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Gabriel V. Markov, Jean Girard, Vincent Laudet, Catherine Leblanc. Hormonally active phytochemicals from macroalgae: a largely untapped source of ligands to deorphanize nuclear receptors in emerging marine animal models. *General and Comparative Endocrinology*, 2018, 265, pp.41-45. 10.1016/j.ygcen.2018.06.004 . hal-02393542

HAL Id: hal-02393542

<https://hal.science/hal-02393542>

Submitted on 4 Dec 2019

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Hormonally active phytochemicals from macroalgae: a largely untapped source of ligands to deorphanize nuclear receptors in emerging marine animal models

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Abstract

Hormonally active phytochemicals (HAPs) are signaling molecules produced by plants that alter hormonal signaling in animals, due to consumption or environmental exposure. To date, HAPs have been investigated mainly in terrestrial ecosystems. To gain a full understanding of the origin and evolution of plant-animal interactions, it is necessary also to study these interactions in the marine environment, where the major photosynthetic lineages are very distant from the terrestrial plants. Here we focus on chemicals from red and brown macroalgae and point out their potential role as modulators of the endocrine system of aquatic animals through nuclear hormone receptors. We show that, regarding steroids and oxylipins, there are already some candidates available for further functional investigations of ligand-receptor interactions. Furthermore, several carotenoids, produced by cyanobacteria provide candidates that could be investigated with respect to their presence in macroalgae. Finally, regarding halogenated compounds, it is not clear yet which molecules could bridge the gap to explain the transition from lipid sensing to thyroid hormone high affinity binding among nuclear receptors.

Keywords: hormonally active phytochemicals; macroalgae; ligands; nuclear receptors

1. Introduction: what are HAPs and why do we need a systematic look at them to understand the endocrinology of emerging marine model organisms

Hormonally active phytochemicals (HAPs) are molecules that are endogenously synthesized by plants and have a modulatory effect, either positive or negative, on the endocrine physiology of animals (Lambert and Edwards, 2017). The best-studied examples are estrogenic compounds from land plants, which were first described in a pioneer study on red clover effect on fertility of ewes (Bennets, 1944). These compounds, mainly coumestans and flavonoids, compete with endogenous estrogens to bind to nuclear estrogen receptors (ERs) in vertebrates resulting in disruption of reproduction. This phenomenon has already been brought into an evolutionary perspective, stressing that flavonoids involved in root-microbe interactions were recruited for their estrogenic effects on vertebrates (Baker 1995; McLachan et al., 2001; Fox et al., 2004; Lambert and Edwards, 2017), and lead to practical results in conservation biology (Tubbs et al., 2014). In parallel, marine chemical ecology has matured into a very ample research field, including algal-herbivore interactions, but with a strong focus on chemicals that either mediate repellent effects, or contribute to the recruitment of predators (Hay, 2009). With the exception of the so-called « insidious » effects of diatom grazing on copepod reproduction in laboratory experiments (Miralto et al., 1999), for which the ecological relevance is still under active investigation (Paul et al., 2012; Ianora et al.,

2015), very little is known about the effect of marine phytochemicals on the endocrinology of interacting animals, especially in the natural environment. However, biotic interactions between animals and macroalgae started 635 million years ago, in the Ediacaran, well before the rise of land plants (Figure 1). They then underwent a major transition with the rise of Chlorophyll c-containing algae deriving from secondary endosymbiosis, including brown macroalgae, from the middle of the Phanerozoic (Brocks et al., 2017). Therefore, it is not possible to investigate the origin of hormonal signaling systems in animals without knowledge of the ecological context in which they arose. Reciprocally, there is an increasing awareness of the importance of biotic interactions in shaping the evolution of algae (Brodie et al., 2017). Chemical warfare related to eukaryotic predation has already been documented before the Ediacaran (Brocks et al., 2016), and has likely been present before the rise of multicellularity.

