

Dorzolamide

Carbonic anhydrase belongs to the zinc metalloenzymes and is responsible for the reversible hydration of carbon dioxide. There is a case report of a 49-year-old man who underwent therapy with timolol 0.5 % and dorzolamide 2 % in a fixed combination (Cosopt®), because of primary open-angle glaucoma. His case supports the hypothesis that the carbonic anhydrase inhibitor dorzolamide may affect human olfaction. Due to an increase in intraocular pressure, the man received dorzolamide as an additional therapy to the beta-blocker timolol. Six months later he went to the clinic with anosmia. One month after introduction of the combination therapy, the man perceived a distortion of smell. Anosmia had been present since the second month of treatment. As a consequence, Cosopt® was discontinued and latanoprost, a prostaglandin $F_{2\alpha}$ analogue, was prescribed. 20 days later olfaction performance recovered to normal values. Further trials which included varying different glaucoma agents by the blinded patient, confirmed the assumption that the carbonic anhydrase inhibitor dorzolamide was responsible for his smelling disability.[76]

Dichlorphenamide

Cavaliere et al.[77] detected the presence of carbonic anhydrase in the columnar ciliated respiratory epithelium by using histochemical reaction. During further investigations, 15 patients who suffered from endocranial hypertension were treated with the carbonic anhydrase inhibitor dichlorphenamide. The aim of the study was to explore whether the drug affects the balance of the ions Na^+, K^+ and Cl^- or the pH-value in the nasal secretion. As a result, the pH-value which was assessed with a surface electrode at baseline and 30, 60 and 90 minutes after drug administration, increased significantly. A peak was registered after 60 minutes. Before and 60 minutes after drug administration, potentiometry was applied, in order to determine the concentrations of the ions, both in the nasal secretion and in the plasma. Results exposed no influence of dichlorphenamide on the plasma, but increased concentrations of Na^+ and Cl^-, as well as diminished concentrations of K^+ in the nasal secretion. As a result, a decline of Na^+ and K^+ gradients between plasma and secretion was observed, whereas the Cl^- gradient increased. The

findings of the present study imply that carbonic anhydrase is involved in the maintenance of the balanced composition of ions in the olfactory mucosa and in the maintenance of the pH of nasal secretions. Furthermore, the transport of electrolytes through the epithelium is probably controlled by carbonic anhydrase.[77]

Nasal decongestants and rhinitis medicamentosa

Nasal decongestants are applied in different medical conditions, such as *"allergic rhinitis, nonallergic rhinitis, acute or chronic sinusitis, nasal polyposis, rhinitis secondary to pregnancy, or rhinitis due to nasal septal deviation or obstruction"*[78] and due to viral respiratory tract infections, in order to relieve nasal congestion.[78] A variety of drugs used in the treatment and prevention of these diseases are available. The most used topical vasoconstrictive agents belong to the sympathomimetic amines and imidazoline derivatives. Agents of both classes act as α-adrenoceptor agonists.[79] Candidates of these classes are listed below.

Nasal decongestants
Sympathomimetic:
-Amphetamine
-Benzedrine
-Caffeine
-Ephedrine
-Mescaline
-Phenylephrine
-Phenylpropanolamine
-Pseudoephedrine
Imidazolines:
-Clonidine
-Naphazoline
-Oxymetazoline
-Xylometazoline

Table 3- Decongestants inducing Rhinitis medicamentosa (newly drawn according to Ramey et al.[78])

Stimulation of α-adrenoceptors by sympathomimetics results in vasoconstriction, which consequently leads to a reduction in mucosal swelling.[80] Although these

agents are helpful in reducing symptoms of the listed diseases as described later, they can originate olfactory disorders in long-term treatment as well. This condition is termed rhinitis medicamentosa:

"*Rhinitis medicamentosa (RM) is a drug-induced, nonallergic form of rhinitis that is associated with prolonged use of topical vasoconstrictors, i.e. local decongestants.*"[81]

After the effect of the vasoconstrictor has disappeared, rebound swelling and nasal congestion can occur, which tempt patients to use higher doses of the nasal decongestant, and more frequently. A vicious cycle begins. Some hypotheses exist concerning the pathological mechanisms that are responsible for rebound swelling after usage of α-sympathomimetic agents. Scientists speculate that treatment with α-sympathomimetics leads to reduced norepinephrine synthesis and release due to a negative feedback mechanism. This results in a diminished vasoconstriction of vessels.[81] Baldwin et al.[82] postulated that vasodilatation after administration of nasal decongestants is a consequence of additional stimulation of β-adrenoceptors. This effect is long-lasting.[82] A further assumption is that tissue hypoxia leads to reactive hyperaemia, which induces vasodilatation. Moreover, vasopressor fatigue due to overuse of nasal decongestants might be another explanation.[79]

The first step in the treatment of rhinitis medicamentosa is to discontinue the use of the decongestant immediately.[78] Different treatment opportunities are proposed, in order to relieve and overcome the rebound swelling after ending the use of nasal decongestants. Treatment options include antihistamines or systemic decongestants, corticosteroid injections into the inferior turbinate, surgery, and nightly sedation. A combination therapy of systemic and topical corticosteroids also seems to be very effective.[79]

Benzalkonium Chloride

In this context, the role of benzalkonium chloride in rhinitis medicamentosa deserves to be mentioned. Benzalkonium chloride is a quaternary ammonium compound added to a multitude of nasal decongestants as a preservative, in order to prevent microbiological contamination.[83] Several studies indicated that benzalkonium chloride may provoke or amplify rhinitis medicamentosa. Graf et al.[84] conducted a study in which he and his research team analyzed the impact of oxymetazoline with or without benzalkonium chloride on the development of rhi-

nitis medicamentosa in 20 healthy subjects. 10 subjects received a nasal spray which consisted of oxymetazoline and benzalkonium chloride, 10 subjects received only oxymetazoline. The nasal spray was administered to the subjects three times a day for 30 days. Ultimately, both decongestants led to rebound swelling and nasal stuffiness. Nevertheless, mucosal swelling and nasal stuffiness were greater in patients who received the decongestant which contained oxymetazoline and benzalkonium chloride.[84]

