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REVIEW

Odorant Metabolism in Humans

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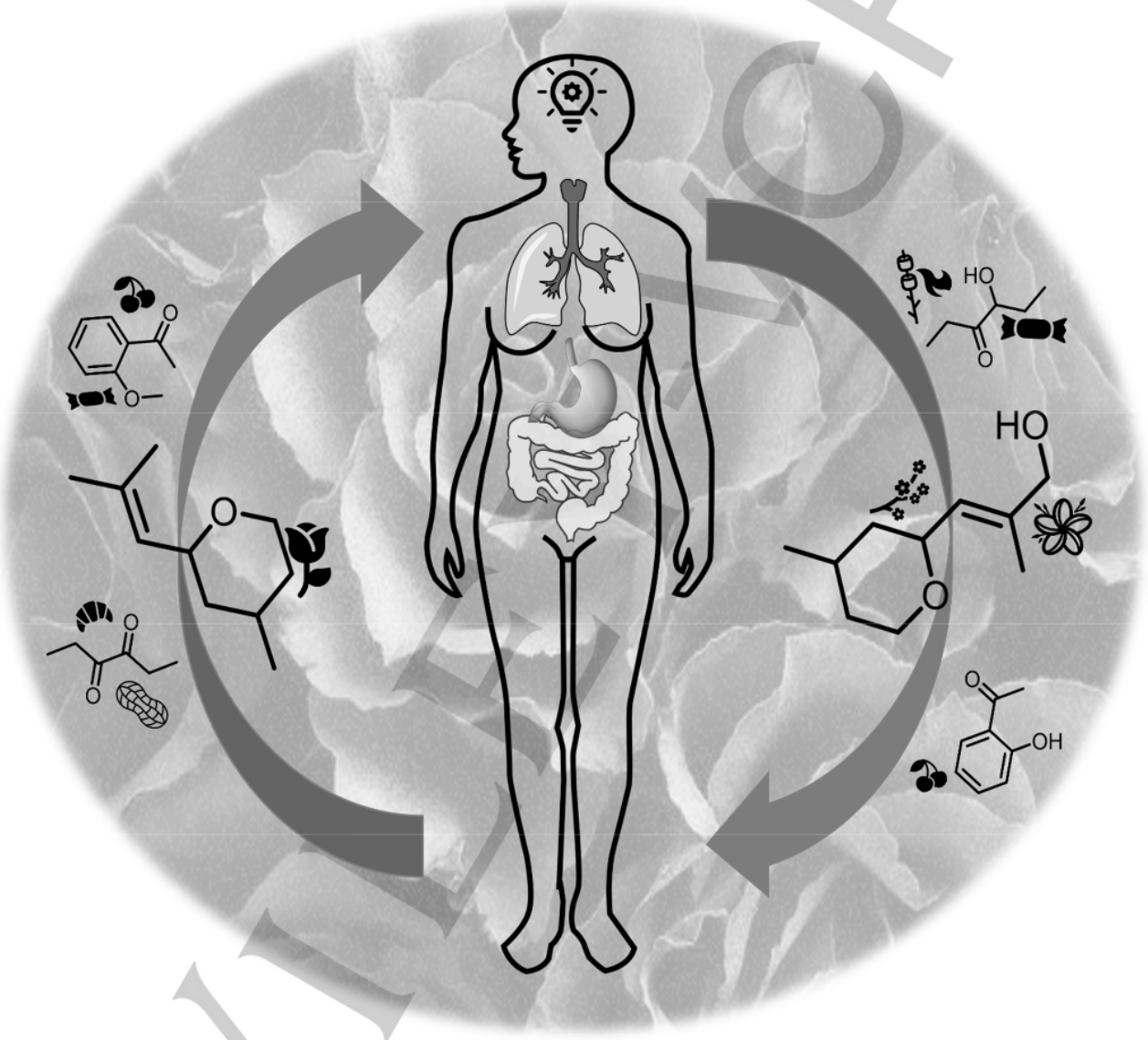

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REVIEW

Abstract: Odorants are relatively small molecules which are easily taken up and distributed in the human body. Despite their relevance in everyday life, however, only a limited amount of evidence about their metabolism, pathways, and bioactivities in the human body exists. With this review, we aim to encourage future interdisciplinary research on the function and mechanisms of the biotransformation of odorants, involving different disciplines such as nutrition, medicine, biochemistry, chemistry, and sensory sciences. Starting with a general overview of the different ways of odorant uptake and enzymes involved in the metabolism of odorants, a more precise description of biotransformation processes and their function in the oral cavity, the nose, the lower respiratory tract (LRT), and the gastrointestinal tract (GIT) is given together with an overview of the different routes of odorant excretion. Finally, perspectives for future research are discussed.

1. Introduction

In 1991, thus almost exactly 30 years ago, Buck and Axel published a report on a novel multigene family in rats, encoding olfactory receptors (ORs)[2]. The discovery of the ORs within the olfactory epithelium (OE) paved the way for further research, and how important Buck's and Axel's work was for achieving a better understanding of olfaction has been recognized in 2004 by the Nobel Committee for Physiology or Medicine. Up to now the theory behind odor perception *via* ORs remained the same: An odorous molecule binds to an OR and thereby triggers conformational changes, by which a signal cascade is started. The chemical information is translated into an electrical signal which is further processed by the brain[3-5]. Later, it was also demonstrated in humans that ORs are expressed, not only in nasal tissues, but also extranasally, and several researchers got interested in the function of ORs in these tissues. For instance, Braun et al.[6] investigated ORs expressed in the gastrointestinal tract (GIT) in humans. By OR activation serotonin release was triggered, which was shown to impact the gut mobility and further physiological processes[6]. Further investigations showed a wide distribution of ORs across the human body, such as muscles, adipose tissue, and the kidney, and their involvement in physiological processes[6-8]. In a recent review, Shepard highlights that several ORs are expressed within different parts of the human renal system, which can bind different odorants, such as β-ionone, or α-pinene. Hereby ORs can influence the regulatory function of the nephron, by which the blood pressure or the glucose concentration within the human body can be influenced, which was already shown in mice[7]. Therefore, ORs are not only important in olfaction, for detecting dangers, such as fire or spoilt food, and for our well-being, but also have additional physiological functions, see also Urbani et al. (2022)[8] for an excellent review. Within this context, it needs to be considered that not only recognition of odorants affects many physiological processes, but also odorant recognition itself is influenced by several mechanisms. Different processes taking place in the vicinity of an OR before, during, or after odorant recognition, the so-called perireceptor processes, are able to modulate chemosensation. In olfaction, perireceptor processes are known to be important factors shaping the perceived odor quality of an odorant. Odorless compounds can be biotransformed into odor-active ones and the other way round[9]. Odor perception is indeed no simple process, but rather a complex one, which is influenced by many factors.