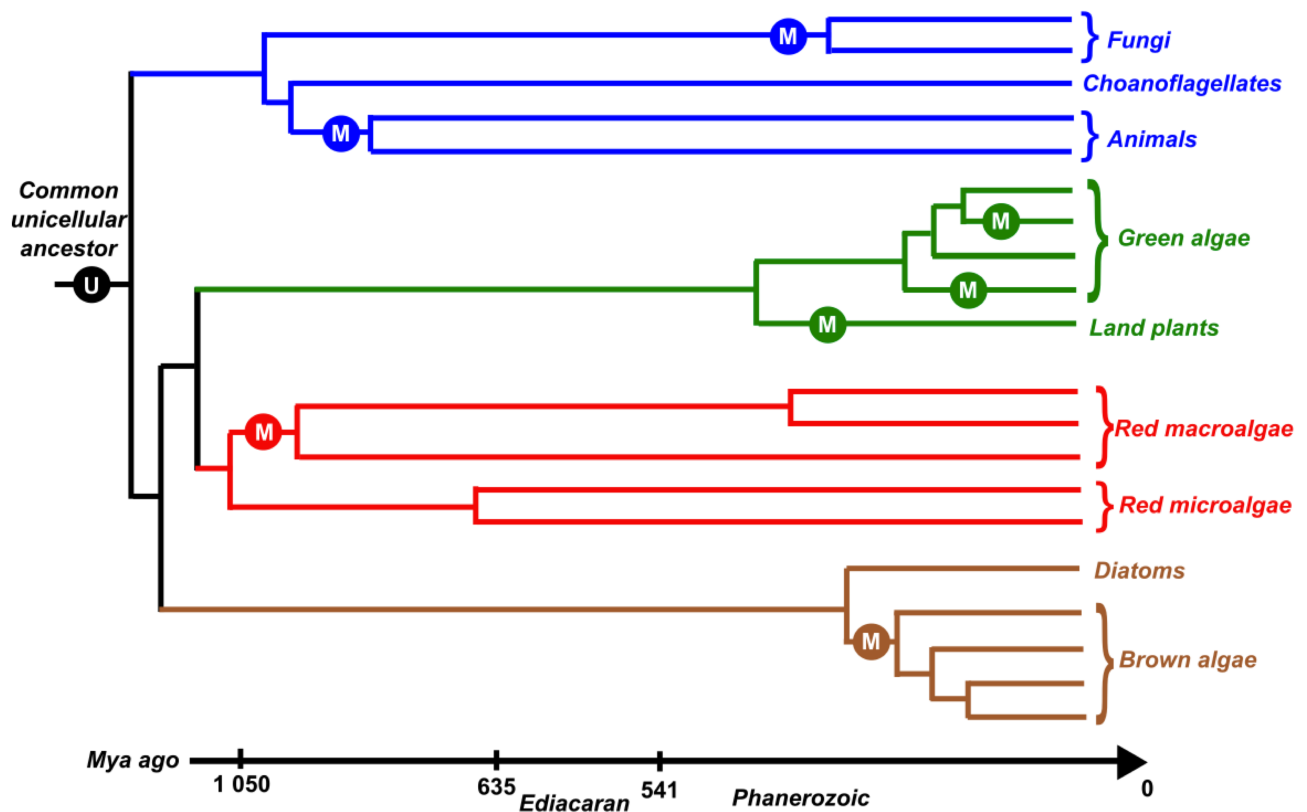


Figure 1 : timing of the independent appearance of the main multicellular lineages (M) from a common unicellular ancestor. Divergence dates are taken from Brocks et al., 2017.

Since these early origins of chemical interactions between algae and animals, life has probably experienced an increase in the diversity of the involved molecules, alongside the increase of organismal complexity. This is especially true in the context of changing global chemical conditions, which depend on geological events (Saul, 2008). One should also keep in mind that the general chemical context was different between marine and freshwater habitats and that there were numerous transitions from one to the other (Dittami et al., 2017). The availability of chemicals has an effect on biomolecule composition, as strikingly shown by the abundance of sulfated polysaccharides in marine angiosperms and algae, compared to terrestrial plants. This is at least partially related to the high abundance of sulfate ions in marine seawater (Aquino et al., 2005; Olsen et al., 2016). Similarly, as discussed below, halogenated molecules are especially abundant in halogen-rich marine environments. The chemical nature and exact physiological role of algal phytohormones are largely unknown and under debate (Tarakhovskaya et al., 2007), but technical

advances in chemical profiling and genomics are changing this quite rapidly (Mori et al., 2017). Here, we provide an overview of molecules that have been identified in red and brown macroalgae and that, in addition to their endogenous role in algae, may play a modulatory role for the endocrinology of marine animals through nuclear hormone receptor signaling. In line with the increasing awareness that relationships between nuclear receptors and their ligands are much more plastic than previously thought (Holzer et al., 2017), this should be seen as an invitation for marine biologists interested in the endocrinology of animal models to broaden the spectrum of molecules to test for biological activity in a meaningful ecological context. We therefore concentrate on four classes of molecules, corresponding to the four classes of well-documented nuclear receptor ligands.

