Toxicology Letters 225 (2014) 1–11

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Mini review

Consequences of metal exposure on retinoid metabolism in vertebrates: A review

M.A. Defo [a], P.A. Spear [b], P. Couture [a,*]

[a] Institut national de la recherche scientifique (INRS), Centre Eau Terre Environnement, 490 de la Couronne, Québec, QC, Canada G1K 9A9
[b] Centre de Recherche TOXEN and Département des Sciences biologiques, Université du Québec à Montréal, C.P. 8888, Succursale Centre-Ville, Montréal, QC, Canada H3C 3P8

HIGHLIGHTS

- Basis mechanisms of metal toxicity on retinoid metabolism pathways in vertebrate.
- Retinoids as antioxidants and their potential as biomarkers of metal contamination.
- Imbalance of retinoid storage in relation to metal contamination.

ARTICLE INFO

Article history:
Received 6 August 2013
Received in revised form
18 November 2013
Accepted 20 November 2013
Available online 27 November 2013

Keywords:
Chronic metal exposure
Retinoid metabolism
Antioxidants
Vertebrates

ABSTRACT

What we generally refer to as 'vitamin A' is a group of naturally-occurring molecules structurally similar to retinol that are capable of exerting biological activity. These retinoids are essential to diverse physiological functions including vision, immune response, bone mineralization, reproduction, cell differentiation, and growth. As well, some retinoids have antioxidant properties. Independent studies published over the last few decades have revealed that many fish and wildlife populations living in highly polluted environments have altered retinoid status possibly associated with retinoid metabolic or homeostatic mechanisms. Substantial evidence links organic contaminant exposure with changes in retinoid status in animal populations, but only a few detailed studies have been published implicating inorganic contaminants such as metals. This mini-review selectively deals with field and laboratory studies reporting associations between environmental contaminants, especially trace metals, and alterations in retinoid status. Both essential and non-essential trace metals have been reported to affect retinoid status. This review focuses on metabolic imbalances of retinoids in relation to metal contamination and illustrates possible modes of action. The role of retinoids as antioxidants and their potential as biomarkers of metal contamination are discussed.

Contents

* Corresponding author. Tel.: +1 418 559 3825; fax: +1 418 654 2600.
E-mail addresses: patrice.couture@ete.inrs.ca, amerymichel@yahoo.fr (P. Couture).

0378-4274/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.toxlet.2013.11.024

1. Introduction

Technological development has improved the quality of human life in industrial countries, but has also engendered a number of ecological crises and stress in ecosystems. At the top of the list of anthropogenic activities that have considerably impacted the environment are agriculture, deforestation and metal mining and smelting. Traditionally, scientists distinguish two groups of environmental contaminants: man made contaminants (organic contaminants) and inorganic contaminants especially metals. Organic and inorganic contaminants have widely different ecotoxicological properties. For example unlike the organic pollutants, metals are naturally occurring elements, they are an integral part of Earth and are found in all ecosystems (Campbell and Couillard, 2004). Certain metals are essential for life and are required micronutrients for biological functions (Atli and Canli, 2011; Campbell and Couillard, 2004; Niyogi et al., 2007). Anthropogenic activities are known to have a considerable influence on the local environment and ecology. Toxicological effects caused by environmental pollutants have been highlighted elsewhere. For instance, evidence of metabolic disturbances linked to metal contamination has been reported in fish chronically exposed in the field (Couture and Pyle, 2011). In their review, the authors proposed that the mechanisms of chronic metal toxicity in fish living in contaminated natural environments are subtle and involve energy costs for fighting oxidative stress, metal detoxification and protein repair. Presumably, the toxic mode of action of metals under conditions of chronic exposure is largely similar to oxidative stress induced by oxygen; both share multiple mechanisms of cellular response aiming at fighting cellular oxidative damage (Clarkson, 1995; Couture and Pyle, 2011).

Literature reporting impacts of environmental pollutants on retinoid metabolism is largely focused on organic contaminants, especially persistent organochlorine pollutants (Novák et al., 2008; Rolland, 2000; Simms and Ross, 2000), while literature on metal effects is much scarcer. In the two last decades, trace metals have been reported to induce alterations of retinoid status in wildlife, mostly in fish. In this brief review, we describe the current knowledge and recent reports of relationships between inorganic contaminants and retinoid metabolism in fish and other vertebrates. The role of retinoids as antioxidants of metal exposure and the mechanisms of retinoid metabolism disruption by inorganic pollutants will be discussed.