Since 2019 the importance of our sense of smell and, at the same time, its vulnerability has come into public awareness, and it became even more apparent that a fundamental understanding of odor perception is needed. During the SARS-CoV-2 pandemic, many patients suffered from the loss of their ability to perceive odors. In some cases, this inability remained for several months or a dysfunction of the sense of smell was reported for even longer durations[10]. Up to now it is not fully understood how odor perception is influenced by this disease or other diseases such as Alzheimer's or Parkinson's disease[11]. Studies regarding COVID-19 suggested that cilia may be damaged, but without an involvement of the attached OR. Therefore, other mechanisms need to be in charge for the loss of smell. Shelton et al. suggested that enzymes, namely UGT2A1, UGT2A2, UGT2B4, and ST1B1 may be involved.[12] All named enzymes belong to the phase II metabolism and have been shown to be harbored in the human nose, and other organs, being involved in signal termination of odorants. Consequently, the lack of a signal termination may reduce the sensitivity of the ORs[12]. Additionally, other enzymes are currently investigated to predict their involvement in smell impairment[13]. Yet, metabolization of odorants does not only occur in the OE. Especially the liver is known as the major hub for the biotransformation of xenobiotics in humans (for further information on general metabolism within the human body see e.g. Rodrigues and Rowland, (2020)[14]). Also, in other organs such as the kidney, the spleen, the gastrointestinal tract (GIT), and the lungs metabolization of odorants takes place, yet has received less attention. Recognizing the relevance of odorant metabolism in olfactory and other physiological processes of the human organism, astonishingly little knowledge exists about it.

This review aims to highlight our current understanding of the uptake, metabolism, distribution, and excretion of odorants within the human body. The complete passage and turnover of odorants, from their uptake to biotransformation and excretion, is shown in Figure 1 so that the focus of this article - the metabolism of odorants within in the human nose, the oral cavity, the lower respiratory tract (LRT; the LRT comprises the lung and the trachea) and the GIT - can be placed in the overall picture of odorant metabolism. These four cases have been selected in view of their relevance in olfactory perception and uptake of odorants *via* the oral and inhalatory route, and the urgent need for further research related to odorant metabolism in these tissues.

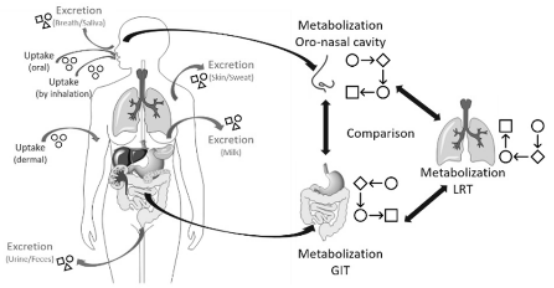

Figure 1: Uptake, metabolism, and excretion of odorants in the human body. Blue: Representation of possible uptake pathways of odorants; Red: Metabolism of odorants in the nose, the lower respiratory tract, the oral cavity, and the GIT (focus of this article); Yellow: Possible routes of excretion. Odorants and metabolites are represented by different forms.

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Nicole Kornbausch was born in Altdorf b. Nbg., Germany. She obtained her M. Sc. in Molecular Life Science from the Friedrich-Alexander-Universität Erlangen-Nürnberg. Her master thesis was conducted in the field of microbiology under the supervision of Prof. A. Burkovski, investigating the induction of biofilm formation by environmental stresses in *Corynebacteria*. Afterward, she started her Ph.D. in Prof. A. Buettner's group. The focus of her research is on biotransformation processes within the nasal cavity.

Marcel W. Debong was born in Saarbrücken, Germany. He graduated with the first state examination in food chemistry at the Friedrich-Alexander-Universität Erlangen-Nürnberg. His final thesis was conducted under the supervision of Prof. A. Buettner on monitoring the biotransformation of *Matricaria chamomilla* aroma compounds in a static *in vitro* digestion model. Currently, he is doing his Ph.D. in Prof. Buettner's group and is investigating dietary aroma transfer in the human body.

Andrea Buettner is Head of the Chair of Aroma and Smell Research at the Friedrich-Alexander-Universität Erlangen-Nürnberg since 2017 and is Executive Director of the Fraunhofer Institute for Process Engineering and Packaging IVV. The current focus of her research is on improving and maintaining food and product quality, on contaminant and metabolite analysis, and on developing analytics and diagnostics in networked and intelligent systems to ensure the highest product quality and consumer acceptance. She pays special attention to sustainable and resource-saving management as well as to product safety and consumer protection.

Jean-Marie Heydel is a Professor in biochemistry and molecular biology and research deputy of the Pharmacy department at the University for Health Science, Dijon, France. All his career was dedicated to the study of Xenobiotic Metabolizing Enzymes from their characterization to their regulation. His current research interests focus on the function of Odorant Metabolizing Enzymes in the olfactory process using different animal models.

Helene Loos is Junior Research Group Leader at the Chair of Aroma and Smell Research at the Friedrich-Alexander-Universität Erlangen-Nürnberg and research associate at the Fraunhofer Institute for Process Engineering and Packaging IVV. Her research focus is on the characterization of volatiles and odorants from biological materials and the impact of odors on human behavior and physiology.

