



REVIEW

Microbial transformation of widely used pharmaceutical and personal care product compounds [version 1; peer review: 2 approved]

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Abstract

Pharmaceutical and personal care products (PPCPs) are commonly used chemicals that are increasingly detected in urban-impacted environments, particularly those receiving treated wastewater. PPCPs may have toxicological effects on the macrofauna that are exposed through contaminated water; thus, there is interest in microbially mediated transformations that may degrade PPCPs. This review discusses specific examples of PPCP transformations that may occur in anoxic environments, including O-methylation and O-demethylation.

Keywords

Biotransformation, anaerobic O-demethylation, anaerobic O-methylation, pharmaceutical biodegradation

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Introduction

Pharmaceutical and personal care products (PPCPs) contain chemicals that are widely distributed in surface waters, sediment, and soil^{1,2}. Pharmaceuticals enter wastewater treatment plants through ingestion and subsequent excretion³, through improper disposal down a household drain⁴, or from pharmaceutical manufacturing plant discharge⁵. Wastewater treatment plants are not designed to remove these complex organic contaminants, which can result in incomplete PPCP removal. A major concern is, therefore, that treated effluent may contain low concentrations of PPCPs that can enter receiving waters or soils when biosolids are used as fertilizer⁶⁻⁸.

A range of adverse effects has been reported for wildlife that is exposed to treated effluent. When released into the environment, pharmaceuticals can be toxic⁹ or can cause unwanted physiological responses to non-target organisms, including endocrine disruption (e.g. feminization of fish), altered development of aquatic organisms including fish and frogs, and changes to behavior¹⁰⁻¹³. In addition, bioaccumulation in aquatic organisms is a concern, particularly in fish intended for human consumption¹⁴. Not only are these findings a potential public health problem, but they also raise concerns about the health of the ecosystem and overall water quality. While the concentrations of an individual chemical may be in the ng L⁻¹ range (for example, see 15), PPCPs are typically found in wastewater as complex mixtures and may have additive effects that remain to be understood.

Microbial toxicity

Some PPCPs are designed specifically to have antagonist effects against microorganisms. Notably, this includes antibiotics, preservatives (e.g. parabens), and antimicrobial compounds (e.g. triclosan and triclocarban). Others may have unexpected inhibitory effects. Ibuprofen, for example, has been shown to inhibit the growth of a variety of microorganisms¹⁶. Pharmaceuticals such as propranolol, diphenhydramine, and diclofenac sodium have also been reported to have inhibitory effects on the methanogenic microbial community found in anaerobic digesters^{17,18}. Furthermore, the metabolites produced during microbial transformation of pharmaceuticals are not always further degraded¹⁸⁻²⁰ and could also have negative effects on the microbial community. Alternatively, the microbial community may still carry out the desired function, such as methanogenesis, but the microbial community composition may be altered or enriched for antibiotic resistance genes^{21,22}. In addition, these metabolites can still be pharmacologically active and can exhibit toxicity to eukaryotic organisms, although these effects have not yet been documented in prokaryotic organisms such as bacteria and archaea^{23,24}. As prokaryotes provide ecosystem services for all environments, the effects of PPCPs and their metabolites on prokaryotes are valuable to know.

Biodegradation

PPCPs enter changing environmental conditions and encounter diverse microbial communities as they pass from households through the wastewater treatment process and ultimately into the environment. The initial stages of wastewater treatment are designed to first use well-oxygenated units to support aerobic

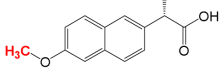
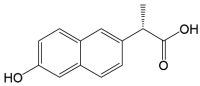
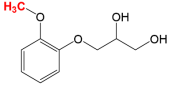
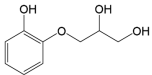
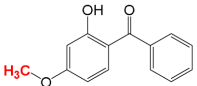
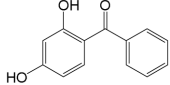
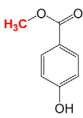
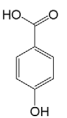
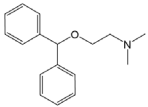
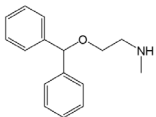
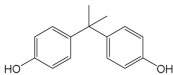
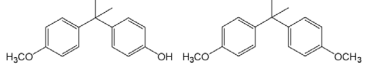
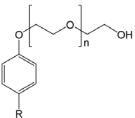
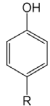
degradation. Later in the process, further degradation of the sludge solids takes place in anaerobic digester units that promote a fermenting and methanogenic community operating under low oxidation-reduction potential (<-350 mV). Treated wastewater effluent is released into oxic surface water; however, some PPCPs will eventually migrate into anoxic sediments²⁵⁻²⁸. In freshwater systems, nitrate, iron, or carbonate are predominant electron acceptors available for respiration, whereas coastal marine waters would additionally have sulfate as a respiratory electron acceptor. These different conditions, therefore, support diverse microbial communities that may also be capable of divergent biochemical mechanisms for biodegradation in surface waters and anoxic sediments. This must all be taken into account when modeling the environmental fate of PPCPs, as degradation might be more likely to occur, proceed to a greater extent, or produce different intermediates depending on the location. Naproxen transformation, for example, has been shown to occur under sulfate-reducing and methanogenic conditions in constructed wetlands, estuarine sediment, and anaerobic digester sludge, yet nitrate-reducing conditions in constructed wetlands yielded little transformation activity^{20,29}. Oxybenzone, in contrast, was transformed under aerobic, nitrate-reducing, iron-reducing, sulfate-reducing, and methanogenic conditions^{30,31}. PPCPs have diverse chemical structures that underscore the need for a broader understanding of how microbes in different environments will metabolize the different classes of compounds. This is valuable for predicting potential activity in the environment, as partial microbial transformations may make the original PPCP undetectable by standard methods, yet the new transformation product may have ecotoxicological effects.