2. Steroids

Steroids are ligands for nuclear hormone receptors belonging to two evolutionarily distant subfamilies, the NR1 family comprising vertebrate bile acid and oxysterol receptors, arthropod ecdysone receptors, and nematode dafachronic acids, as well as the NR3 family comprising receptors to side-chain cleaved vertebrate steroids such as estrogens, androgens, progestagens and corticoids (Markov et al., 2011). Among these receptors, the estrogen receptor is the most extensively studied both from a biomedical and an evolutionary perspective (Lambert et al., 2017). To date, the best-characterized phytoestrogens are molecules from a different chemical family than steroids, but some recent data suggest that, even among steroids with structural similarities with estradiol, there is much to explore in terms of potential ER ligands (Fig. 2).

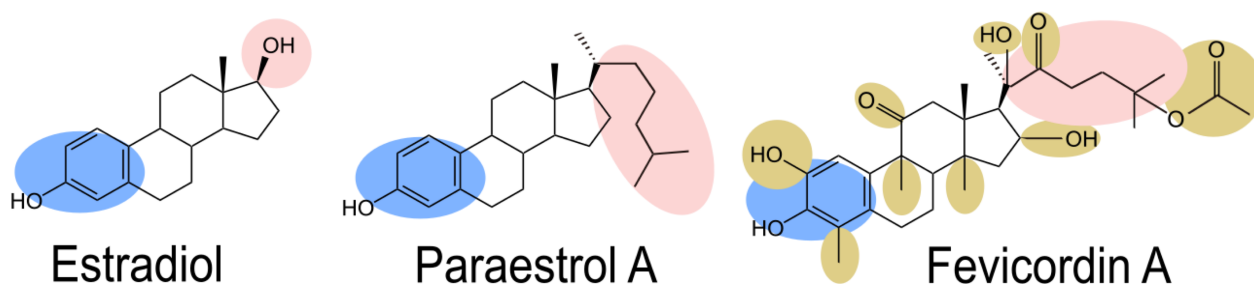


Figure 2. Structural comparison of aromatic steroids binding to the vertebrate estrogen receptor. In blue, the aromatic A ring common to the three molecules. In red, the sterol side-chain, which is still present in paraestrol A and fevicordin A, but cleaved in estradiol. In brown, specific modifications to the sterol skeleton in fevicordin A.

Estradiol (Fig. 2) is the classical steroid ligand for the estrogen receptor. Its two main features are an aromatization of the A ring (in blue; Fig. 2) and a cleaved side-chain (in red; Fig. 2). Evolutionary studies on steroid synthesis pathways indicate that, aromatization of the sterol ring A appeared before side-chain cleavage, implying that side-chain cleaved aromatized steroids like estradiol were predated by aromatized steroids that still bear a side chain, like paraestrol A (Markov et al., 2017). Consistent with this, aromatized steroids with a side-chain have also been found in some sponges that lack an estrogen receptor (Wang et al., 1996; Lu et al., 2010) and in some land plants, mainly cucurbitacids from the genus *Fevillea* (Chen et al., 2005). The most deeply investigated example to date is Fevicordin A, isolated independently from two distant rosid angiosperms, the central american cucurbit *Fevillea cordifolia* (Achenbach et al., 1986), and the indonesian malvale *Phaleria macrocarpa* (Kurnia et al., 2007). Fevicordin A has been proposed to

be an antagonist of the animal estrogen receptor, based on its cytotoxicity on breast cancer cells and molecular modeling studies (Muchtaridi et al., 2014). So far, sterols with an aromatized A-ring have not been described in algal lineages, but there are other sterols with structural features that make them strikingly similar either to terrestrial plant or animal hormones (Fig. 3).