2. Uptake of odorants

Odorants can be taken up by inhalation, orally, or *via* the dermal route. Inhaled odorants reach the mucous membranes of the nasal cavity, the pharynx, the trachea, and the lungs[15-17]. From there, they can enter the brain, the bloodstream, and the GIT. The inhalative uptake of aroma substances is thought to take place very quickly and depends, amongst others, on the lipophilicity (logP value) of the substances, on the blood flow in the alveoli or in the respective epithelia, on the breathing frequency, and on mucociliary clearance[15, 17-19]. In both the upper and the lower respiratory tract, a first-pass metabolism can take place[16, 18].

The dermal uptake of odorants usually occurs upon application of cosmetic or therapeutic products to the skin or from ambient air. Despite the skin being a strong barrier for many drugs[20], it has been shown that several odorants diffuse partially unhindered through the skin layers into the bloodstream, reaching plasma maximum levels within few minutes after application to the skin[21]. Terpenes, essential oils and especially sulfur containing chemicals such as dimethyl sulfoxide are even known for promoting drug permeation through the skin[22-25]. Little evidence exists with regard to enzymes present in human skin[26] and potential first-pass effects are subject to strong interindividual variations[23, 27].

The largest quantity of odorants is usually delivered to the human body along with food intake. Whereas part of the aroma compounds can be absorbed already in the mouth-pharynx area *via* the mucous membranes, as well as simultaneously by inhalation, a large part of food-derived odorants is absorbed *via* the GIT [28]. In general, enzymes are found in most mucous membranes and in saliva, so that odorant metabolism can take place both in the oropharynx and in the GIT (see Table S1, Supporting Information). Our studies, for example, provided evidence that the intestinal epithelium shows metabolic activity towards odorants[29]. Furthermore, the pH conditions in the GIT are of great relevance regarding biotransformation, not only with regard to the pH optima of the respective enzymes but also with regard to directly pH-dependent reactions[30].

Once they are taken up by the body, odorants can either undergo biotransformation or be directly absorbed and distributed in the human body. For instance, Buettner and colleagues showed that the latter can be the case for several aroma compounds ingested with our daily nutrition. After consumption of food such as wine, coffee, or strawberries, the original aroma compounds could still be detected in the exhaled breath [28, 31-33]. Aroma compounds (and their metabolites) can also be detected in human adipose tissues[34-35]. Specifically, lipophilic aroma compounds showed an increased accumulation in adipose tissue of humans and mice[36-37], which may result in a delayed onset of physiological effects or delayed excretion.

3. Function and main steps of the metabolism of xenobiotics

In general, the metabolism of xenobiotics and thus the odorant metabolism can be divided into three phases. In phase I, various reactions take place, such as epoxidation, hydroxylation, dealkylation, oxidation, reduction, and/or ester cleavage. These are catalyzed by enzymes such as cytochrome P450 (CYP), to name the most important representatives of phase I enzymes (see Table S1 in Supporting Information for an overview of enzymes involved in odorant metabolism within the human body). In principle, phase I metabolism is intended to promote the excretion of substances, either by increasing their water solubility or by functionalizing them in preparation for subsequent conjugation in phase II metabolism. However, it can also lead to the toxification of certain molecules. This is exemplified in Figure 2 for pulegone, a monoterpenoid odorant. After monooxygenation (phase I), further reactions in the human body may produce menthofuran, which leads to hepatotoxic and pneumotoxic effects of pulegone at higher concentrations[38-41].

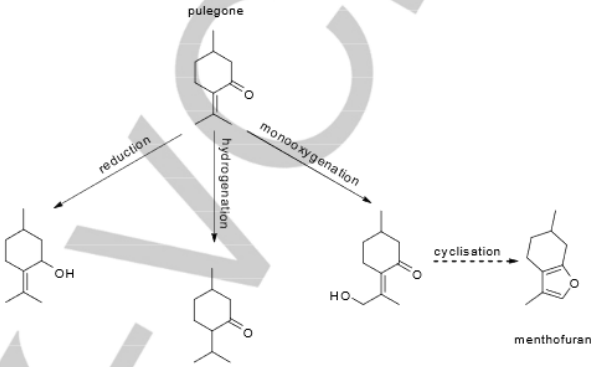

Figure 2: Representative steps of the pulegone metabolism in humans. The monoterpene pulegone is the main component of peppermint oil, which is used, for example, in sweets. The product of monooxygenation can be cyclized to menthofuran, which leads to hepatotoxic and pneumotoxic effects of pulegone. (Graphic based on Rychlik, 2017 p. 622)[42]

In the subsequent phase II, the previously generated metabolites are conjugated with polar groups to increase hydrophilicity and thus facilitate excretion. Common polar conjugation moieties are glutathione, glucuronic acid, and sulfate, which are linked to odor-active compounds by enzymes such as glutathione-transferase (GST), UDP-glucuronosyl transferase (UGT), or sulfotransferase (ST). Table S2 (Supporting Information) provides an overview of enzymes involved in phase II of odorant metabolism.

Phase II metabolites are often relatively large and polar molecules and therefore difficult to excrete by passive transport. This is where phase III of the metabolism comes into play, to which transporters such as ABC transporters (ABC: ATP binding cassette) can be assigned. Important representatives of these transporters in human metabolism are MRP1, MRP2, MRP3, MRP5, and MRP6 (MRP: Multidrug Resistance-Related Protein). For example, the phase III transporters MRP1 and MRP3 are located at the basolateral side of polarized liver cells, excreting metabolites into the blood, from where they reach the renal tract for final urinary excretion. In contrast, MRP2 transporters are generally localized at the apical membrane of these cells, which means that metabolites transported by MRP2 are preferentially conveyed *via* bile into the digestive tract[43].

All these processes can occur to varying degrees in different parts of the human body, e.g., in the kidney, the spleen, and the LRT [18, 44-54], though the liver is the most important and prominent metabolic organ[38-39, 55-57]. The liver is thereby responsible for the utilization of food components and the breakdown of metabolic products, drugs, and toxins. Odorants are also metabolized in the liver, as shown exemplarily for rose oxide (Figure 3) [57], or 1,8-cineole[58-60].