2. Molecular structure of retinoids

The molecular structures of common retinoids are illustrated in Fig. 1, while Table 1 illustrates the main physico-chemical characteristics of the principal forms of retinoids. The predominant forms of retinoids are all-*trans*-retinol and its esters which are found in mammals, amphibians, birds and fish. Other forms of retinoids have also been reported in vertebrates, namely all-*trans*-dehydroretinol (3,4-didehydro-all-*trans*-retinol) and dehydroretinyl esters, which have been found in some fish species (Defo et al., 2012; Goswami and Barua, 1981; Pereira et al., 2012) some bird species (Müller et al., 2012) and in frogs, although the amount was low in amphibians (Boily et al., 2005). The prevalence and the abundance of different forms of retinoids in fish are reported to be related to fish morphology and life traits (dietary habits, migratory potentiality and habitat) (Goswami and Barua, 1981). According to the classification of Goswami and Barua (1981), two categories of fish exist: Retinol-type (vitamin A1) and dehydroretinol-type (vitamin A2). However, the limited available data for the dehydroretinol type makes it difficult to really understand the tissue distribution, metabolism and roles of these substances (Gesto et al., 2012b). Photosynthetic organisms are the main source of pro-retinoids (beta-carotene) and retinoids for animals (Garner et al., 2010).

3. Physiological functions and metabolism of retinoids

Retinoids are natural or synthetic compounds with structures similar to retinol and, among this sizable composite of molecules, those naturally-occurring forms capable of exerting biological activity have historically been referred to as vitamin A (Debier and Larondelle, 2005; Novák et al., 2008). The inability of animals to perform *de novo* synthesis of retinoids forces them to incorporate these essential molecules from their diet (Garner et al., 2010; Novák et al., 2008), which is consistent with the definition of vitamins. The most active retinoids (*e.g.* retinoic acid) act as hormones by regulating gene transcription through high-affinity binding to nuclear receptors belonging to the steroid-thyroid family of hormones (Rolland, 2000; Simms and Ross, 2000). Retinoids are essential to diverse vital biological functions such as growth, development, cell differentiation, immune system, reproduction and vision (reviewed in D'Ambrosio et al., 2011; Debier and Larondelle, 2005; Novák et al., 2008). Some retinoids are also known to mitigate oxidative stress (Alpsoy et al., 2009; Defo et al., 2012; Dragsted, 2008; Rodríguez-Estival et al., 2011b). The alcohol form, retinol, acts as a precursor for the biosynthesis of two critical metabolites (retinal and retinoic acid). Retinol is essential in reproduction while the aldehyde form plays a crucial role in vision (Janošek et al., 2006), especially in the metabolism of the pigment rhodopsin, involved in photoreceptor cells of the retina (D'Ambrosio et al., 2011; Debier and Larondelle, 2005). Perhaps the most biologically active forms of retinoids are the different isoforms of its retinoic acid (Fernández and Gisbert, 2011; Wu and Ross, 2010). This molecule is a potent hormone that controls the expression of genes through binding to nuclear receptors acting on genomic targets (Ross and Zolfaghari, 2004). Through the activation of specific transcription factors (Amann et al., 2011a,b; Sucov and Evans, 1995), the acid form of retinoids is

Table 1
Some physico-chemical characteristics of the principal forms of vitamin A.

	Retinoids/vitamin A1				Didehydroretinoids/vitamin A2			
Form	Alcohol form	Aldehyde forms	Acid form	Ester form	Alcohol form	Aldehyde forms	Acid form	Ester form
Vitamin A	All trans retinol	All trans retinaldehyde	All trans retinoic acid	All trans retinyl palmitate	All trans 3,4-didehydro retinol	All trans 3,4-didehydro retinaldehyde	All trans 3,4-didehydro retinoic acid	All trans 3,4-didehydro retinyl palmitate
Molecular formula	$C_{20}H_{30}O$	$C_{20}H_{28}O$	$C_{20}H_{28}O_2$	$C_{36}H_{60}O_2$	$C_{20}H_{28}O$	$C_{20}H_{26}O$	$C_{20}H_{26}O_2$	$C_{36}H_{58}O_2$
Molar mass (g/mol)	28,644	28,444	30,044	52,486	28,444	28,244	29,844	52,286
Cell status	Transport	Semi active[a] active (vision)	Active	Storage	[b]	[b]	[b]	[b]

[a] Immediately precursor of the active form (retinoic acid).
[b] Active cell status unknown however could be the same like their retinoid homologues.