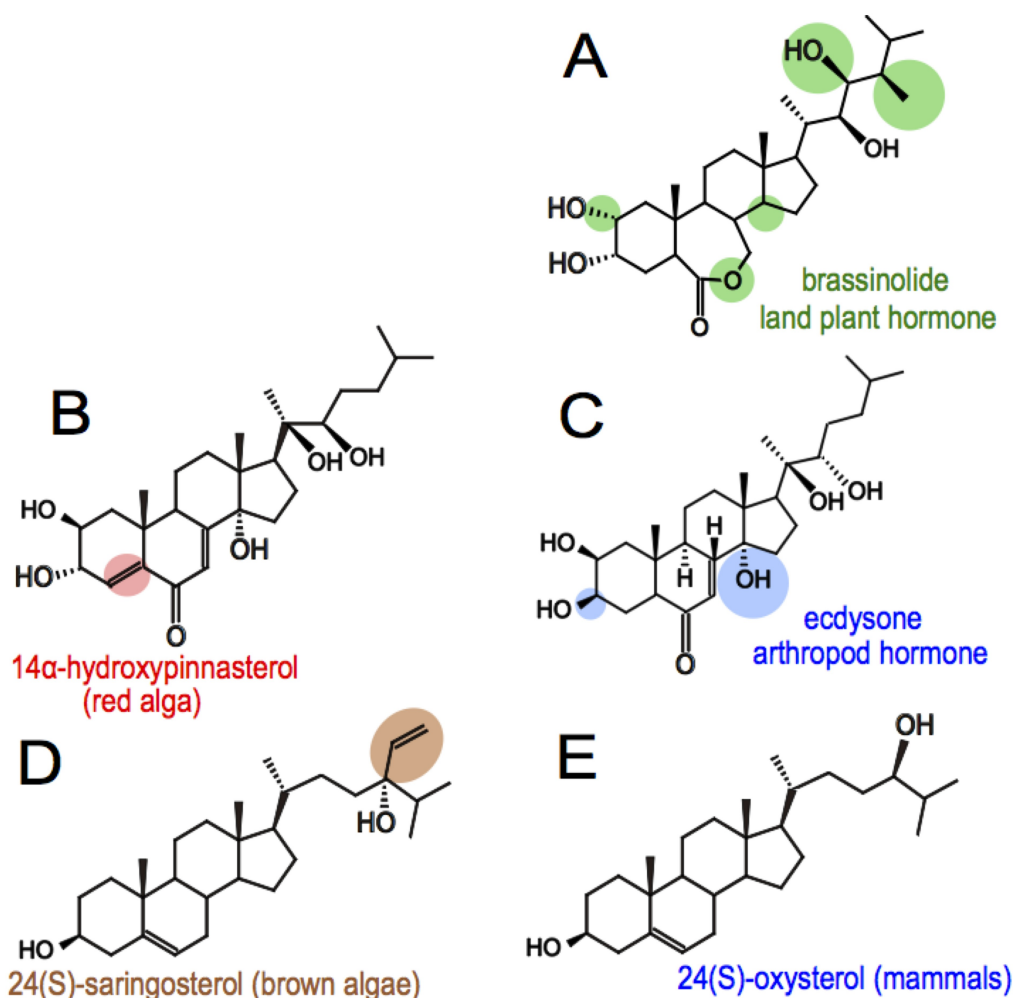


Figure 3. Structural comparison between marine algal sterols and steroid hormones from land plants and animals. (A) Brassinolide, a land plant hormone. (B) 14 α -hydroxypinnasterol, isolated from the red alga *Laurencia pinnata*. (C) Ecdysone, the main arthropod molting hormone. (D) Saringosterol from brown algae. (E) 24(S)-oxysterol from mammals. The specificity of each chemical structure is highlighted with taxon-specific colors and further discussed in text.