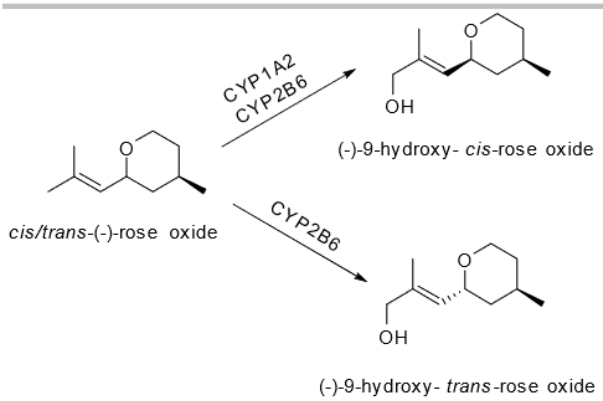

Figure 3: Hepatic metabolism of rose oxide by different CYPs[57].

The same principle of catalysis can be found in all other organs which harbor any kind of CYP450. In Figure 4 the mechanism of oxygen insertion catalyzed by CYPs is shown.

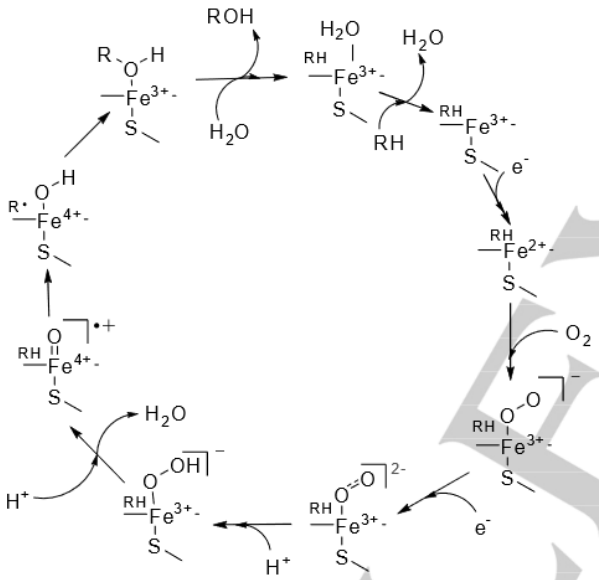

Figure 4: Catalytic cycle of CYP450. In accordance with Meunier et al. (2004)[61]

4. Odorant metabolism in the nasal and oral cavities, the LRT, and the GIT

4.1. Odorant metabolism in the nose

The nose is permanently exposed to volatiles, and accordingly exhibits numerous enzymes of phase I and phase II metabolism such as CYPs, flavin monooxygenases (FMOs), NADPH-cytochrome P450 oxidoreductases (CPRs) (NADPH: nicotinamide dinucleotide phosphate), GSTs, and UGTs[62]. These are predominantly located in the olfactory and/or respiratory nasal epithelium, and partially in the mucus. To date, nasal metabolism has only been studied for a few odorants, some examples of which are presented below. For instance, Schilling (2017)[9] reported that 2-methoxyacetophenone is metabolized by demethylation to 2-hydroxyacetophenone (Figure 5).

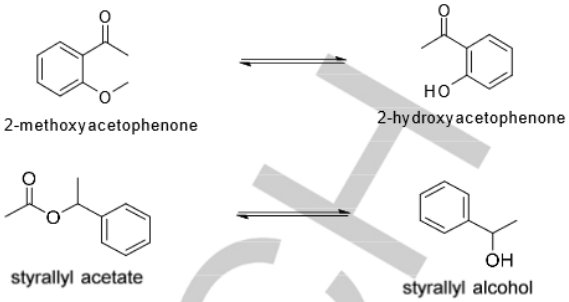

Figure 5: Nasal metabolism of 2-methoxyacetophenone and styrallyl acetate.

A similar observation was made for styrallyl acetate (Figure 5). In this case, an ester cleavage occurs, forming styrallyl alcohol. In these experiments, participants inhaled the odorants and then exhaled into a glass funnel so that the breath could be analyzed in real-time by APCI-MS (Atmospheric Pressure Chemical Ionization Mass Spectrometry). In both cases, the metabolites were detected in the first breath following inhalation[9].
Robert-Hazotte et al. (2019)[63] investigated the nasal metabolism of pentane-2,3-dione, hexane-3,4-dione, and isoamyl acetate in rats (Figure 6). The metabolites were shown to elicit a different odor impression than the original molecules.

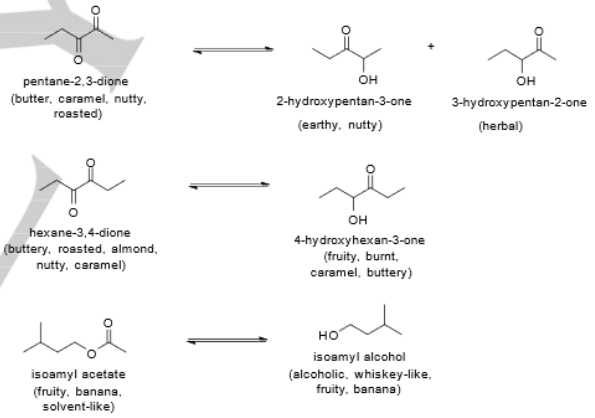

Figure 6: Enzymatically catalyzed reduction of diketones via dicarbonyl/L-xylulose reductase (DCXR), and enzymatically catalyzed ester cleavage via carboxylesterase in the respective nasal metabolism of pentane-2,3-dione, hexane-3,4-dione, and isoamyl acetate[38, 63-64]. Odor qualities were compiled from Heydel et al. 2019[38] and from an in-house odorant database of the Chair of Aroma and Smell Research, FAU (unpublished data).

