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Review

Mussel digestive gland as a model tissue for assessing xenobiotics: An overview

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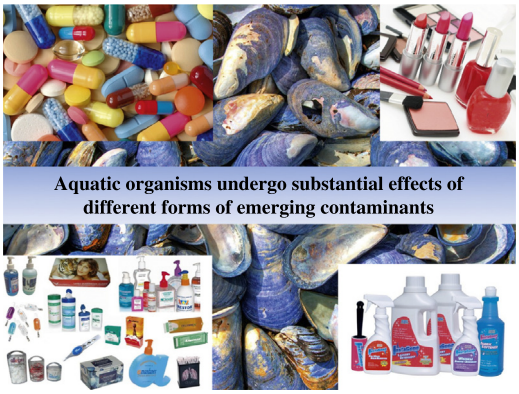
HIGHLIGHTS

- Mussel digestive gland is a target-tissue of xenobiotics' impact on coastal areas.
- It consists a reliable tool to investigate xenobiotics' mode of action.
- Multiple methods and biomarkers are widely applied in mussels' digestive glad.
- Tissue-specific alterations indicate mussels health and the environmental quality.

GRAPHICAL ABSTRACT



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ABSTRACT

Control strategies and routine biomonitoring programs are commonly performed worldwide using sentinel marine invertebrates, such as mussels of the genus *Mytilus*, for assessing the "health status" of the aquatic environment. Those species can accumulate and tolerate xenobiotics at levels higher than those being present into the aquatic environment, thus providing accurate and reliable biological endpoints (e.g. physiological, behavioral, cellular, biochemical and molecular indices) that can be measured in their tissues. Taking under consideration the significance of bivalves for assessing the environmental hazard of xenobiotics being present into the water medium, as well as the key role of digestive gland as a target-tissue for the compounds ingested in the organism, the present study aimed to summarize available data on the effects of different categories of xenobiotic compounds, previously characterized as a potential threat for the marine ecosystems. In this context, different types of pharmaceuticals and personal care products (PPCPs), biocides, microplastics (MPs) and nanoparticles (NPs), currently investigated in mussels' digestive gland, using a battery of experimental approaches and analytical methods, as well as stress indices evaluation, are briefly described and further discussed in order to elucidate not only the presence and the toxic mode of action of xenobiotics, but also the important role of the digestive gland as a reliable target-tissue for investigating the effects of xenobiotics at cellular, biochemical, and molecular levels.

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Contents

1. Introduction

The levels of aquatic pollution are increased worldwide, requiring control strategies and routine monitoring of contaminants in the aquatic environment. Heavy metals (Aliko et al., 2015; Aliko et al., 2018; Fazio et al., 2014; Matozzo et al., 2001; Torre et al., 2013a; Wang et al., 2010), radioactive pollution (Balbus et al., 2013) and xenobiotics (Bartoskova et al., 2013; Chromcova et al., 2015; Messina et al., 2014; Pagano et al., 2016) can cause long-term effects on ecosystems even when their impact has no visible influence (e.g. effects on organisms traced to molecular and cellular responses, as pollution impact, does not necessarily lead to directly observable effects on population or ecosystem). Evaluation of aquatic pollution levels is based not only on measurements of the abiotic components, but also on analysis of the abundance and bioaccumulation of xenobiotics in selected sentinel organisms (Catsiki and Florou, 2006; Burgos-Aceves and Faggio, 2017). Among them, bivalves possess a critical thesis, not only because of their involvement within trophic chain as a key organism, but also as a useful sensitive marker for monitoring the effects of anthropogenic substances on the health status of the aquatic environment. In fact, the use of mussels as bioindicators has been well-documented in monitoring studies all over the world, because of the continuously anthropogenic-induced impacts on the environmental health status (UNEP/RAMOGE, 1999). Among them, mussels of the genus *Mytilus*, such as the species *Mytilus edulis* and *M. galloprovincialis* are commonly used for the monitoring of marine pollution (Dailianis, 2011; Capillo et al., 2018).