The algal sterol that is structurally most similar to animal hormones is 14 α -hydroxypinnasterol (Fig. 3B), which was isolated from the Japanese red alga *Laurencia pinnata* (Fukuzawa et al., 1986). This molecule differs from ecdysone, the main molting hormone from arthropods (Fig. 3C), only by the stereochemistry of two hydroxy bonds, the absence of a C25-hydroxy group (highlighted in blue; Fig. 3C) and by the presence of a double bond at C4-C5 position (highlighted in red; Fig. 3B). 14 α -hydroxypinnasterol consistently induced molting activity in an *in vivo* assays on fly larvae (Fukuzawa et al., 1986). Thus, this compound may have a defense role against arthropod grazers. More recently, other polyhydroxylated steroids were isolated from brown algae, and their structural similarity to intermediates in the synthesis pathway of the plant hormone brassinolide highlighted (Hamdy et al., 2009). Furthermore, even if compounds like 14 α -hydroxypinnasterol show a higher number of differences with brassinolides (highlighted in green; Fig. 3A), it is equally possible that

some of these algal polyhydroxylated steroids also have endogenous hormone-related functions. Disentangling both hypotheses will necessitate further investigations, in particular regarding the quantitative variation of 14 α -hydroxypinnasterol across algal life cycle stages, and depending on exposure to grazers. Exploring the biosynthetic pathways leading to 14 α -hydroxypinnasterol would also be useful, as it would provide the possibility to follow the dynamics of pathway expression by transcriptomics. However this cannot be a short-term goal, due to the multiplicity of steps and the possibilities for enzymatic convergence (Langlois et al., 2010), which would complicate the elucidation of the pathway. Besides these complex polyhydroxylated steroids, algae also produce simpler oxysterols. One of them is 24(S)-saringosterol (Fig. 3D), which was identified in a wide spectrum of brown algae. 24(S)-saringosterol differs from 24(S)-oxysterol from mammals (Fig. 3E) only by the presence of an additional ethylene group on the side chain (highlighted in brown; Fig. 3D). 24(S)-oxysterol is involved in brain cholesterol homeostasis through binding to the LXR β receptor (Okabe et al., 2013), a steroid receptor from the NR1 family, like the arthropod ecdysone receptor. Similarly, saringosterol acts as an LXR β agonist (Chen et al., 2014). Those chemical similarities suggest that, in addition to the pharmacological effects of medical interest, oxysterols from algae may modulate the cholesterol homeostasis of their grazers.

3. Carotenoids

Carotenoids are originally membrane-stabilizing molecules that were recruited as photoprotective pigments during photosynthesis, vision, or egg formation (Vershinin, 1999). The main carotenoid from red algae is lutein, which also accumulates in vertebrate gonads. In brown algae, the main carotenoid is fucoxanthin (Takaichi, 2011). In vertebrates and land plants, cleavage of some carotenoids leads to the formation of signaling molecules, like all-trans retinoic acid and abscisic acid (Fig. 4).