It can be deduced that nasal metabolites can influence odor perception, given that their concentration is above their detection threshold. Ijichi and colleagues[65] recently confirmed this notion. Among others, they investigated the metabolism of 2-furfurylthiol and hexanal and proved that the metabolites furfuryl methyl sulfide and hexanol can be formed *in vivo* in a concentration range relevant for odor perception[65]. More recently, the same group investigated the conversion of aldehydes to their corresponding alcohols in the human mucus obtained from the olfactory cleft or respiratory tissue, the latter showing a lower metabolism for octanal, hexanal, and 2-methybutanal. Additionally, hexanal

mucus metabolism was significantly lower in participants with idiopathic olfactory impairment[66]. Takaoka et al. showed the enzymatically driven oxidation of aldehydes to their corresponding carboxylic acid, and the involvement of aldehyde oxidases in mouse. Since AOX are also found in in the human OE this might give a starting point for further investigations[67]. Previous studies additionally showed that the speed of the enzymatic generation of metabolites is in a similar time scale to odor perception (hundreds of milliseconds range)[38]. Consequently, inhibition of the relevant enzymes present in the nose – referred to as odorant metabolizing enzymes (OME) – and thus inhibition of metabolite formation can be suggested to have an impact on odor perception[68]. Schilling (2017)[9] showed indeed that a molecule described as woody, fruity, and raspberry-like was in most cases only perceived as woody and fruity when nasal metabolism was suppressed. For this purpose, an odorless, volatile inhibitor was presented to the participants to block the enzymatic reaction[9]. Additionally, competitive effects may modulate odor perception, as suggested by a study of Hanser et al. (2017)[69] in rabbit pups. They showed that the mammary pheromone is perceived at sub-threshold concentrations when a so-called metabolic challenger odorant is simultaneously present, preventing phase II metabolism of the pheromone and thereby increasing its relative concentrations at the receptor level. Similar results were obtained when enzymatic activity was reduced by *in vivo* mucus washing (Robert-Hazotte 2019)[39]. Phase II enzymes are also thought to contribute to perireceptor events in human olfaction. Schwartz et al. (2020), for instance, determined the localization of GSTs in respiratory epithelium obtained from the olfactory cleft and showed both binding and conjugation of odorants by recombinant human GSTs[70].

4.2. Odorant metabolism in the LRT

A largely investigated topic concerning the human LRT is the role of xenobiotic-metabolizing enzymes in the development of lung cancer. One focus of the related research is placed on the major carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (nicotine-derived nitrosamine ketone: NNK) and its metabolites which are formed by the CYPs harbored in the lung. Although studies were extensively conducted, the literature is still partly conflicting with regard to the subfamilies of CYPs and their localization in the human lung tissue. These discrepancies can be traced back to very low amounts of CYPs within the human lung and their specific distribution regarding different cell types of lung tissue[45, 71]. Besides CYPs a great variety of other enzymes are found in the lung, including EPHX (epoxide hydrolase), NQOs (quinone oxidoreductase), STs, and GSTs (glutathione transferase)[71], which is not surprising since the lung forms one of the first lines of defense against inhaled xenobiotics. Moreover, as stated by Hukkanen et al. (2002)[45], the lung can also be considered to contribute to systemic metabolism: All substances which are applied topically, subcutaneously, intravenously, or intramuscularly are transported *via* the bloodstream through the lung before reaching the liver – the lung thus also forming the first line of defense in these cases. Further, a fraction of potentially harmful substances that are formed by the hepatic first-pass effect is transported to the lung which then acts as second line of defense.

Concerning the metabolism of odorants within the human lung, only few investigations were conducted and most of these were motivated by toxicological aspects. Harrison et al. (2003)[72], for instance, demonstrated that the common anesthetic and additionally odorous compound propofol (2,6-diisopropylphenol) is metabolized by the human lung. Using proton transfer reaction mass spectrometry (PTR-MS), they detected the metabolites 2,6-diisopropylquinone and 2,6-diisopropylquinol in exhaled breath after intravenous application of propofol. The odor attributes of these metabolites were not determined[72]. Another example has been provided by Zaccone et al.[73], who studied biotransformation of diacetyl and 2,3-pentanedione by cultured airway epithelial cells and report acetoin and 2-hydroxy-3-pentanone as the respective metabolites. Given the diverse metabolic activities along the respiratory tract, the distinction between nasal cavity metabolism and the metabolism within the LRT appears thus not trivial in *in vivo* conditions.

4.3. Odorant metabolism in the oral cavity

During eating or drinking, several mechanisms can significantly influence retronasal aroma perception. Aroma compounds can be released *via* mechanical and enzymatic processes, can be absorbed to the oral mucosa, or derivatized by enzymes or chemical reactions. If odorants, such as 2-furfurylthiol, are rapidly metabolized, the likelihood of accumulation decreases. Less volatile, lipophilic flavor substances, however, are often absorbed by the oral mucosa to a considerable extent and can form a depot from which they can be gradually released, resulting in an "aftertaste" effect. Indeed, a high metabolizing activity toward odorants (2,3-pentanedione and octanal) in oral mucosa and saliva was associated with a lower persistence measured by analytical and sensory means[74]. Additionally, there may be comparable processes as reported for drugs; these are often resorbed by mucosal tissue and transported to other body parts. In 2002, Buettner showed in a pioneering work that esters, aldehydes, and thiols can be modified by human saliva[75-76]. This phenomenon could be attributed to enzymes since it was not observed after thermal denaturation of saliva[31, 77]. Enzymatic activity is present in saliva, but also in oral epithelia: amongst others, ALDHs (aldehyde dehydrogenase), AKRs (aldo-keto reductase), ADHs (alcohol dehydrogenase), and CYPs have been described in the salivary glands and/or oral mucosa[55, 78] and can contribute to the metabolization of odorants, as reviewed recently by Schwartz et al. (2021)[79]. Itobe et al. confirmed these findings and broadened them by showing that after swallowing a model drink, containing 10 ppm of e.g. hexanal, thiols or other aldehydes, metabolites could be detected by the first exhale through the nose. Hexanol was formed in the case of hexanal and methylated thiols in case of the thiols. However, their experimental setup did not allow for localizing the metabolic activity, which could have taken place either in the nose or in the mouth[80]. Ployon et al. (2020)[55] recently showed that in addition to aldehydes and esters, diketones and alcohols are also metabolized by salivary enzymes, such as ALDHs, reductases, and carboxylesterases (CESs) (Table 1). For the latter one the mechanism of ester hydrolysis is shown in Figure 7 for styrallyl acetate, according to a mechanism suggested by Wang et al[1].

