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Effects of water warming and acidification on bioconcentration, metabolization and depuration of pharmaceuticals and endocrine disrupting compounds in marine mussels (*Mytilus galloprovincialis*)☆

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ABSTRACT

Warming and acidification are expected impacts of climate change to the marine environment. Besides, organisms that live in coastal areas, such as bivalves, can also be exposed to anthropogenic pollutants like pharmaceuticals (PhACs) and endocrine disrupting compounds (EDCs). In this study, the effects of warming and acidification on the bioconcentration, metabolization and depuration of five PhACs (sotalol, sulfamethoxazole, venlafaxine, carbamazepine and citalopram) and two EDCs (methylparaben and triclosan) were investigated in the mussel species (*Mytilus galloprovincialis*), under controlled conditions. Mussels were exposed to warming and acidification, as well as to the mixture of contaminants up to 15.7 $\mu g\,L^{-1}$ during 20 days; followed by 20 days of depuration. All contaminants bioconcentrated in mussels with levels ranging from 1.8 $\mu g\,kg^{-1}$ dry weight (dw) for methylparaben to 12889.4 $\mu g\,kg^{-1}$ dw for citalopram. Warming increased the bioconcentration factor (BCF) of sulfamethoxazole and sotalol, whereas acidification increased the BCF of sulfamethoxazole, sotalol and methylparaben. In contrast, acidification decreased triclosan levels, while both stressors decreased venlafaxine and citalopram BCFs. Warming and acidification facilitated the elimination of some of the tested compounds (i.e. sotalol from 50% in control to 60% and 68% of elimination in acidification and warming respectively). However, acidification decreased mussels' capacity to metabolize contaminants (i.e. venlafaxine). This work provides a first insight in the understanding of aquatic organisms' response to emerging contaminants pollution under warming and acidification scenarios.

1. Introduction

The effects that climate change may have on the environment are a topic of increasing concern. The release of carbon dioxide to the atmosphere, mainly attributed to human activities, has contributed to global warming (IPCC, 2014; Pinguelli-Rosa and Kahn-Ribeiro, 2001). In addition, the carbon dioxide deposition in water bodies promotes seawater acidification (Sabine et al., 2004). Warming and acidification are two major threats to the marine environment. The forecasted rise of few Celsius degrees in seawater temperature, accompanied by a decrease of few tenths in seawater pH, may provoke huge changes in aquatic organisms' lifestyle in the future (IPCC, 2014; Wernberg et al., 2011). Several studies described adverse effects in marine organisms submitted to warming and acidification, including reduction of calcification rates, changes in metabolism functioning and increase of oxidative stress, among others (Duarte et al., 2014; Ko et al., 2014; Kroeker et al., 2014, 2013, 2010; Lesser, 2016; Poore et al., 2013; Rosa et al., 2012).

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In addition to the direct effects on organisms' physiology, climate change impacts are also expected to influence the behavior of chemical contaminants in aquatic systems (Schiedek et al., 2007). Thus, warming and acidification may alter the way that organisms interact with contaminants present in the environment and in their potential to accumulate them. Previous studies revealed changes in contaminants accumulation, like metals, in bivalve species under warming and acidification (López et al., 2010; Maulvault et al., 2016). However, to the best of our knowledge, there is no information available about the influence of climate change on the accumulation, metabolization and depuration of emerging contaminants like pharmaceuticals (PhACs) and endocrine disrupting compounds (EDCs) in marine organisms. PhACs may pose a risk for aquatic communities since they are designed to be pharmacologically active in organisms, even at very low concentrations. Different studies reported the presence of these compounds in water bodies and its accumulation in freshwater and marine biota worldwide (Álvarez-Muñoz et al., 2015; Li, 2014; Llorca et al., 2016; Rodriguez-Mozaz et al., 2017, 2016; Serra-Compte et al., 2017)). In addition, adverse effects in aquatic organisms due to an exposure of PhACs have been reported (Corcoll et al., 2015; Cortez et al., 2012; Godoy et al., 2015; Minguez et al., 2016; Santos et al., 2010; Serra-Compte et al., 2018). On the other hand, EDCs are substances that can mimic the activity of endogenous compounds, altering the normal functioning of an organism (Tijani et al., 2013). EDCs have been found in marine bivalves in concentrations ranging from below MDL up to 39.4 ng g^{-1} dw (Vandermeersch et al., 2015). Some of the most frequently detected EDCs in marine bivalves from the Mediterranean zone are caffeine, TCEP, TBEP, methylparaben, ethylparaben, propylparaben, triclosan and bisphenol A; and they were proposed as priority contaminants for future studies (Álvarez-Muñoz et al., 2015; Huerta et al., 2015). Alterations in organisms' molecular and gene expression (Park and Kwak, 2010), changes in the immunological system (Casanova-Nakayama et al., 2011) or an increased frequency of gonadal regression and atresia in mussels (*Mytilus trossulus*) (Smolarz et al., 2017) have been described in different organisms due to EDCs exposure. These contaminants (PhACs and EDCs) reach to the marine environment mainly through waste water treatment plant (WWTP) effluents as they are not completely removed in WWTPs (Kostich et al., 2014). Therefore, coastal areas receiving an input of WWTP effluents (mainly through rivers discharge), are some of the most impacted marine aquatic ecosystem, concerning wastewater derived contaminants. Organisms living in these areas, like bivalves, are thus exposed to chemical pollution (i.e. PhACs and EDCs, among others) and are also particularly vulnerable to changes in environmental conditions (e.g. temperature, pH). Bivalves are filter feeding organisms thus easily accumulating contaminants (Ismail et al., 2014); therefore, they are used as sentinel organisms to monitor chemical pollution in coastal areas (Hellou and Law, 2003; OSPAR, 2016). In addition, they have an important role in the ecosystem by filtering toxins and bacteria from the surrounding water, and serve as food source for many species, including humans (Zippay and Helmuth, 2012).