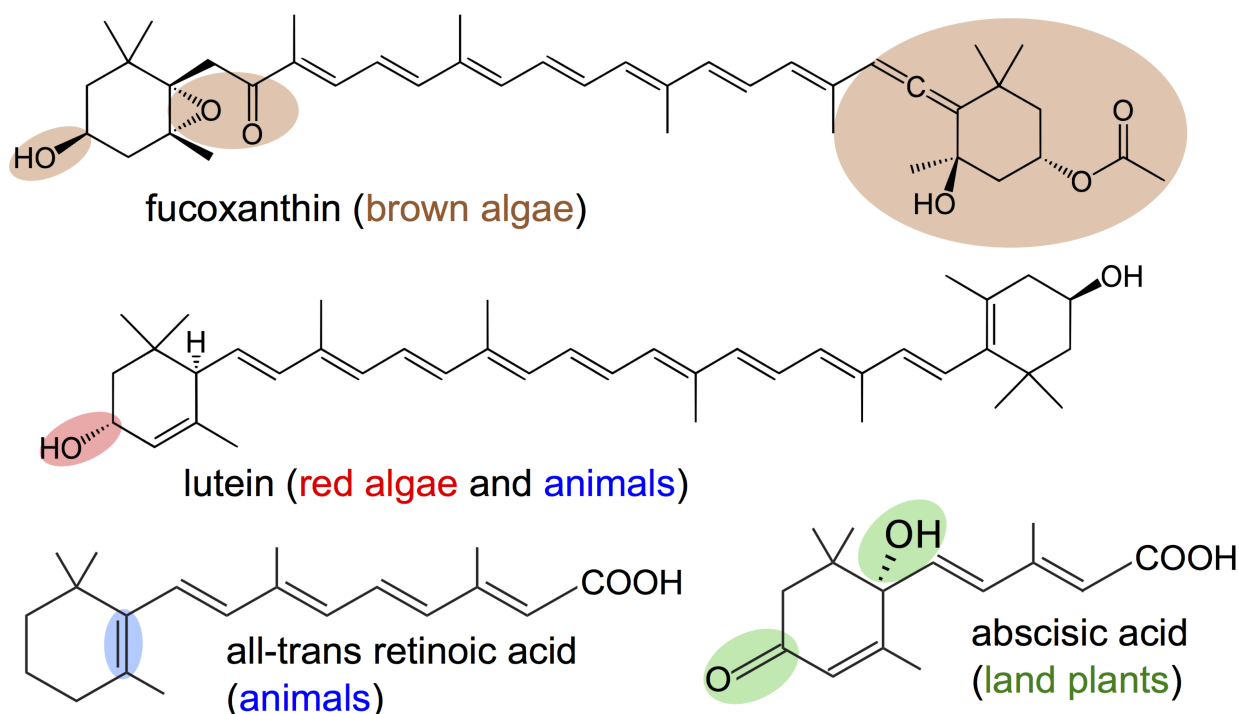


Figure 4. Main carotenoid pigments from red and brown algae, compared with animal and land plant bioactive derivatives. Color dots highlight specific chemical differences between the terminal parts of the four molecules.

In vertebrates, the best-characterized carotenoid ligand for nuclear receptors is all-trans retinoic acid. It is involved in paracrine signaling in a broad range of biological processes during development and adulthood through RAR, a receptor from the NR1 family. Its stereoisomer 9-cis retinoic acid may also have some physiological roles through binding to the RXR receptor from the NR2 family, but its presence *in vivo* in mammals is debated (Gutierrez-Mazariegos et al., 2014). So far, there is only very preliminary evidence of functional interactions between macroalgal carotenoids and nuclear receptor signaling. The only reported case is about the role of β -cryptoxanthin on adipogenesis via RAR binding (Shirakura et al., 2011). β -cryptoxanthin has been detected in the red alga, *Gracilaria cliftonii*, which is consumed by the Australian greenlip abalone (Hoang et al., 2016). Furthermore, 4-oxo-retinoic acids and carotenoid glycosides from cyanobacteria have been shown to have teratogenic effects on the development of *Xenopus* tadpoles and zebrafish larvae, and these effects were clearly linked to their capacity to bind to RAR (Wu et al., 2012; Jaja-Chimedza et al., 2017). This suggests that it would also be worth further investigate the signaling potential of carotenoids from macroalgae through RAR especially as RAR orthologs are present in mollusks and annelids, where they are low-affinity sensors, and not high-affinity receptors as in vertebrates (Handberg-Thorsager et al., 2018).

4. Fatty acid derivatives: oxylipins

Oxylipins are fatty acid derivatives, produced either by enzymatic or non-enzymatic peroxidation. Some of them, especially cyclic derivatives, are important signaling molecules (Fig. 5). In animals, prostaglandins deriving from eicosanoic acid (C20) mediate inflammatory reactions, mainly through membrane receptors, but also through PPAR nuclear receptors belonging to the NR1 family (Funk, 2001). In land plants, the linoleic acid (C18) derivative jasmonate is a major player in the defense response of land plants (Wasternak and Song, 2017).