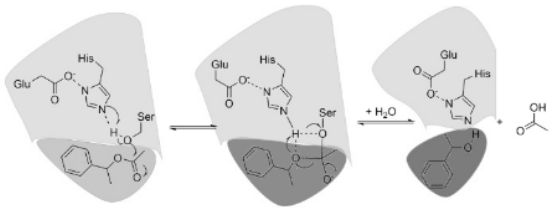

Figure 7: Mechanism of ester hydrolysis of styrallyl acetate by CES according to Wang et al.[1]

The resulting metabolites may elicit additional or different odor impressions as compared to the parent compounds, as shown for 2-furfurylthiol by Ijichi et al. (2019)[65]. Consequently, metabolism in the oral cavity influences retronasal odor perception[55, 65, 75-76, 81]. In that regard, it is interesting to note that various substances, such as 6-gingerol or citric acid, are able to increase the activity of enzymes or their formation in the oral cavity. Bader et al. (2018), for instance, showed that 6-gingerol promotes the release of sulfhydryl oxidase 1 so that a lower concentration of the substrate 2-furfurylthiol was detected in exhaled air, whereas an increased furfuryl disulfide (metabolite) concentration was observed[82-83].

Table 1: Examples of odorant metabolism due to conversion by human saliva[55]*. Odor qualities were compiled from the Leibniz-LSB@TUM odorant database*[84] *and from an in-house odorant database of the Chair of Aroma and Smell Research, FAU (unpublished data).*

Compound	Odor	Metabolite	Odor
Nonan-2-one	fruity, musty	Nonan-2-ol	fruity, green
Decan-2-one	fruity, flowery	Decan-2-ol	soapy, sour
Pentane-2,3-dione	buttery	2-Hydroxy-3-pentanone,	truffle, earthy, nutty, hay-like, buttery
		3-Hydroxy-2-pentanone	fruity, green, berry-like
Ethyl hexanoate	fruity, pineapple	Hexanoic acid	sweaty
***trans*-2-Hexen-1-al**	green apple, bitter almond	Hexenoic acid	musty
Octanal	citrus-like, soapy	Octanol	citrus-like, soapy, fatty

4.4. Odorant metabolism in the GIT

After the food has undergone initial breakdown processes in the mouth and pharynx, the food pulp is transported further into the GIT *via* the esophagus. A variety of enzymes are active in the GIT to break down the food and make it absorbable. Because the GIT is confronted with an abundance of xenobiotics and endogenous substances on a daily basis, it is equipped with diverse enzymes that become active if required. As part of this phenomenon, some of these enzymes may also be involved in the metabolism of aroma compounds. All in all, the GIT is able to adapt the metabolism to the diet as well as to different exposure scenarios[85]. For example, Michelsohn showed that an increased protein and fat content of the diet can increase the secretion of trypsin in humans[86]. In model studies on animal cells, it was possible to show that intestinal epithelial cells are also modulated in their morphology and functionality by exposure to aroma substances[29]. Possible effects on potential biotransformation processes, but also resorption processes can be assumed[87]. Furthermore, Heinlein and Buettner (2012)[30] showed that aroma compounds, especially terpenoids, are derivatized in an *in vitro* digestion system and that both the derivatives and the reactants, being readily taken up, can exert physiological effects [30, 87].

Nevertheless, many questions are still barely answered today. As one aspect of consideration concerning the processes in the human intestine, one needs to differentiate between the small and the large intestine. In the case of the small intestine, the acidic chyme leaving the stomach is buffered to neutral pH and is mixed with hydrolytic enzymes, such as proteases, lipases, and amylases. These stem primarily from the pancreatic secretion in the duodenum but further digestive agents such as the bile and other secretions also play their roles in the intestinal digestion and uptake processes. In the large intestine, on the other hand, fermentative conversion needs to be considered additionally. All in all, the diverse processes are complex [88]. Since pH gradients, numerous enzymes, as well as 10,000 to 100,000 different kinds of bacteria are active in the large intestine, a differentiation between bacterial and human metabolism is difficult under *in vivo* conditions[89-90].

4.5 Comparison of potential odorant metabolizing activities in the nose, LRT, saliva, and GIT

Table 2 lists enzymes that are considered to be involved in odorant metabolism and occur in at least one of the four body sites under consideration here. By compiling this data, we aimed to compare the potential odorant metabolizing capacities of these body sites, based on the available data reported so far in literature. With the protection of the tissue being a main function of metabolization, one could predict that those parts of the human body, which frequently encounter odorants or potentially toxic volatile compounds, are well equipped with enzymes. This is expected to be an effective protective mechanism of the human body since phase I metabolism predominantly causes detoxification and possible pollutants can be excreted more easily [65].

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Table 2: Phase I enzymes in the nose, LRT, saliva, and GIT according to Table S1 (Supporting Information).