In another study[85] with a parallel, double-blind, randomized design the influence of different nasal sprays on the olfactory mucosa was studied. 30 subjects participated in the study which extended over 28 days. 10 subjects received oxymetazoline, 10 subjects received benzalkonium chloride and 10 subjects received a placebo as nasal sprays. As a result, benzalkonium chloride led to an increase in mucosal swelling, whereas administration of oxymetazoline produced a significantly higher score for nasal stuffiness when compared to patients treated with benzalkonium chloride. In addition, oxymetazoline induced a significant increase in nasal reactivity in comparison to the placebo. Increased nasal reactivity was also observed in subjects with long-term use of benzalkonium chloride and placebo, but not to such a great extent as with oxymetazoline.[85] All in all, additional side effects of oxymetazoline and benzalkonium chloride on the sense of smell, after long-term treatment, might be responsible for the extended use of nasal decongestants and the occurrence of rhinitis medicamentosa.[80] Furthermore, the finding that the preservative benzalkonium chloride induced increased nasal swelling might be a reason for an exacerbation of rhinitis medicamentosa.[85]

Antithyroid drugs

Methimazole

Even antithyroid drugs may affect smelling capacity. Methimazole is an agent that is applied in the treatment of hyperthyroidism. Its mechanism of action is an irreversible inhibition of thyroid peroxidase, an enzyme which is essential for the synthesis of thyroid hormones.[86] Scientists examined the effects of methimazole on the olfactory system of rodents. For this purpose, rodents were injected with ^{3}H-labeled methimazole intravenously. In addition, some rodents received the cytochrome P450-inhibitor metyrapone, or the thyroid hormone thyroxine, as a

pretreatment 30 minutes before methimazole injection. Results showed that ^{3}H-labeled methimazole bound covalent in the Bowman's glands in the olfactory mucosa which consequently led to widespread lesions in the olfactory mucosa. Furthermore, the findings revealed that pretreatment with metyrapone preserved against both toxicity and covalent binding of methimazole in the Bowman's glands. Metabolic activation of methimazole in the liver by cytochrome P450 is supposed to be the reason for its toxicity. On the contrary, administration of thyroxine before methimazole injection seemed not to be protective against methimazole-provoked damage of the olfactory mucosa. Thus, it is assumed that damage of the olfactory mucosa does not correlate with a low level of thyroid hormones. Mucosal damages were impermanent. Three months after methimazole injection, a recovery of the olfactory mucosa was observed.[86]

Carbimazole

The influence of the agent carbimazole was also investigated with respect to its toxicity on the olfactory mucosa. Carbimazole is an antithyroid drug which is also applied in the treatment of hyperthyroidism. It is metabolized and activated to methimazole.[87] In an animal experiment, rats received carbimazole either perorally via gavage or intraperitoneally. Histopathological examination of rats' olfactory mucosa revealed a distinct degeneration after both methods of administration. Intraperitoneal administration of carbimazole led to more considerable degeneration. The no-observed effect level (NOEL) for administration of carbimazole via gavage amounted to 100 mg/kg.[87]

Local anesthetics

The analgesic properties of local anesthetics are mainly applied in local and regional analgesia. Local anesthetics act at peripheral nerves and their terminals and also at spinal terminals. Local anesthesia arises due to a block of voltage-gated sodium channels which consequently suppresses the initiation of an action potential and signal transduction.[88] Different authors have explored the influence of local anesthetics on olfactory performance.

Tetracaine, lidocaine

In 2003, Welge-Lüsse et al.[89] released a study in which the effects of local anesthesia on human olfaction were examined. 20 volunteers attended the study. A cotton swab soaked with 1 % tetracaine was situated at three different locations within the nasal cavity: In the middle nasal meatus, in the upper nasal meatus and both in the middle and in the upper nasal meatus simultaneously. During another test session, 10 of the 20 volunteers received 4 % lidocaine in both nostrils in a head-down position. Psychometric testing, self-assessment, assessment of olfactory event-related potentials and assessment of chemosomatosensory event-related potentials were conducted before and after administration of the anesthetics. All in all, rating of self-assessed smelling capability declined both after tetracaine and lidocaine administration. Application of the tetracaine swab in the middle nasal meatus increased the odor threshold and reduced odor discrimination. It also prolonged event-related potential and chemosomatosensory event-related potential latencies. Complete transient anosmia was only evoked by direct application of lidocaine into the olfactory cleft in a head-down position.[89]

Lidocaine

A case report of a 62-year-old man illustrates that topical nasal anesthesia can result in permanent anosmia. The man consulted a physician because of breathing impairment, facial pain and cough. Lidocaine 4 % spray was administered to the patient in both nostrils before a fibreoptic flexible endoscopy of the nasal cavity was performed. Physicians diagnosed nasal septal deviation and inferior turbinate hypertrophy. Approximately 10 minutes after the medical examination, the patient noticed anosmia. Anosmia was approved using the ‘Sniffin’ Sticks’ test. A head computer tomography scan was performed in order to exclude other causes of smelling disorder such as infection, tumor or obstruction. Even three months after the appearance of the smelling disorder anosmia was still present and the ‘Sniffin’ Sticks’ test was repeated. Results underlined prior findings.[90]

Agents applied in general anesthesia

Like local anesthetics, general anesthetics are also under suspicion to induce olfactory impairments. Only few reports deal with the effect of drugs used in general anesthesia on olfactory function.

Combination of different drugs

There is a case report[91] concerning a 60-year-old woman who developed anosmia after general anesthesia. The woman was healthy except for thyroid hypofunction, for which she received pharmacotherapy. The woman underwent an urological surgery for treatment of female urinary incontinence. To anesthetise she received 100 µg fentanyl and 180 mg propofol intravenously. Later she received sevoflurane for the maintenance of narcosis. Immediately after recovery from narcosis the woman complained about parosmia, anosmia and dysgeusia. Parosmia was present as *"an unpleasant smell of benzene while eating vegetables."*[91] The woman was admitted to a clinic and a complete otorhinolaryngological examination was performed. Medical examination was not able to detect pathological alterations. The 'Sniffin' Sticks' test was used in order to confirm and classify the smelling dysfunction. Total TDI score revealed that the woman was anosmic. It became apparent that her gustatory function was within the normal range. Therefore, dysgeusia was regarded as a result of loss of smell. A computed tomography scan of the brain and the nasal cavities and a single photon emission computed tomography were performed but could not reveal any pathological abnormalities. Due to an olfactory training, the patient appeared at the clinic with a significant improvement of smell four months later. The TDI revealed that anosmia changed to hyposmia. Moreover, parosmia had disappeared.[91] Another incident of alterations in smelling ability after general anesthesia affected a 47-year-old woman. 6 weeks after cystoscopy and ureteroscopic stone extraction, for which she received a combination of different drugs, such as 50 mg lidocaine, 200 mg propofol, 80 mg succinylcholine and 1-2 % isoflurane in 60 % N_2O with oxygene, the woman reported altered taste and smell.[92] A case report[93] of a 57-year-old woman also underlines a possible impact of drugs used in general anesthesia on human olfaction. The woman underwent elective laparoscopic cholecystectomy due to cholecystitis. For therapy of different diseases such

as depression, acute sinusitis and migraine headaches, she received the drugs fluoxetine, Aspirin®, sumatriptane, calcium/vitamin D, gingko biloba, vitamin C and a multivitamin medicament. Sinusitis was not accompanied by loss of smell. On the day of surgery, the woman received 2.0 mg midazolam for premedication. Afterwards the woman was given 250 µg of fentanyl, 150 mg of propofol and 50 mg of rocuronium. For maintenance of narcosis, sevoflurane (2.5 %), a mixture of oxygen and air, and propofol (25 µg/kg/min) was administered. Furthermore, she received 10 mg morphine for postoperative analgesia and a 1.5 mg transdermal scopolamine patch, 4 mg ondansetron and 8 mg dexamethasone for postoperative nausea and emesis. Two weeks after surgery the woman complained about loss of smell and taste. A sinusitis was excluded. The woman recovered from smell and taste impairments by degrees and regained normal smell and taste abilities six months after surgery.[93]

