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In vivo exposure of marine mussels to carbamazepine and 10-hydroxy-10,11-dihydro-carbamazepine: Bioconcentration and metabolization

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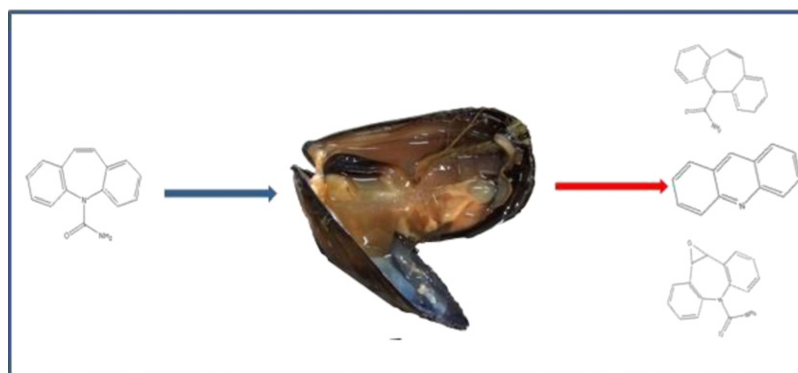
HIGHLIGHTS

- Carbamazepine and 10-hydroxy-10,11-dihydro-carbamazepine bioconcentrate weakly in marine mussels.
- The bioconcentration factors (BCFs) are 3.9 and 4.5 L kg^{-1} dry weight, respectively.
- Uptake and depuration kinetics show a quick first-order pattern.
- Mussels metabolize carbamazepine.
- Two metabolites (carbamazepine-10,11-epoxide and acridine) are detected in mussel tissues.

GRAPHICAL ABSTRACT



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ABSTRACT

Aquatic organisms are exposed to pharmaceuticals present in natural waters, but few data are available on the accumulation of these substances in such organisms. The present study evaluated the in vivo bioconcentration of two anticonvulsants – carbamazepine (CBZ) and 10-hydroxy-10,11-dihydro-carbamazepine (10OH) – in marine mussels (*Mytilus galloprovincialis*) exposed to nominal 10 μg L^{-1} concentrations for one week. The bioconcentration factors (BCFs) were 3.9 and 4.5 L kg^{-1} dry weight (dw) for CBZ and 10OH, respectively. CBZ accumulation reached an average tissue concentration of 29.3 ± 4.8 ng g^{-1} dw, and 10OH accumulated up to 40.9 ± 4.6 ng g^{-1} dw in tissues within one week, showing first-order kinetics. BCF obtained with linear QSAR models correctly estimated the CBZ bioconcentration and overestimated the 10OH bioconcentration to some extent. The detection of two metabolites (carbamazepine-10,11-epoxide and acridine) among the five sought suggested an active metabolism for CBZ. In contrast, none of the 10OH metabolites were detected in mussels exposed to 10OH. CBZ showed higher accumulation in the digestive gland, where some relevant metabolites were detected, than in other studied tissues. The implication of those findings on field biomonitoring is discussed.

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1. Introduction

Previous studies on carbamazepine (CBZ) as an environmental contaminant have revealed the widespread occurrence of this chemical in both freshwater and seawater. It is therefore well known that this pharmaceutical is poorly eliminated by sewage treatment plants (STPs), and frequently detected in surface waters (Verlicchi et al., 2012; Pal et al., 2010) and in the sea. Reported CBZ concentrations in marine water (maximum of 200 ng L^{-1}, except for sites directly receiving wastewaters) are generally lower than those found in freshwater (which sometimes exceed 2000 ng L^{-1}), with the highest concentration quantified in areas closely impacted by STP effluents, i.e. harbors and bays where urban activities are located and estuaries subject to surface water contamination (Arpin-Pont et al., in press). Despite the lower concentrations reported in marine waters, on the nanogram per liter level, some authors have reported the occurrence of CBZ in marine organisms such as bivalves (Wille et al., 2011; Martinez Bueno et al., 2013). Bivalves (mussels, oysters, scallops and clams) are the most frequently studied organisms because filter feeders concentrate contaminants through the gills (via the dissolved phase) and/or through the digestive gland (via the particulate phase) (Baumard et al., 1998). These organisms were easily directly sampled at sites of interest (Martinez Bueno et al., 2013, 2014; Almeida et al., 2014) or by caging (Hoenicke et al., 2007; Kookana et al., 2013; McEneff et al., 2014).

In both STP effluents and receiving waters, some CBZ metabolites, such as trans-10,11-dihydroxy-10,11-dihydro-carbamazepine (TRANS), have been detected at higher concentration than the parent compound (Leclercq et al., 2009; Miao and Metcalfe, 2003; Writer et al., 2013). More recently, CBZ and TRANS were detected in coastal waters, as well as 10-hydroxy-10,11-dihydro-carbamazepine (10OH), the active metabolite of oxcarbazepine (OX) that is also prescribed for neurological disorders (Martinez-Bueno et al., in press). Carbamazepine-10,11-epoxide (EPOXY), another CBZ metabolite, was also detected in this latter study, but less frequently. Taken together, current data in the presence of CBZ and OX metabolites in marine waters strongly suggest contamination of the marine environment by pharmaceuticals and a high variety of metabolites, even though metabolites have not been the main focus of research to date.