Fate in wastewater treatment plants and receiving aquatic habitats

There have been many reports of PPCP removal during the biological stages of wastewater treatment (for reviews, see 32,33) or quantifying PPCPs in effluent-impacted water and sediment^{2,34}. Treated wastewater effluents are one of the main pathways by which PPCPs enter watersheds. While some removal during wastewater treatment can be attributed to the biological activity of microorganisms, there are few simplified consortia or pure cultures available to demonstrate the biochemistry involved in PPCP transformation. Without biochemical evidence, it is difficult to determine if the PPCP in question has been mineralized³⁵, lost due to abiotic processes such as sorption to solids³⁶⁻³⁸, or transformed into unknown metabolites^{31,39}.

Some anaerobic transformation reactions may lead to persistent metabolites that present additional environmental problems. Nonylphenol and octylphenol, for example, are produced from the sequential removal of ethoxyl groups from the nonionic surfactants nonylphenol polyethoxylate and octylphenol polyethoxylate, as shown in Table 1^{40,41}. These metabolites have been shown to mimic estrogen¹³ and are frequently detected in wastewater treatment systems and in the aquatic environment². The genes and biochemical intermediates for nonylphenol and octylphenol degradation have been reported under aerobic conditions⁴²⁻⁴⁴; however, only limited data exist regarding their

Table 1. Anaerobic and aerobic transformation reactions may lead to persistent metabolites.
Specific examples of pharmaceutical and personal care products with corresponding transformation products are shown.

Parent compound	Transformation product	References
O-Demethylation		
Naproxen Over-the-counter non-steroidal anti-inflammatory drug 	6-O-Desmethylnaproxen 	20,31
Guaifenesin Expectorante 	3-(2-hydroxyphenoxy) propane-1,2-diol 	31
Oxybenzone UV light absorber Found in sunscreens and plastics 	2,4-Dihydroxybenzophenone 	31
Methylparaben Preservative in cosmetics, pharmaceuticals, and food 	4-Hydroxybenzoic acid 	31
N-Demethylation		
Diphenhydramine Anti-histamine 	N-Desmethyl diphenhydramine 	18
O-Methylation		
Bisphenol A (BPA) Plastic precursor 	BPA monomethyl ether (left), BPA dimethyl ether (right) 	45
De-ethoxylation		
Octylphenol and nonylphenol polyethoxylate Nonionic surfactant 	Octylphenol or nonylphenol 	40

fate under anaerobic conditions and the biochemical pathways are largely unknown⁴⁶⁻⁴⁹. With the identification of nonylphenol and octylphenol as persistent metabolites with toxicological effects, it is now imperative to monitor their concentrations in the environment and quantify their potential estrogenic impact.

Other types of anaerobic biotransformation reactions include O-demethylation. Recently, we reported on the complex microbial strategy of naproxen transformation by a methanogenic consortium enriched from anaerobic digester sludge²⁰. The methanogenic consortium O-demethylated naproxen to

form the persistent metabolite 6-O-desmethylnaproxen, which is illustrated in Table 1. Acetogenic bacteria were responsible for this step and produced acetate that subsequently enriched for a population of syntrophic acetate-oxidizing bacteria. The latter supported a methanogenic community that produced the amount of methane that was consistent with O-demethylation²⁰. This model is an example of an anaerobic microbial food web that was supported through pharmaceutical biotransformation.

Similarly, diphenhydramine can be transformed by anaerobic digester sludge microbes via N-demethylation to N-desmethyl diphenhydramine (see Table 1;¹⁸), a metabolite formerly known

to be generated only by mammals and fungi⁵⁰. While the parent compound, diphenhydramine, suppressed both fermentative and methanogenic activity in the anaerobic digester community, the metabolite suppressed only methanogenic activity. In contrast, there was negligible toxicity of naproxen and 6-O-desmethylnaproxen to the same community²⁰. These differences highlight how chemically different PPCPs and their transformation products may have different effects on the same microbial community, further underscoring the complexity of the fate and effect of the PPCPs.