Ketamine

Ketamine acts as a NMDA receptor antagonist, but different other mechanisms of action are also co-responsible for the effects of ketamine.[94] Anosmia is one of the reported side effects initiated by ketamine although these reports are rare. In a double-blind, placebo-controlled, randomized, crossover trial the efficacy and safety of intranasal ketamine as a breakthrough agent in chronic pain was investigated. 20 patients participated in the study. It turned out that 2 of the patients were affected by adverse drug reactions concerning the sense of smell. One subject complained about rhinorrhea, and one subject experienced nasal passage irritation.[95] One case report[96] concerns a middle-aged woman who received methadone in combination with intranasal ketamine for pain relief. Ketamine was administered by a metered dose inhaler. One puff of the nasal ketamine spray contained 14 mg of ketamine. The woman was allowed to use up to four puffs of the spray within four hours in order to treat breakthrough pain. Six months after initiation of ketamine treatment, the woman reported anosmia. Loss of smell was lasting. The medical examination was not able to reveal any pathological changes as a reason for anosmia.[96]

Hormones

Insulin

Administration of insulin is essential to compensate insulin deficiency in patients suffering from type 1 diabetes mellitus. The disease is characterized by a lack of insulin due to autoimmune destruction of insulin producing pancreatic β cells. It is also used to treat type 2 diabetes mellitus, which is caused by insulin resistance and a deficiency in insulin secretion.[97,98] Werther et al.[99] found a high distribution of insulin receptors within the rat brain, including the olfactory bulb, by using techniques of *in vitro* audioradiography and densitometry.[99] Thus, it was hypothesized that an increase or a drop in brain insulin might influence olfactory processing. A trial was carried out to verify this assumption.[100] Seventeen normal weight normosmic subjects were included in a double-blind, placebo-controlled, balanced within-subject design. Subjects received either a single dose of 40 IU insulin intranasally or placebo. Thirty minutes after administration of insulin or placebo the discrimination test and the n-butanol threshold test of the 'Sniffin' Sticks' test were applied in order to evaluate subjects' smelling ability. Furthermore, blood concentrations of glucose, cortisol and insulin were measured before and 20 minutes after administration of either insulin or placebo. It became obvious that intranasal insulin administration resulted in a higher olfaction threshold for n-butanol whereas the olfaction discrimination ability was not affected by insulin. A significant decrease in plasma glucose level within euglycemic levels was another finding of the study. The results of the present study lead to the assumption that peripheral olfaction capacity is rather influenced by insulin than processes in higher brain regions.[100] Ketterer et al.[101] revealed that short-term hyperinsulinemia led to an increase in olfaction thresholds in normosmic subjects. The 'Sniffin' Sticks' test was used in order to measure the olfactory threshold. A hyperinsulinemic-euglycemic clamp was performed in 8 thin subjects. Measurements were compared to 8 thin fasted subjects who did not receive an insulin infusion. As a result, an increase in odor threshold was observed during euglycemic hyperinsulinemia. No significant alterations in odor thresholds were found in subjects of the control group. All in all, high insulin levels are able to reduce olfactory function.[101]

Neuroleptics

The correlation between extrapyramidal symptoms and olfactory dysfunction has been observed frequently, but the appearance of drug-induced extrayramidal symptoms (EPS) in patients treated with neuroleptics associated with olfactory dysfunction, has not been explored yet.[102]

Haloperidol, flupenthixol, risperidone

Thus, Krüger et al.[102] recruited 79 depressed patients to conduct a study which examined the olfaction ability of patients who underwent treatment with neuroleptic agents and suffered from drug-induced parkinsonism compared to patients who underwent neuroleptic treatment and developed no extrapyramidal symptoms (no-EPS), and also to patients who did not receive neuroleptic agents (no-NL). Smelling capacity including odor thresholds, odor identification and odor discrimination was measured using the 'Sniffin' Sticks' test. All patients were treated with either a selective serotonin re-uptake inhibitor (SSRI) or a serotonin and norepinephrine re-uptake inhibitor (SNRI). Fifty-nine of the 79 patients who suffered apart from depression under psychotic features received one of the D2 receptor antagonists haloperidol, flupenthixol or risperidone. Fifteen of the 59 patients treated with neuroleptics developed EPS. It became evident that olfactory scores decreased significantly in the EPS group, when compared to patients who belonged to the no-EPS and no-NL group. Olfaction capability of no-EPS patients and no-NL patients revealed no significant differences between both groups. In contrast to odor discrimination, odor thresholds and odor identification were correlated with the severity of extrapyramidal symptoms. This implies that olfactory capability deteriorates when EPS increase in severity. It can be assumed that involvement of the basalganglia and dopaminergic pathways in odor processing and *"damage of dopaminergic D2 nerve terminals"*[102] due to the D2 receptor antagonism were causes of present findings.[102] This hypothesis was underlined by results of a study in rats, in which scientists found a direct axonal dopaminergic connection between the substantia nigra and the olfactory bulb, by using axonal tracing studies.[103]

Statins

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme-A-reductase (HMG-CoA reductase). They lower de novo synthesis of cholesterol in the liver. High blood cholesterol levels are associated with atherosclerosis.[104]

Lovastatin

A case of a drug-induced hyposmia was noted in a 69-year-old man, who received 20 mg lovastatin daily for dyslipidemia. 8 days after onset of the statin therapy, he noticed a decline in smell and taste capacity. A complete medical examination was not able to detect pathological causes for his complaints. The man went to the clinic 6 months later. The symptoms remained unchanged. Accordingly, a toxic drug-induced hyposmia was diagnosed.[105]