Phase I	Nose	LRT	Saliva	GIT
CYP	21	52	12	12
ALDH	4	20	16	16
Aldehyde reductase	1	0	1	0
AKR	1	14	7	2
ADH	7	9	6	8
CES	1	5	3	2
DCXR	0	1	1	0
Epoxide hydrolase	2	2	3	3
FMO	2	6	5	5
Sum	39	108	43	50

The highest number of phase I enzymes was described in the LRT (Table 2). Since substances taken up *via* the lungs can bypass the first-pass effect of the liver, this finding is more than plausible considering the lung being one of the first lines of defense after the nasal and the oral metabolism which form the very first lines of defense to the exterior world. In comparison, the nose, saliva, and the GIT appear to have a less versatile enzyme equipment. One possible explanation regarding the GIT is that odorants can be transported from the GIT to the liver where further metabolism occurs so that a complete metabolization within the GIT is not required. Additionally, plenty of bacterial enzymes can be expected to be active in parts of the GIT. Furthermore, humans generally avoid the uptake of potentially hazardous substances, e.g. by adjusting their breathing and food intake behavior – the sensory systems harbored by the nose and the mouth playing a major role in determining the quality of inhaled or ingested odorants. Thereby, food intake allows a more thorough screening and can be more easily controlled than inhalational processes. Looking at the subsequent phase II metabolism, it is striking that, according to Table 3, only few phase II enzymes appear to be present in saliva and the nose whereas significantly more would be present in the GIT and the LRT. Regarding the lung, a high number of enzymes can be expected because over 40 different types of tissues were detected, with each tissue type harboring distinct enzymes[45].

Table 3: Phase II enzymes in the nose, LRT, saliva, and GIT according to Table S2 (Supporting Information).).

Phase II	Nose	LRT	Saliva	GIT
GST	15	22	16	20
NAT	0	4	3	4
Rhodanase	1	1	1	1
MT	0	8	9	8
ST	3	18	6	17
UGT	11	21	14	18
Sum	30	74	49	68

Phase II enzymes are, in any case, surely important in oral and nasal epithelia as they support the fast elimination of potentially hazardous substances. Rapid derivatization and removal of odorants appear also to play a crucial role in maintaining the sensitivity with respect to odor perception, regenerating the olfactory system, and staying alert for further stimuli [39, 91]. Nevertheless, there might be several reasons for the apparently lower occurrence of phase II enzymes in saliva and the nose. The oral cavity gets first in contact with potentially essential nutrients. An extensive phase II metabolism at this early stage could lead to a reduced bioavailability and be disadvantageous regarding the uptake of beneficial trace compounds and their metabolites, nutrient supply, and energy balance. Additionally, phase II enzymes are often membrane-bound and require cofactors that might not be readily available in saliva. Finally, current literature concerning odorant metabolization in the nose and oral cavity is still limited and often focuses on the effects of CYPs, due to their activating potential and additional role in detoxification and elimination, but also due to the initial focus on this enzyme class in the context of the so-called perireceptor events. Nonetheless, there might be far more enzymes harbored in the oral and nasal cavities that still await their revelation, and are, accordingly, not yet listed in Tables 2 and 3.

5. Excretion

Excretion is the final step of a substance's passage through the human body. It occurs primarily *via* breath, urine, or feces, while the concrete pathways and partitions depend on various factors and can vary greatly. Even if the available evidence originates from distinct studies and therefore prevents direct comparison, this variability can be illustrated by exemplary reports on eugenol and linalool (and their metabolites), for which the renal pathway has been reported to account for 95% and 60% of excretion, respectively[92-93]. The pulmonary and fecal route were additionally mentioned to contribute to excretion of linalool. However, other routes of excretion such as *via* skin, sweat, or human milk can also play a role in the elimination of aroma compounds, and influence the time course of excretion, though they have been neglected in most studies so far. As a further example demonstrating the different routes of excretion, garlic-derived odor-active compounds can be mentioned. It is well known that breath is tainted with a garlic-like smell after ingestion of garlic, and this has been traced back to sulfur compounds such as diallyl

disulfide and allyl methyl sulfide[94]. Additionally, the excretion of garlic-derived metabolites was shown by Scheffler et al.[95-98] for urine and breast milk. Three metabolites of allicin were detected, namely the garlic-like smelling allyl methyl sulfide, and the odorless molecules allyl methyl sulfoxide and allyl methyl sulfone. All three were detected in human breast milk and urine, first after about 1 h and up to 8 h[95-96]. Recently, Sato et al. further showed that ingested sulfur-containing foods, such as garlic, are further metabolized within the human body and that metabolites, namely diallyl disulfide and allyl methyl sulfide, are emitted *via* skin, in a time- and body part-depending manner[99].

In general, the elimination of most aroma compounds in their original, unmodified form is to be regarded as a fraction compared to the elimination of their metabolites[21]. Furthermore, in those cases where aroma compounds exert a caloric contribution, the major part may be excreted as CO_2 *via* the lungs. This affects mainly short-chain fatty acids or alcohols like hexanoic acid or ethanol, and potentially some other components as well[100]. Other odorants are subjected to an enterohepatic circulation, which is characterized by excretion *via* the bile followed by reabsorption via the small intestine. This has been demonstrated for menthol and linalool, for instance[101-102]. All in all, most aroma compounds are biotransformed and distributed within the human organism according to quite complex routes, which is why the time until final excretion is sometimes difficult to estimate. Similarly, an accurate and fully comprehensive prediction of the route of an aroma substance through the human body is still difficult due to the complexity of the involved processes. A rough estimation of the most likely excretion route of an aroma compound can, however, be achieved based on the work of de Lacy Costello et al. (2014)[103], which lists reports from various publications on the excretion of numerous volatile substances in humans[103].

6. Future perspectives of research in the field of odorant metabolism and its applications

This review article provides an overview of the uptake, metabolism, and excretion of odorants. In addition to compiling enzymes possibly involved in odorant metabolism in different organs and body sites, a special focus is set on highlighting our current understanding of odorant metabolism in the nose, the LRT, the oral cavity, and GIT.

The metabolism of odorants still holds many open questions. On the one hand, further fundamental research is needed to fully characterize the enzymes involved in odorant metabolism, including their expression patterns and the kinetic as well as biochemical principles of odorant conversion in model but also in authentic systems. Further studies should also address activation of ORs by odorants and their metabolites, to get a comprehensive view of the interplay of enzymes, receptors, and their ligands (see Asakawa et al. 2017)[104]. Especially little is known concerning individual factors that influence odorant metabolism. By applying pharmacogenomics[105], the genetic variability of phase I and phase II enzymes can be mapped, and ultimately a more accurate picture of the probable metabolization pathways can be drawn, even in individual organisms. In this respect, modulation of metabolism pathways due to dietary or other types of exposure needs to be considered in more detail. For example, individuals being exposed to chemosensory stimuli due to their work or leisure time environment may be subjected to modulated metabolic processes.