Understanding the bioaccumulation of emerging contaminants in marine organisms under expected climate change conditions becomes of great interest, not only from an ecological perspective but also in relation to seafood consumption safety. In this work, an *in vivo* exposure experiment of mussels (*Mytilus galloprovincialis*) to five PhACs (sotalol, sulfamethoxazole, venlafaxine, carbamazepine and citalopram) and two EDCs (methylparaben and triclosan) under water warming and acidification scenarios was carried out in order to evaluate the effects of temperature and pH on the bioconcentration and depuration of these compounds. In addition, the formation of the main metabolites of sulfamethoxazole, venlafaxine and carbamazepine was also investigated. Finally, linear quantitative structure-activity relationship (QSAR) models were evaluated for the prediction of PhACs and EDCs accumulation in bivalves; the predicted values were compared with those obtained experimentally providing further information about the mechanisms of emerging contaminants accumulation in biota.

2. Material and methods

2.1. Chemicals and reagents

Pharmaceutical standards were of high purity grade (>90%). All pharmaceutical standards (listed in Table 1) were purchased from Sigma-Aldrich, whereas the metabolites N-desmethylvenlafaxine, O-desmethylvenlafaxine, NN-didesmethylvenlafaxine, NO-didesmethylvenlafaxine, NN-didesmethyl-O-desmethylvenlfaxine, carbamazepine-10,11epoxy, carbamazepine-2-hydroxy, N-acetylsulfamethoxazole and desamino-sulfamethoxazole were obtained from Toronto Research Chemicals (TRC). HPLC grade methanol, water and acetonitrile were purchased from Merck (Darmstadt, Germany). The QuEChERS extract tubes (AOAC method), and the QuEChERS for dispersive solid phase extraction

Table 1
List of target compounds analysed. Precursor ion, retention time (RT), and the two MRM transitions used for compound identification.

Therapeutic family	Compound	Precursor ion	RT (min)	Q3	Q3
Psychiatric drugs	Venlafaxine	278 $[M+H]^+$	2.75	58	260
	Citalopram	325 $[M+H]^+$	2.90	109	262
	Carbamazepine	237 $[M+H]^+$	3.19	193	194
(metabolite)	O-desmethylvenlafaxine	264 $[M+H]^+$	2.14	134	198
(metabolite)	NN-didesmethyl-O-desmethylvenlafaxine	235 $[M+H]^+$	2.15	159	218
(metabolite)	NO-didesmethylvenlafaxine	250 $[M+H]^+$	2.16	43	214
(metabolite)	NN-didesmethylvenlafaxine	250 $[M+H]^+$	2.77	214	232
(metabolite)	N-desmethylvenlafaxine	263 $[M+H]^+$	2.76	215	246
(metabolite)	Carbamazepine-2-hydroxy	252 $[M+H]^+$	2.71	208	210
(metabolite)	Carbamazepine-10,11-epoxide	252 $[M+H]^+$	2.72	180	236
Antibiotics	Sulfamethoxazole	254 $[M+H]^+$	1.98	92	156
(metabolite)	N-acetylsulfamethoxazole	296 $[M+H]^+$	2.38	134	198
(metabolite)	Desamino-sulfamethoxazole	238 $[M+H]^+$	2.66	77	131
Beta-blocker	Sotalol	273 $[M+H]^+$	1.10	255	133
Endocrine disrupting compounds	Methylparaben	151 $[M-H]^-$	1.30	92	136
	Triclosan	286 $[M-H]^-$	3.50	34	–