3. Drugs applied in the treatment of smelling disorders

Although there is a great number of people suffering from smelling disorders, there is still no approved treatment plan available. Consequently, a wide range of recommendations concerning the treatment of olfactory dysfunction are made. Treatment usually comprises different opportunities: Pharmacotherapy, surgery and others.[106] Olfactory training is another possibility to treat olfactory disorders.[107] Pharmacotherapy of olfactory dysfunction is the most common practice.[106]

Corticosteroids in the treatment of different olfactory disorders

Corticosteroids are agents which are most frequently applied. Both systemic and topical administration can lead to a recovery of smelling capacity. Unfortunately, systemic administration of corticosteroids is accompanied by numerous side effects. Several researchers have explored the effects of glucocorticoids on the sense of smell.[106]

Methylprednisolone

In order to explore the effectiveness of systemic glucocorticoids on olfactory dysfunction of different etiologies, Schriever et al.[106] carried out a retrospective study, in which 425 patients with subjective olfactory dysfunction were included. Inclusion criteria were distinct etiologies for smell loss, i.e. post-traumatic, sinunasal, idiopathic, post-infectious and post-surgical. After a thorough medical examination, patients were allocated to one of three etiology groups: idiopathic, sinunasal or other reasons (post-infectious, post-traumatic etc.). Accordingly, the glucocorticoid methylprednisolone was administered to the patients perorally for 14 days. A dose of 40 mg was gradually reduced by steps of 5 mg every other day. Smelling performance was assessed using the 'Sniffin' Sticks' test before and after the treatment with methylprednisolone. As a result the average TDI-score and each sub-test of the 'Sniffin 'Sticks' test including odor threshold, odor discrimination and odor identification revealed a significant improvement after glucocorticoid therapy. Patients with a low TDI score before treatment profited more from treatment, because increase of TDI score after treatment was greater in patients with lower start-TDI. Moreover, findings were not affected by age, gender

or duration of smelling disorder. Glucocorticoid therapy was most effective in patients suffering from sinunasal olfactory disorders. In this group methylprednisolone led to an improvement in 36.7 % of all patients. Especially patients with nasal polyps showed a great increase of their TDI-score. Contrary to that, an improvement of idiopathic smelling dysfunction was only found in 12.1 % of the patients. Glucocorticoids like methylprednisolone act due to their anti-inflammatoric properties. The mechanism of how they lead to an improvement of olfactory dysfunction is not fully understood yet.[106] Findings of another study suggest that glucocorticoids activate the apoptosis pathway in nasal polyps.[108]

Corticosteroids in the treatment of nasal polyposis

Methylprednisolone, fluticasone proprionate

The purpose of the study of Tuncer and co-workers[109] was to evaluate the effectiveness of local and systemic steroid therapy in combination in patients with nasal polyposis. 17 patients with bilateral nasal polyposis participated in the prospective study. Initially, oral methylprednisolone (1 mg/kg) was administered to the subjects. Every fourth day, the dose was reduced gradually by a ¼ of the initial dose within 16 days. Moreover, throughout the whole study period 0.1 mg fluticasone proprionate nasal spray was administered to the subjects twice daily. Patients additionally received an antacid. After the oral corticoid therapy was finished, subjects maintained fluticasone proprionate nasal spray further 2 months. Scores of polyp size, sense of smell, nasal symptoms, facial pain and headache were assessed before and after the treatment by using a scoring system. It became obvious that due to combined steroid therapy, the polyps had disappeared for 12 % of the subjects, while for 76 % of the subjects an involution of the nasal polyps was diagnosed. 12 % of the subjects were refractory. Steroid treatment further led to an improvement of headache, rhinorrhoea, sneezing, facial pain and nasal obstruction. A significant improvement of sense of smell was also ascertained after the steroid treatment. Unfortunately, an eradication of the nasal polyps was impossible.[109]

Mometasone furoate

In 2005, a large randomized, multinational, double-blind, placebo-controlled study was initiated to investigate whether the corticosteroid mometasone furoate is safe and efficient in the treatment of nasal polyposis. 354 subjects suffering from bilateral nasal polyps and nasal obstruction attended the study. The recruited subjects were assigned to three treatment groups. Subjects received either 200 µg mometasone furoate nasal spray once or twice a day or a placebo over a four month period. Compared to placebo, both dosage regimes led to a significant decrease in bilateral polyp grade score and nasal congestion and further improved the loss of smell, postnasal drip and anterior rhinorrhea over the first month. In addition, administration of 200 µg mometasone furoate twice a day was more effective in improving nasal congestion than administration of 200 µg once a day. These findings underline the effectiveness of mometasone furoate in the treatment of nasal polyposis, which consequently delays nasal polyp surgery in patients suffering from nasal polyposis.[110]

Corticosteroids and zinc in the treatment of traumatic anosmia

Prednisolone, zinc

Jiang et al.[111] carried out a study in which the effects of prednisolone and zinc on the recovery of traumatic anosmia were investigated. Patients were randomly assigned to one of four groups. Group 1 received zinc gluconate for one month and the corticosteroid prednisolone for 2 weeks with tapering, patients in group 2 received zinc gluconate. Those in group 3 were treated only with prednisolone and patients in group 4 received no medication. The phenyl ethyl alcohol threshold test was applied in order to assess patients' odor detection threshold and magnetic resonance imaging was performed to determine the olfactory bulbs' volume. All in all, 11 patients (28.2 %) of group one, 9 patients (25.7 %) of group 2, 4 patients (11.8 %) of group 3 and only 1 patient (2.7 %) of group 4 recovered from olfactory dysfunction. Patients of group 1 and 2 showed significantly higher recovery rates compared to group 4 whereas olfactory bulb volumes did not differ significantly between the 4 groups. The findings of the study demonstrate a superior effect of zinc in the treatment of traumatic anosmia. Further research will be nec-

essary in order to confirm the promising effect of zinc in the therapy of olfactory disorders, and to explore the impact of zinc on human sense of smell.[111]

Efficacy of different nasal decongestants

Sympathomimetics

Ephedrine, Pseudoephedrine

As mentioned previously, ephedrine and pseudoephedrine are important decongestants which are applied in different medical conditions to relieve nasal congestion.[78] Ephedrine is an alkaloid found in *Ephedra* genus. The mechanism of how ephedrine and pseudoephedrine exert influence on smelling capacity is a vasoconstriction of blood vessels, which finally mitigates symptoms of nasal congestion.[112] Several studies dealt with the effects of the sympathomimetic amines ephedrine and pseudoephedrine, trying to investigate and confirm the efficacy of both agents in the treatment of nasal congestion.