Mussels are important suspension filter feeders and thus represent an important element on coastal waters ecology. Moreover, since mussels are edible and sessile species, they have been harvested and cultured worldwide for human consumption. Given that those species can tolerate and accumulate xenobiotics in their tissues at levels higher than those being present into the aquatic environment (Livinstone, 1991; Torre et al., 2013b), bivalves are considered as important and well recognized species in (eco)toxicological and biomonitoring studies for assessing the "health status" of the aquatic environment (Matozzo et al., 2012; Torre et al., 2013b; Savorelli et al., 2017), thus providing accurate and reliable biological endpoints of the environmental quality. Those endpoints are based on physiological, behavioral, cellular, biochemical and molecular alterations that can be measured in tissues or body fluids of challenged mussels (e.g. hemocytes, digestive gland and gills), thus providing evidence of the exposure to and/or the effects of one or more xenobiotics (Depledge, 1993; Burgos-Aceves et al., 2017). Those observable structural and/or functional changes (endpoints), called stress indices or biomarkers, can accurately reflect the health status of the organism and the concomitant quality of the surrounding environment, thus offering an effective "early warning" system in biomonitoring strategies (Adams, 1990; Depledge, 1994, 1999; Depledge et al., 1993; Lowe and Fossato, 2000; McCarthy and Shugart, 1990; Moore et al., 2004a,b; UNEP, 1997).

The digestive gland of mussels is among tissues commonly used for estimating the impact of xenobiotics on mussel's health. Specifically, the digestive gland includes numerous blind-ending epithelial tubules which are mainly composed of basophilic and digestive cells. The first cellular type possesses a highly developed rough endoplasmic reticulum and numerous secretory granules, and thus play important role in enzyme-production and secretion, while digestive cells consist of a well-developed endocytic lysosomal vacuolar system, including heterophagosomes, heterolysosomes and residual bodies, thus being responsible for the intra-cellular digestion processes (Dimitriadis et al., 2004 and references therein). Moreover, the digestive cell's lysosomes are not only responsible for the intra-cellular digestion of nutrients and antioxidant defense (Faggio et al., 2016), but they are also considered as the main organelles of toxic metal and organic pollutant sequestration and detoxification (Marigómez et al., 2002; Pagano et al., 2017), thus suggesting them as a potential 'early warning tool' for xenobiotics mediated adverse biological effects (Domouhtsidou and Dimitriadis, 2001; Zorita et al., 2007). Specifically, since '70s, digestive gland of mussels have been used for stress indices determination and chemical analysis in biomonitoring campaigns previously performed in the Thermaikos and Strymonikos Gulfs (Greece) (Dailianis et al., 2003; Domouhtsidou and Dimitriadis, 2001; Domouhtsidou et al., 2004; Koukouzika and Dimitriadis, 2005), the Moroccan Coasts (El Haimeur et al., 2017), the Basque Coast (Spain) (Marigómez et al., 2013), the Algerian West Coast (Benali et al., 2017), as well as the Sardinian and other Italian coasts (Balbi et al., 2017; Capolupo et al., 2017; Moschino et al., 2017), while it has been proposed as a significant tissue for screening the metabolic effects of endocrine disruptors both in field and laboratory studies (Balbi et al., 2017; Canesi et al., 1998; Lowe and Pipe, 1994). Moreover, given that certain xenobiotics, such as heavy metals, organophosphate pesticides (OPs) and polycyclic aromatic hydrocarbons (PAHs), are preferentially accumulated in this tissue (Beyer et al., 2017; Franzellitti et al., 2014; Gomes et al., 2011, 2012; Marigómez et al., 2002; Perić et al., 2017; Rocha et al., 2015a, 2015b, 2015c; Vidal-Liñán et al., 2018; Walsh and O'Halloran, 1997), the digestive gland of mussels is considered suitable for biomarkers' estimation and is commonly used for assessing pre-pathological alterations in challenged mussels (Bocchetti and Regoli, 2006; Dailianis and Kaloyianni, 2007; Martins et al., 2012).

Given the significance of digestive gland as a target-tissue of xenobiotics, being present into the water medium, the present study aimed to summarize and present recently published studies (field and laboratory), performed for elucidating not only the presence but also the mode of action of "emerging" xenobiotics that are considered as a threat for the marine ecosystems, such as pharmaceuticals and personal care products (PPCPs), biocides, microplastics (MPs) and nanoparticles (NPs). Moreover, experimental procedures, different endpoints, and analytical methods, commonly performed in mussel digestive gland are also presented, thus indicating the important role of the mussel digestive gland as a model tissue for assessing xenobiotics potential risk.

2. Investigation of pharmaceuticals and personal care products (PPCPs) in the digestive gland of mussels

Pharmaceuticals and personal care products (PPCPs) represent a large class of xenobiotics, which includes a great variety of different