It must also be kept in mind that metabolism does not represent a rigid, but an adaptive system. If, for example, the uptake of an aroma substance becomes too high, its usual excretion pathway may be oversaturated, and alternative routes may be recruited[106]. Apart from that, many other factors influencing metabolic routes are yet to be explored, such as developmental phases in life, changes in hormonal status, or individual microbiota. One aspect to be highlighted here relates to the communication and transmission of social information *via* chemical cues and signals – be it about the physiological or psychological status of a human being. Smell emanations and volatile signatures are in this context related to metabolism processes. Amongst others, body odors are implicated in breastfeeding[107-109] and mate choice[110], and both their production and perception can be expected to be shaped by odorant metabolism.

On the other hand, further research is needed to enhance our understanding of the physiological significance of odorant metabolism concerning the bioactivity of the respective odorants and their metabolites. In this regard, both sensory and non-sensory activities, and their interrelation, need to be considered. The potential physiological effects of many aroma substances, let alone their metabolites are still widely unclear. As the derivatives change their smell properties, they might also gain other physiological functions – or lose them. As an example, Kirsch and Buettner[60] were able to determine the partially divergent odor activities for the metabolites of 1,8-cineole and could even show that some of these metabolites were higher in smell intensity than the initial compound itself. Aroma compounds do not only smell but often exert additional physiological properties that can even be quite pronounced like the acute toxicity of thujone which blocks the chloride channel of γ-aminobutyric acid (GABA)[111]. In the case of linalool, which has been shown to have $GABA_A$ receptor-modulating potency, several of its metabolites, e.g. 8-hydroxylinalool, turned out to be less GABA-active[112]. Other essential oil aroma compounds can inhibit or activate CYPs, such as the clove aroma compound eugenol, which can inhibit the activity of CPY1A1 as well as CYP1B1[113]. Surely it becomes evident that the complexity of the intertwined processes involving odorants and human physiology is enormous – and is likely to bring about even higher variation if considered on an individual basis.

New methodologies and models need to be developed to enable a comprehensive investigation and evaluation of odorant metabolism, notably when it comes to realistic scenarios and thus trace concentrations and mixtures of volatile compounds[106]. Procedures for the accurate application and quantitative detection of odorants also in small-scale environments need to be developed. For instance, in the nose, usually, only the gaseous phase has been assessed, but not the aqueous mucus. This is especially interesting as the mucus has been shown to retain a large proportion of the aroma compounds in the nose and thus should not be neglected[114]. In many cases, however, the concentrations of highly odor-active compounds present in breath or mucus are still below the detection limit of current analytical instrumentation or require time-consuming sample preparation.

Besides the manifold possibilities to advance fundamental knowledge in this area, understanding odorant metabolism also offers the potential for being translated into our daily life. One aspect relates to the sensory perception of food and food

preferences. Recently, metabolic activity in the oral cavity has been linked to the liking of cauliflower in children[115]. Similarly, individual metabolic processes in the nasal and oral cavities may determine the hedonic evaluation of other food and non-food items. Another aspect relates to the development of diagnostic tools. Understanding odorant metabolism in health and disease could help developing non-invasive screening methods for a variety of diseases. Prominent markers such as acetone in diabetic diseases[116] could be established as indicators for other diseases such as cancer or Parkinson's disease[117]. This points into the direction that consequently, acetone cannot serve as the sole marker for either of these and that more complex – or at least other markers – would be required. Volatile fingerprints eventually can contribute to diagnosis *via* analysis of breath, stool, or urine samples, sparing patients costly or more uncomfortable procedures. Taking a sniff so often helps us in recognizing if something is wrong with our loved ones. Understanding odorant metabolism and its effects in more detail is therefore likely to provide a sound basis for the future identification of biomarkers that might even be relatively easy to monitor given the respective development of detection tools. This would consequently target a fascinating field of research - with the appropriate diagnostic tools and adequate data handling the odorous and volatile world will surely open up a window into ourselves and our individuality as never seen before.

But also, our own sensory impression can tell us that something is wrong, as especially in the framework of the Covid-19 pandemic acute or longer lasting symptoms like anosmia, parosmia or phantosmia received more attention in the broader scientific discourse. Ijichi et al. showed recently that the odorants hexanal, octanal, and 2-methylbutanal were metabolized by respiratory and olfactory cleft human mucus in *in vitro* experiments. Hexanal metabolism showed a significantly lower metabolism in the mucus of patients with idiopathic impairment. Disease and injury conditions as well as influences by respective medication are thus further factors which deserve to be considered when studying individual differences in odorant metabolism[66]. In a recent study it was shown that patients undergoing chemotherapy and having smell impairment had bigger problems with food intake than patients without olfactory impairment[118]. In this regard Schiffman provided a great overview of different drugs and related effects, and how enzymes may play a major role in this up to now rarely investigated phenomenon[119]. A better understanding of the involved mechanisms might improve the quality of life of humans suffering from different diseases and help ensuring adequate food intake which may be crucial for their physical and psychological health.

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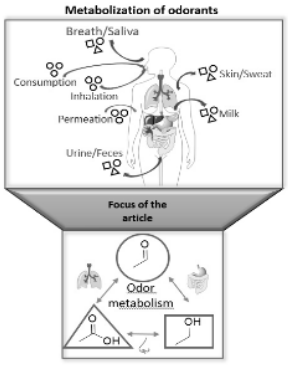

In this publication we delineate the complete passage and turnover of odorants within the human organism, beginning with the various routes of odorant uptake, followed by biotransformation and excretion. Special emphasis is placed on a comparison of the involved enzymes concerning the nasal, oral, respiratory tract- and gastrointestinal metabolism of odorants and the respective functions of odorant metabolism in these body sites.