To evaluate the outcomes of single and multiple dose administration of peroral pseudoephedrine, in terms of nasal congestion in patients suffering from common cold, a double-blind, placebo-controlled, randomized, parallel-group designed trial was carried out. 238 patients with nasal congestion due to acute upper respiratory tract infection (URTI), participated in the study. As an objective method of measurement, rhinomanometry was performed to assess nasal airway resistance. Subjective scores of nasal congestion were measured as well. Findings of the study demonstrated that a single dose administration of 60 mg of pseudoephedrine resulted in better subjective and objective results, in terms of nasal congestion, when compared to placebo. Multiple doses of pseudoephedrine administration led only to significant improvements of objective measurements compared to placebo. Subjective scores on day 3 did not differ significantly from each other.[113]

Another study published in 2014[114] approached the question whether a combination therapy of Aspirin® and pseudoephedrine is effective in the treatment of upper respiratory tract infection symptoms. 833 patients with acute upper respiratory tract infection were included in the trial. Rhinomanometry and subjective congestion rating were used to assess olfactory performance. As a result it was observed that Aspirin® plus pseudoephedrine was more effective in nasal congestion relief over 4 hours than placebo or acetylsalicylic acid alone. These findings were ob-

served with both rhinomanometry and subjective ratings. Eccles et al.[114] ascertained that after 3 days of combination therapy with Aspirin® plus pseudoephedrine, better results were achieved regarding improvement of nasal congestion when compared to Aspirin® plus placebo. On the contrary, Aspirin® plus pseudoephedrine was not superior to pseudoephedrine alone.[114]

Temmel et al.[115] tried to explore the impact of ephedrine on the human chemosensory function. For this purpose, he and his team included 24 healthy subjects in a randomized, placebo-controlled, double-blind study. Subjects were allocated to one out of three groups (A, B or C). Group A received placebo, group B received 0.12 mg ephedrine, and group C received 0.24 mg ephedrine. Measurements were taken at baseline and 15 minutes after administration of either placebo or ephedrine. To assess the olfactory performance, olfactory and trigeminal methods (odor discrimination, intensity ratings, butanol and formic acid thresholds) were applied. Anterior rhinoresistometry was performed in order to assess nasal patency. All in all, application of ephedrine led only to marginal higher nasal airflows. Saline placebo produced an improvement regarding nasal airflow by 3 %. 0.12 mg ephedrine led to an improvement by 9 %, and 0.24 mg ephedrine resulted in an improvement by 5 %. These findings were not statistically significant. Other measures of olfactory function were neither influenced significantly by ephedrine except for formic acid intensity ratings. Those were correlated with nasal airflow measurements.[115]

Oxymetazoline

Like ephedrine and pseudoephedrine, oxymetazoline is an α-sympathomimetic agent. Its impact on olfactory performance in acute rhinitis was investigated in a randomized, placebo-controlled, double-blind study. 36 subjects were divided into three groups. In each subject, a placebo was administered to the left nostril. To the right nostril either a placebo or 0.25 mg x ml^{-1} or 0.5 mg x ml^{-1} oxymetazoline was administered. Following methods were used in order to assess olfactory function: Chemosensory event-related potentials and 'Sniffin' Sticks'. Furthermore, acoustic rhinometry gave information on the nasal volume. Measurements of olfactory function were performed 2, 4, 6 and 35 days after the beginning of rhinitis in order to observe possible effects of the α-sympathomimetic agent on olfaction. Results revealed that oxymetazoline increased the nasal volume. The effect was

not dose-dependent. Differences between both dosages were not statistically significant. Measurements showed that neither olfactory nor trigeminal function were affected by oxymetazoline except an increase of H_2S overall intensity ratings.[116]

Antihistamines in the treatment of allergic rhinitis

Histamine is involved in allergic inflammatory processes and immune modulation. It is known to play a key role in the development of allergic rhinitis. The interaction of histamine with the H_1-receptor evokes allergic symptoms such as nasal congestion, rhinorrhea and sneezing. H_1-Antihistamines prevent allergic symptoms by their antagonistic action at the histamine-receptor.[117]

Levocetirizine

Levoceterizine belongs to the second generation of H_1-antagonists and is applied in the treatment of allergic rhinitis and urticaria. The effect of levocetirizine on patients suffering from persistent allergic rhinitis was investigated by Guilemany et al..[118] 27 patients with persistent allergic rhinitis (PER) and subjective loss of smell participated in the study. The design was a double-blind, placebo-controlled, randomized trial. 14 Subjects received 5 mg levocetirizine daily, 13 subjects received a placebo. Olfactory performance was assessed at baseline, after seven days, and finally after thirty days of levocetirizine or placebo treatment. Measurements in order to assess olfactory performance comprised nasal endoscopy, nasal symptoms, acoustic rhinometry, a skin prick test, peak nasal inspiratory flow, olfactometry (Barcelona Smell Test-24; BAST-24) and nasal nitric oxide. It became apparent that seven days, but not 30 days after the beginning of levocetirizine treatment, loss of smell improved significantly in comparison to the placebo. These findings were observed using a visual analog scale (VAS). On the contrary, olfactometry (BAST-24) could not detect statistically significant differences between levocetiricine and placebo seven days after levocetirizine administration. Nasal symptoms such as nasal itching, sneezing and the global rhinitis score improved significantly both after seven days and after 30 days of drug administration. Furthermore, quality of life and nasal inflammation improved 7 days after the beginning of levocetirizine treatment. It has to be pointed out that the improvement of smelling capacity due to levocetiricine administration was more a

result of reduction of nasal inflammatory processes than of changes in nasal patency.[118]

Azelastine, loratadine

Gambardella[119] conducted a randomized, double-blind, double-dummy, parallel-group study in which 30 patients with seasonal allergic rhinitis were included. For 6 weeks, patients were either treated with azelastine nasal spray (0.14 mg nostril/twice a day) or loratadine tablets (10 mg day). Symptoms including sneezing, nose and eye itching, rhinorrhoea, smell loss, nasal congestion, and nasal mucosa swelling were rated by using a 4-point rating scale. Treatment with both azelastine and loratadine induced reduction of symptoms compared to baseline ratings. Besides, no significant differences between the two treatment regimes were observed.[119]

Drugs with influence on signal transduction pathways

If we pay attention to the role of cAMP in olfactory signal transduction, as previously mentioned[5], it becomes obvious that a lack of cAMP may result in reduced olfactory function. This leads to the assumption that drugs with influence on cAMP level may be interesting candidates for the treatment of smelling disorders. Henkin and co-workers[120] assessed the concentrations of the cyclic nucleotides cAMP and cGMP in nasal mucus in patients affected by smell and taste disorders. For this purpose, a sensitive spectrophotometric 96 plate ELISA technique was applied. It turned out, that if severity of the smell disorder increased gradually, then concentrations of cAMP and cGMP declined gradually. These findings confirm that an alteration in mucus composition of cyclic nucleotides correlates with a decrease in smelling ability.[120]