While anaerobic O-demethylation of aromatic compounds has been well established (see 51), less is known about this transformation in PPCPs. We have evidence that PPCPs with diverse uses and chemical structures but share a phenylmethyl ether functional group can be transformed via O-demethylation³¹. Microbial communities enriched under both methanogenic and sulfate-rich conditions showed this capability when provided with naproxen, guaifenesin, methylparaben, or oxybenzone³¹. The sulfate-rich cultures formed O-demethylated metabolites, shown in Table 1, that were not further degraded. A similar pattern was observed in the methanogenic cultures³¹.

In contrast, many phenolic compounds can be transformed by microbial O-methylation (see 52). For example, bacteria are able to O-methylate bisphenol A (BPA) to its monomethyl and dimethyl ether derivatives, as pictured in Table 1 (BPA MME and BPA DME, respectively)⁴⁵, resulting in metabolites with increased toxicity as shown from differences in survival and occurrence of developmental lesions in developing zebrafish embryos exposed to BPA, BPA MME, and BPA DME. The monomethyl and dimethyl ether derivatives were more toxic than BPA, resulting in increased mortality. Furthermore, exposure to either of the O-methylated metabolites resulted in an increase in the incidence of developmental lesions as compared to BPA exposure⁴⁵. These data illustrate a new mechanism for the microbial transformation of BPA, producing metabolites warranting further study to understand their prevalence and effects in the environment. In addition, the O-methylated transformation products could serve as potential substrates for O-demethylation by the organisms described above^{31,51}. The interconversion between O-methylated and O-demethylated forms thus presents a mechanism by which a PPCP compound can be transformed in one environment and the original parent compound regenerated by microbes that are active in another environment. This is similar to reports of flame-retardant and antimicrobial compound transformations that have been described in plants^{53,54}.

Predicting anaerobic biodegradation

Identifying common functional groups may serve as a basis for predicting transformation products. Gulde *et al.*⁵⁵ used a systematic approach to identify potential metabolites of PPCPs that contain an amine group, applying this method to predicting reactions in aerobic activated sludge. Alternatively, we used a culture-based approach to examine the range of O-demethylation substrates in anoxic sediments and anaerobic wastewater digestion³¹. Gonzalez-Gil *et al.*⁵⁶ used enzyme assays

to examine co-metabolic transformations of diverse PPCPs, including naproxen, nonylphenol, octylphenol, triclosan, and BPA, that were mediated by acetate kinase. The extent to which transformation occurred varied with the substrate from 10–90% and suggested the involvement of additional transformation pathways⁵⁶, which could lead to a mixture of different transformation products existing from the same parent compound. Laboratory-based assays, such as those conducted by Gonzalez-Gil *et al.*⁵⁶ and Wolfson *et al.*³¹, represent a starting point for the identification of potential metabolites, although it may not be representative of the dominant transformation mechanism that occurs in the environment. Likewise, the microbial community composition may have an effect on PPCP transformations, especially under methanogenic conditions^{20,57}. Additionally, the effects that mixtures of PPCPs and associated transformation products will have on microbial community function cannot be overlooked.

Future directions for PPCP removal

Recognition of the expanding extent of PPCP contamination has stimulated the search for solutions that remove pharmaceuticals from wastewater before they can reach the environment, including technologies like advanced oxidation processes and membrane bioreactors^{58–62}. These new technologies have shown promise with higher removal rates in pilot treatment plants than with conventional treatment^{61,63}. In combination with increased removal efficiencies, re-designing PPCPs to promote biodegradability could lead to a reduction in the environmental load in the future^{64,65}. Understanding transformation products is important not only to the health of impacted aquatic ecosystems and humans but also for monitoring the safety of reclaimed wastewater reuse (for review, see 66) and for the accuracy of wastewater-based epidemiology to follow human health and pharmaceutical use^{67–70}.

Conclusions

An Organization for Economic Cooperation and Development report projects that sales of chemicals worldwide will increase by 3% annually between now and 2050⁷¹, thus providing a steady stream of diverse chemical structures that may be entering wastewater treatment and the environment. Given that pharmaceuticals are used daily throughout the world, their release into the environment is both a public and an environmental health concern. Understanding not only the microbial transformation processes but also the metabolites that are formed is essential for comprehensive accounting of pharmaceuticals and potential pharmaceutically active compounds in the environment. The environmental context, be it the engineered anaerobic digester or freshwater or estuarine sediments that are impacted by treated wastewater, is critical for understanding potential microbial activities and biodegradation mechanisms to determine if biodegradation will occur or if potential metabolites may form and accumulate under the given redox conditions. This knowledge may provide solutions to remove these pharmaceuticals during wastewater treatment and prevent environmental deposition as well as to understand environmental processes that may occur to remove pharmaceuticals that have already entered the environment.

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