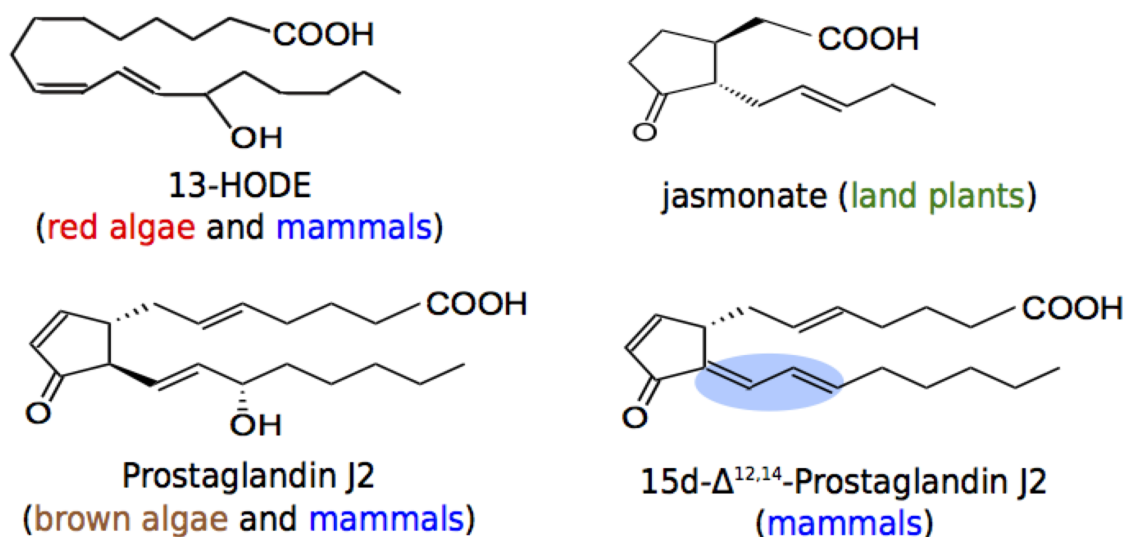


Figure 5. Examples from bioactive oxylipin molecules in mammals and land plants, compared with closely related compounds that are also present in red and brown algae. The blue highlight indicates the structural difference between 5deoxy- $\Delta^{12,14}$ -prostaglandin J2 and its biosynthetic precursor prostaglandin J2.

A number of oxylipins, deriving either from C18 or C20 fatty acids, have been described in macroalgae (Barbosa et al. 2016). Among those, 13-HODE, which is present in the red alga *Chondrus crispus* (Bouarab et al., 2004), is a PPAR γ ligand (Nagy et al., 1998). In the brown algae

Laminaria digitata and *Lessonia spicata*, one of the oxilipins that are differentially regulated in response to grazing by mollusks is prostaglandin J2 (Ritter et al., 2017). This latter compound is also a PPAR γ ligand, even if less potent than its derivative 15deoxy- Δ 12,14-prostaglandin J2 (Forman et al., 1995). A PPAR ortholog was characterized in the Pacific oyster, and its ligand-binding pocket was predicted to be much smaller than in vertebrates, making extrapolation from a human model not reliable (Vogeler et al., 2017). Apart from that, there is nothing known about the structure and function of PPAR orthologs in mollusks.

5. Halogenated compounds

Thyroid hormones are somewhat special among nuclear receptor ligands, being the only ones that derive from proteins and not from lipids. Their phenolic rings derive from tyrosine residues that underwent iodinating peroxidation. However, halogen metabolism is widespread across all organisms, especially in the marine environment. It concerns a large variety of molecules, that are often involved in biotic interactions (Valverde et al., 2004). Halogenated compounds are frequently metabolized after ingestion, and modified through the food chain (Miller and Heyland, 2010). Some halogenated compounds from algae are similar to thyroid hormones either from the structural or functional viewpoint (Fig. 6).