Theophylline

Theophylline exerts its effects by inhibition of phosphodiesterase which consequently induces higher cAMP and cGMP levels. In addition, theophylline is a potent adenosine receptor antagonist. It is used in the treatment of obstructive pulmonary diseases like asthma bronchiale.[121] To figure out if theophylline affects smelling disorders positively, Henkin et al.[122] included 312 patients suffer-

ing from hyposmia into a fixed design open-label trial. The study lasted six years. Increasing doses of theophylline (200 to 800 mg) were administered to the patients daily within periods lasting 2 to 8 months. After each period, psychophysical and subjective measurements of olfactory function as well as theophylline plasma level checks were performed. Subjective ratings revealed an improvement of olfactory disorder in 157 (50 %). In 34 patients (21.7 %) smelling ability was considered normal. Recognition threshold and mean detection measurements improved significantly with any dose of theophylline, as well as magnitude estimation and hedonic response. Doses of 600 and 800 mg were more effective than doses of 200 and 400 mg. The effect continued throughout the whole period of oral theophilline administration.[122]

Oral theophylline administration is known to provoke various adverse effects. Especially the gastro intestinal system, cardiovascular system and central nervous system are affected. Adverse effects are generally related to theophylline plasma concentration. Because of its complex pharmacokinetics, plasma monitoring is necessary in order to prevent toxic effects of theophylline.[121] Taking these circumstances into consideration, scientists reflected about how to minimize the side effects of theophylline.[123] Therefore, an open-label, single-source, controlled pilot study was performed, which involved 10 patients who suffered from hyposmia and hypogeusia. The purpose was to find out whether intranasal theophylline has a curative effect on these smelling disorders. The ten patients were chosen from the 312 patients who had attended Henkin and co-workers prior trial. The oral theophylline therapy was interrupted 3 weeks to 4 months before inception of the intranasal trial. The patients were asked to administer 20 µg theophylline daily into each nostril for 4 weeks. Changes in smelling and gustatory capacity were assessed using different methods of measurement. These included subjective assessment of taste and smelling function, gustometry, olfactometry, measurements of body weight and serum theophylline level. It became obvious that oral theophylline improved hyposmia and hypogeusia. The effect on olfaction was observed for the first time after 2 months, the maximal effect was achieved within 4 to 12 months. Moreover, it turned out that intranasal application of theophylline had a superior effect on olfaction compared to oral theophylline administration. A positive effect was measured already after one week of intranasal theophylline administration. All in all, 8 of 10 patients experienced an improvement of

hyposmia and hypogeusia after intranasal theophylline treatment. Additionally, the intranasal application prevented systemic side effects based on the evasion of first-past metabolism. The result was that lower doses of theophylline were sufficient and effective. Besides, intranasal application may also evade drug resistance that appeared with oral theophylline administration. A further benefit of intranasal administration may be the direct interaction of theophylline with the olfactory epithelium, which could eventually enable a more effective activation of olfactory receptors. In the end, it has to be mentioned that patients' body weight increased both under oral and intranasal theophylline treatment. Weight gain was higher in patients treated with intranasal than with peroral theophylline. Patients supposed a correlation between weight gain and enhancement of smelling capacity with increased food flavor.[123]

Pentoxifylline

Due to its mechanism of action, the effect of another agent with influence on phosphodiesterase was analyzed in a study. Pentoxifylline also belongs to the class of unspecific phosphodiesterase inhibitors. Thus, it was presumed that PDE inhibition and subsequent increased cAMP concentration might enhance the responsiveness of olfactory sensory neurons towards chemical stimuli.[124] In order to verify this assumption, Gudziol et al.[124] carried out a longitudinal study with nineteen subjects who received pentoxifylline in order to cure inner ear dysfunction. Fifteen patients received 200 mg pentoxifylline as a 2 hour infusion twice a day, in four patients 200 mg pentoxiphylline was administered perorally three times a day. Self-evaluation and the 'Sniffin' Sticks' test were carried out to evaluate subjects' smelling capacity. Anterior rhinomanometry was performed to assess nasal airflow. In summary, administration of pentoxifylline resulted in a decline in odor threshold, which consequently induced a rise in olfactory sensitivity. Odor discrimination and odor identification were not influenced significantly by pentoxifylline. Interestingly, younger patients seemed to benefit more from pentoxifylline administration, due to the fact that the alteration of odor threshold was especially detected in patients with young age. A modification in olfactory thresholds could not be registered in patients older than 70 years. This might be a consequence of the progressive degeneration of olfactory neurons at an older age. A significant change in nasal airflow could not be observed in any of the patients.

In the future, double-blind, placebo-controlled studies will be necessary in order to determine whether pentoxifylline is a beneficial agent to treat olfactory disorders.[124]

Sodium citrate buffer

Thirty-one patients with smelling disorders of different etiologies took part in a study in which the influence of local administration of a sodium citrate buffer on the sense of smell was examined. Olfactory acuity was measured using the odor identification test of the 'Sniffin' Sticks' test. As a result, administration of the sodium citrate buffer into the olfactory cleft led to improved scores in 30 patients within less than one hour. Furthermore, 23 of the patients noticed improved olfaction capability themselves. Administration of the sodium citrate buffer resulted in diminished mucosal calcium concentration and improvement of hyposmia. The authors of the study concluded that changes in the mucosal calcium composition can influence the sensitivity of CNG channels and therefore the excitability of olfactory receptor neurons. Redundant mucosal calcium might be one reason for a decline in smelling ability.[125]

Neurodegenerative disorders and olfactory dysfunction

Scientists discovered that loss of smell is an early symptom of neurodegenerative disorders including Alzheimer's disease and Parkinson's disease.[2] Haehner et al.[126] conducted a study to explore the impact of the MAO-B inhibitor rasagiline on olfactory function in patients suffering from Parkinson's disease.[126]

MAO-B inhibitors

Rasagiline

In the past, results of different animal studies indicated a promising effect of MAO-B inhibitors with regard to olfactory dysfunction. To date, no clinical trials with humans were able to confirm these findings. In a study published recently, Haehner et al.[126] demonstrated, for the first time, an improvement of olfactory function in Parkinson's disease patients treated with rasagiline. This single-center, cross-sectional study comprised 224 Parkinson's disease patients. 74 patients received rasagiline, 150 patients received different other drugs for treatment of Par-

kinson's disease or no medication at all. Olfactory capability was assessed using olfactory threshold, olfactory identification and olfactory discrimination tests. It turned out that patients who suffered from Parkinson's disease for less than 8 years benefited from rasagiline treatment. In those patients, odor discrimination abilities were significantly better in comparison to patients without rasagiline treatment. However, the positive effect of rasagiline was no longer observed in patients with a longer duration of disease.[126]