To assess the exposure of organisms to these pharmaceutical residues in marine water, the presence of parent compounds or metabolites in organism tissues might be reliable bioindicators of field exposure. However, bioaccumulation properties should be determined to be able to correctly interpret this information as they are essential for gaining insight into the impact of exposure of aquatic fauna to organic micropollutants. However, to date, data on pharmaceutical concentrations in aquatic biota and their bioaccumulation properties are scarce. The bioaccumulation of pharmaceuticals depends on the metabolism and elimination efficiency of marine organisms. Different cytochromes have been characterized in invertebrates (Snyder, 1998; Chaty et al., 2004; Zanette et al., 2013) and could be involved in pharmaceutical metabolism. It is therefore difficult to know how pharmaceuticals are metabolized or excreted in mussels.

The present study thus involved laboratory exposure under controlled conditions with the aim of investigating the concentration and/or metabolization in mussel tissues of two antiepileptic drugs, i.e. CBZ and 10OH, the active metabolite of OX. The objectives were to determine: i) CBZ and 10OH bioconcentration kinetics in marine mussels (*Mytilus galloprovincialis*) and their bioconcentration factors (BCFs), ii) the CBZ distribution among organs and iii) the occurrence of target metabolites in *M. galloprovincialis* after controlled exposure. Finally, the ability of existing linear quantitative structure–activity relationship (QSAR) models to predict CBZ and 10OH bioaccumulation was tested and discussed with regard to the experimental results. Here the term 'bioconcentration' refers to the process of accumulation of waterborne chemicals and was preferred over the term 'bioaccumulation', which refers to accumulation from either water or food.

2. Materials and methods

2.1. Chemicals, reagents, animals and housing

CBZ, EPOXY, OX, iminostilbene (IM), acridine (AI) and acridone (AO) were obtained from Sigma Aldrich (Steinheim, Germany). 2-Hydroxycarbamazepine (2OH), carbamazepine-d8 (CBZ-d8) and 10,11-dihydro-10,11-epoxycarbamazepine-d10 (EPOXY-d10) were purchased from Toronto Research Chemicals (Ontario, Canada). TRANS was from Cluzeau (Courbevoie, France). 10OH was obtained from LGC standards (Molsheim, France). All chemicals used in this study were analytical grade (purity > 90%). Pesticide analysis-grade solvents (acetone, ethanol, ethyl acetate, methanol) and LC/MS-grade solvents (acetonitrile) were from Carlo Erba (Val de Reuil, France). Ultrapure water was generated from a Simplicity UV system from Millipore (Bedford, MA, USA) with a specific resistance of 18.2 MΩ·cm at 25 °C. Formic acid (98% purity) was purchased from Fluka (Buchs, Germany). Dispersive SPE tubes containing Z-C18 sorbent (500 mg/12 mL) and primary secondary amine (PSA) sorbent were obtained from Supelco (Bellefonte, PA, USA), C-18 (40 μm particle size) from Varian (Palo Alto, CA, USA) and Oasis™ HLB cartridges (500 mg, 6 mL) from Waters (Milford, MA, USA). Individual stock standard solutions of the target compounds were prepared at 1 g L^{-1} in methanol and stored at −20 °C. A calibration solution of these compounds at 10 mg L^{-1} in methanol was freshly prepared for each analysis by appropriate dilution in acetonitrile: water (10:90, v/v). The physicochemical properties of the selected molecules and the analytical performances for each target compound are presented in Table 1.

M. galloprovincialis were obtained from Mediterranean Sea cultures (Frontignan, France). Prior to the experiments, mussels were sorted to ensure a uniform size distribution (shell length 5–7 cm), then cleaned and randomly distributed in 1.5 L glass aquaria containing 1 L of filtered seawater and six mussels. Mussels were acclimated for 1 week before each experiment. Temperature was maintained at 18 ± 2 °C with a 14:10 h light:dark cycle. Filtered (GF/F, Whatman) seawater was continuously aerated and renewed daily. During acclimatization, exposure and depuration periods, mussels were fed once a day with *Tetraselmis suecica* (Greensea, Mèze, France) at a constant density (50,000 cells mL^{-1}).

2.2. Exposure and sampling

Three different experiments were conducted. The first was implemented to study the bioconcentration kinetics of CBZ and 10OH. For this, 7 days of exposure (uptake period) to a 10 μg L^{-1} nominal concentration (ethanol, 0.1% was used as vehicle for contamination) was followed by a 7 day depuration period. Exposed mussels from 3 aquaria (n = 18) and control mussels (n = 6, ethanol, 0.1%) were collected at each of the days: 0, 1, 3, 7, 8, 10 and 13 for tissue analysis. The second experiment consisted of studying the bioconcentration of CBZ and 10OH for 7 days at three nominal concentrations (1, 10 and 100 μg L^{-1}). Control mussels were sampled at the beginning of the experiment (3 aquaria, 18 mussels) and at day 7 (3 aquaria, 18 mussels). Eighteen mussels were collected at day 7 for each exposure concentration. The last experiment focused on the bioconcentration of CBZ in different tissues, i.e. digestive glands, gills, mantle and the remaining tissues. Exposure was conducted for 3 days at a nominal 100 μg L^{-1} concentration. Exposed mussels (18) and control mussels (12) were collected for analysis.

After sampling, the soft tissues of mussels were collected by dissection, stored at −20 °C, freeze dried (Heto PowerDry LL 3000, Thermo) and ground into powder. For each aquarium, a homogenized sample was prepared by pooling samples from 6 mussels. The ratio of the dry flesh weight to the dry shell weight was used to determine a condition index (CI) for each sample. The dry weight ratio (DWr) was calculated as the dry flesh weight divided by the wet flesh weight.

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