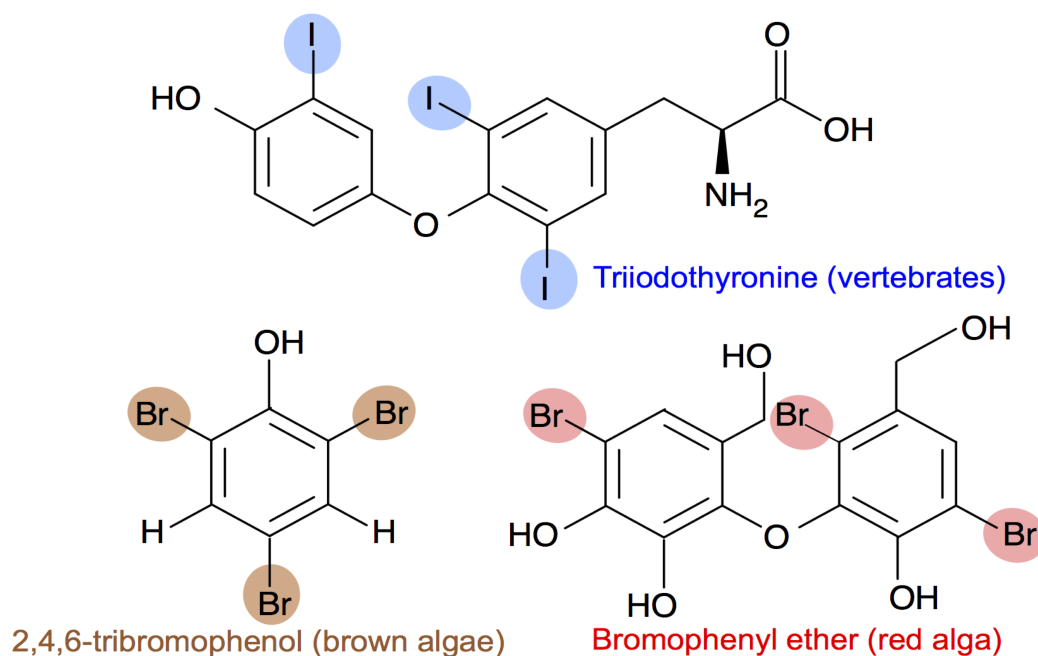


Figure 6. Halogenated phenolics from animals and algae.

Halogenated residues are highlighted with colors.

The volatile 2,4,6-tribromophenol is released into seawater by some brown algae, and inhibits larval settlement as well as reduces the survival of abalones and sea urchins (Li et al., 2009; Li et al., 2011), both grazers of brown algae. However, even if both mollusks and sea urchins have an ortholog of the thyroid hormone receptor (TR) from chordates, there is no evidence that this receptor is involved in the transduction of thyroid hormone-like molecules (Holzer et al., 2017b). Most likely, these molecules act through a different TR-independent pathway (Taylor and Heyland, 2017). One further illustration of those indirect links is provided by bromophenyl ethers from the red alga *Odonthalia corymbifera*, which – despite being structurally even closer to triiodothyronin than tribromophenols (Fig 6), are inhibitors of α -glucosidase (Kurihara et al., 1999).

6. Perspective: towards a connection between environmental cues and physiological processes

To date, the evidence of a physiologically relevant connection between macroalgal signaling molecules and animal endocrine systems through nuclear receptors is not substantiated to the same level in the four main chemical classes of potential ligands. The connections are quite strong for steroids and oxylipins, providing precise candidates for follow-up investigations. Concerning carotenoids, molecules isolated from cyanobacteria also provide candidates to search for in macroalgal metabolomes. Regarding halogenated compounds, more exploratory work will be necessary. The tremendous chemodiversity of biological molecules makes it quasi-impossible to systematically test all possible ligand-receptor interactions in an unbiased way, especially when studying emerging model organisms. It is always necessary to find compromises between exploratory searches including a wide variety of compounds, and detailed physiologically meaningful investigations of a reduced part of the chemical space. Furthermore, we focused here on nuclear receptors, but exactly the same reasoning could be applied to membrane receptors, biosynthetic enzymes, and all kinds of proteins that undergo allosteric modulation by small molecules. Regarding membrane receptors, there is already solid evidence that phytochemicals have strong interactions with the estrogen membrane receptor, GPER (Thomas and Dong, 2006). Endocrinology and natural products chemistry have diverged long time ago, but the increasing availability of genomic data is now changing this situation, making it possible to put metabolic diversity into an evolutionary context in a more and more comprehensive way (Edison et al., 2016). The chemical identification of new hormones is still a challenging task, requiring long-term collaboration between chemists and biologists, but could benefit from the technical improvements in the field of natural product-based drug discovery (Harvey et al., 2015). Indeed, herbal compounds from traditional Chinese medicine have already brought important information about the synergistic effects of multiple molecules (Li et al., 2015). We anticipate that functional assays using available molecules from other, and ecologically-relevant organisms will constitute another promising alternative for this research field. Our hope is that incorporation of molecules that are present in the food of the studied model animals in those assays will accelerate the mechanistic understanding of the connection between environmental cues and physiological processes.

Acknowledgments

This paper was stimulated by presentations and discussions during the 18th International Congress of Comparative Endocrinology. We also thank Simon Dittami for comments on the manuscript. This work benefited from the support of the French Government via the National Research Agency investment expenditure program IDEALG (ANR-10-BTBR-04) to GVM and JG and from Région Bretagne via the grant « SAD 2016 - METALG (9673) » to GVM.

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