Drugs with different mechanisms of action

Antiepileptics

Valproic acid

Research on valproic acid, a drug used in the treatment of epilepsy and other medical conditions such as bipolar disorder or migraine prophylaxis,[127] indicated a regenerative effect on neurons in rodents after optic nerve and spinal cord injury.[128] To explore the hypothesis of neuroregenerative effects of valproic acid on olfactory sensory neurons, Ogawa et al.[128] administered 75 mg/kg methimazole, an agent known to exert toxic effects on olfactory function, to 10-weeks-old male ICR mice intraperitoneally in order to generate degenerative alterations in the olfactory neuroepithelium. Afterwards, daily valproic acid was administered to the mice perorally. Histological analysis was performed in order to reveal the effects of valproic acid on recovery from methimazole-induced damage of olfactory mucosa. As a result, the valproic acid treatment dose dependently led to an increase of number of olfactory marker protein positive cells, and to increased epithelial thickness. Increase of growth-associated protein-43(+) cells (GAP-43) and proteins like Ki-67(+), also were stimulated by valproic acid. GAP-43 is used as a marker for neuronal sprouting.[129] The expression of the Ki-67 protein is a marker for cell proliferation.[130] In summary, thanks to its ability to stimulate the differentiation and proliferation of olfactory precursor cells, and also to facilitate the regeneration of olfactory sensory neurons, valproic acid might be a new therapeutic treatment option for patients suffering from smelling disorder due to degeneration of the olfactory neuroepithelium.[128]

A case report supports the hypothesis that valproic acid might be an useful agent in the treatment of olfactory disorders. This case report concerns a 42-year-old

woman who appeared at the psychiatry outpatient department with olfactory hallucinations. For three years, she perceived episodically *"a strong smell of onions"*.[131] The duration of these appearances lasted between 10 and 15 minutes. Idiopathic olfactory hallucinosis was diagnosed. Different medical examinations could not detect any pathological reasons for the smelling distortions. Valproate 800 mg/day was administered to the woman. This treatment strategy led to a distinct improvement of olfactory hallucinations. Both the duration and the quantity of the episodes were reduced and maintenance of valproate intake gave rise to a continuing improvement of the smelling disorder.[131]

Hormones

17-β Estradiol

In a recently published study, Pooley et al.[132] attempted to give evidence of the promoting effect of the hormone 17-β estradiol on the neurite outgrowth. For this purpose mices' olfactory epithelium cultures were either treated with 100 pM 17-β estradiol in ethanol or ethanol alone. Pooley and his co-workers demonstrated that treatment with 17-β estradiol resulted in significant longer neurite outgrowth compared to olfactory epithelium cultures treated with ethanol. An upregulation of estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) expression was observed. Treatment with the selective ERα agonist propyl pyrazole triol created comparable effects on the neurite outgrowth to estradiol, whereas the specific ERβ agonist 2,3-bis-4-hydroxyphenyl exerted no impact on the neurite outgrowth. Besides, neurite outgrowth increased only in estradiol-treated cultures from ERβ knockout mice, as well as wild-type littermades, but not in knockout mice which were ERα-deficient. These findings imply that estradiol stimulates the neurite outgrowth via ERα activation and that olfactory disorders in chronic neurological dysfunction, where lack of estrogen is a hazard factor, are indicative of insufficient axonal olfactory sensory neuron regeneration.[132]

Insulin

Insulin was mentioned earlier as a drug which possibly elicits impairment of olfactory performance. Interestingly, another research team came to opposite results. The aim of the pilot study by Schöpf et al.[133] was to explore the influence

of intranasal insulin in patients with post-infectious smell loss. 10 subjects participated in the study. They either received 40 IU insulin or a placebo. Olfactory performance was measured before and after administration. It transpired that insulin administration resulted in an instant olfactory improvement regarding intensity ratings and sensitivity. Furthermore, patients were able to identify more odors correctly. In addition, patients with a higher body mass index obtained better outcomes with respect to odor identification.[133]

Statins

Atorvastatin

Kim et al.[134] explored in a mouse model whether statins have a positive influence on the recovery of olfactory function after damage to the olfactory system by application of 3-methylindole. The authors investigated the olfactory capability of 24 healthy female BALB/c mice in a randomized placebo-controlled trial after the intraperitoneal injection of 3-methylindole. Olfaction loss in mice was treated either with atorvastatin (10 mg/kg) or normal saline perorally for three weeks using a gastric tube. Changes in olfaction performance were assessed using Western blot analysis and food-finding tests. All mice lost their sense of smell after 3-methylindole administration. Results revealed that nine out of twelve mice that belonged to the statin group were able to pass the food-finding test, whereas in the placebo group, only two of twelve mice were able to pass the test. These findings were statistically significant. Besides, a higher *"expression level of the olfactory marker protein"*[134] was observed in the atorvastatin-group.[134]

Tetracyclines

Minocycline

In the past, scientists assumed that different olfactory disorders, including rhinosinusitis, might be closely connected with apoptosis of olfactory sensory neurons. Despite its antimicrobial properties, the antibiotic minocycline is able to prevent apoptosis. The research focus of Kern et al.[135] was to examine whether minocycline might be an effective agent in the treatment of olfactory dysfunction. In an animal model, mice were divided into two groups. 12 hours before unilateral bulbectomy, and every 12 hours until death, one group of mice received 45 mg/kg

minocycline intraperitoneally. Unlilateral bulbectomy was performed to trigger apoptosis in olfactory sensory neurons. Both after 2 and 4 days after bulbectomy, mice were killed. Immunohistochemical analysis was performed in order to study the viability of olfactory sensory neurons. In addition, caspase-3 activity was determined. In contrast to untreated mice, minocycline induced a partial suppression of sensory neuron death. These findings were observed 2 days after the bulbectomy.[135]

Reden and co-workers[136] tried to prove the effectiveness of minocycline in postinfectious olfactory dysfunction. In a prospective, randomized, double-blind, placebo-controlled trial, 55 patients who suffered from postinfectious olfactory dysfunction were either treated with minocycline 2 x 50 mg/day or placebo for 3 weeks. Olfactory capacity was measured using the 'Sniffin' Sticks' test before, and 7 months after the trial. It became evident that minocycline had no effect on the recovery of olfactory loss. The authors concluded that other mechanisms than apoptosis were responsible for postinfectious loss of olfaction.[136]

α-Lipoic acid

Viral upper respiratory tract infection is one of the most common reasons correlated with olfactory dysfunction.[12] α-Lipoic acid is applied in the treatment of diabetic neuropathy. Past investigations revealed that α-lipoic acid has strong antioxidative properties, and that it is capable of inducing expression of nerve growth factor. This may be an interesting approach for the development of a new therapeutic strategy in the treatment of olfactory dysfunction.[137] In this context, a prospective clinical trial was carried out to explore and confirm this idea. 23 patients with smell loss after an upper respiratory tract infection were selected and included in the trial. 19 patients were diagnosed as hyposmic, 4 patients as anosmic. Diagnosis was made by an otorhinolaryngologist and by patients' history. α-Lipoic acid was administered to the patients in a dose of 600 mg/day. The timeframe of administration lasted from 3 to 11 months. The median period took four months. The 'Sniffin' Sticks' test was applied in order to assess smelling ability. Findings revealed that 7 of the 23 patients experienced no alteration in their smelling ability. Actually, olfactory function was impaired in 2 patients. On the other hand, a moderate increase in smelling ability was assessed in 6 patients, and 8 patients showed considerable improvement in their smelling ability. All in

all, 2 of the 4 anosmic patients were diagnosed as hyposmic at the end of the trial, and 5 of the 19 patients with hyposmia were assessed as normosmic. Furthermore, results revealed a drop in parosmia. At the end of the trial, only 22 % of the patients were diagnosed as parosmic. In contrast, at the beginning of the study, parosmia had been present in 48 % of the patients. The effect of α-lipoic acid also seemed to be age-dependent. α-Lipoic acid improved the olfactory function more in younger patients than in patients older than 60 years.[137] A decline in proliferation of olfactory neurons in old age might be a possible explanation for this finding.[138] In summary, it can be said that α-lipoic acid might be an useful agent in the treatment of viral upper respiratory tract infection. Because spontaneous recovery is not uncommon in post-upper respiratory tract infection, it is necessary to explore the potential benefit of this agent in double-blind, placebo-controlled studies, which involve a large number of patients.[137]

N-methyl-D-aspartate (NMDA) antagonists

Caroverine

Quint et al.[139] explored the effects of the N-methyl-D-aspartate (NMDA) antagonist caroverine on the sense of smell. For this purpose, he and his research team carried out a study which involved 77 subjects suffering from non-conductive smelling disorders. 120 mg caroverine was administered to 51 subjects for 4 weeks on a daily basis. 26 subjects acted as controls. The controls received 400 mg zinc sulfate daily within the same interval. Methods of measurements to assess subjects' olfactory function comprised odor threshold and odor identification tests. Measurements were performed at baseline and after the trial. The results revealed a significant improvement of odor identification and odor threshold in anosmic subjects treated with caroverine. In hyposmic subjects, caroverine led to a significant improvement in odor identification. In contradiction to these results, it turned out that zinc sulfate did not affect smelling ability significantly. It is suggested that NMDA antagonistic activity results in a decreased *"feedback inhibition in the olfactory bulb"*[139] and that inhibition of the excitotoxic effect of the NMDA receptor agonist glutamate were responsible for the observed effects.[139]

Mental diseases as possible cause of smelling disorder

Serotonine-norepinephrine re-uptake inhibitors (SNRIs)

Venlafaxine

A case of a woman suffering from fluctuating episodes of phantosmia for 27 years revealed that under treatment with venlafaxine, a serotonine-norepinephrine re-uptake inhibitor, not only her mood improved but phantosmia also completely disappeared. Phantosmia was present as *"something between a burnt and rotten fruity odor."*[140] The cause of prescription of venlafaxine was a mild depressive state. The woman was healthy except for a hypertension for which she received irbesartan/hydrochlorothiazide. No medical examination was able to reveal the cause of her smelling disorder. Rinsing the nose with saline solution and sleeping attenuated the symptoms. Phantosmia and depression reappeared after forgetting venlafaxine intake for three weeks. After constant drug intake phantosmia did not reappear again. It is well-known that depressive disorders are often accompanied by quantitative smelling disorders like hyposmia or anosmia, but qualitative disorders like phantosmia as an early symptom of a mild depression haven't been reported yet. The case of the woman raises the question whether unexplained phantosmia should be taken into consideration as a possible symptom of a mild depression.[140]

4. Concluding remarks

Despite its considerable significance in our everyday lives, in the past, small importance has been attached to the sense of smell in contrast to vision and hearing. Often, people are not aware of an impaired smelling ability until the disorder has reached a severe state.

Several drugs have been identified to elicit olfactory disorders, but little is known about the underlying mechanisms. It is not surprising that chemotherapeutic agents can originate severe olfactory disorders. But numerous other agents are able to provoke alterations in smelling capacity as well. The fact that often, only case reports which point to possible drug side effects on olfaction are available, underlines that this research area has often been neglected. Only few double-blind, placebo-controlled trials have been conducted in order to understand and prove the effects of drugs on human olfaction. In addition, controversial studies of some drugs impede the assessment of these agents.

Since the impairment of olfactory function can affect nutrition, mood, behavior and thus the quality of an individual's life, it is important to inform patients about possible drug side effects. Furthermore, the close correlation between impaired smelling ability and neurodegenerative diseases, which include Parkinson's disease and Alzheimer's disease, emphasizes that it is necessary to turn one's attention to this field of research.

Beside surgery, pharmacotherapy is often applied to treat olfactory dysfunction. The efficacy of corticosteroids in the treatment of various etiologies must be accentuated. Moreover, nasal decongestants are able to alleviate nasal symptoms, especially in the common cold. The administration of antihistamines successfully relieves symptoms of allergic rhinitis. Several other promising candidates with different mechanisms of action in the treatment of smelling disorders exist, but different etiologies of smelling disorders make it difficult to develop specialized treatment strategies. Double-blind, placebo-controlled studies including a large number of patients are often missing.

In addition, numerous animal experiments were able to confirm both positive and negative effects of different drugs on olfaction. Unfortunately, results of animal experiments are just indicative and cannot always be transferred to human beings.

In conclusion, future studies will be necessary in order to explore the impact of drugs on human olfaction. Harmful substances must be clearly identified and classified. Research concerning treatment of olfactory disorders should be encouraged, in order to introduce a well-established treatment plan for those who are affected by olfactory dysfunction.

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Lebenslauf

Persönliche Daten

Name: Finja Thiermann

Geburtsdatum: 13.04.1985

Geburtsort: Vechta

Staatsangehörigkeit: deutsch

Bildungsweg

Seit 2007: Diplomstudium der Pharmazie an der Universität Wien

2004-2005: Studium der Ökotrophologie an der Justus-Liebig-Universität Gießen

1997-2004: Gymnasium Lohne