Prostaglandins & other Lipid Mediators 112 (2014) 27–33

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

Minireview

6-Iodolactone, key mediator of antitumoral properties of iodine

Mario Nava-Villalba, Carmen Aceves*

Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus Juriquilla, Querétaro, Mexico

ARTICLE INFO

Article history:
Received 16 April 2014
Received in revised form 20 June 2014
Accepted 1 July 2014
Available online 10 July 2014

Keywords:
Apoptosis
Arachidonic acid
Iodine
Iodolipids
Iodocompounds
Mammary cancer

ABSTRACT

An iodinated derivative of arachidonic acid, 5-hydroxy-6-iodo-8,11,14-eicosatrienoic acid, δ-lactone (6-IL) has been implicated as a possible intermediate in the autoregulation of the thyroid gland by iodine. In addition to antiproliferative and apoptotic effects observed in thyrocytes, this iodolipid could also exert similar actions in cells derived from extrathyroidal tissues like mammary gland, prostate, colon, or the nervous system. In mammary cancer (solid tumors or tumor cell lines), 6-IL has been detected after molecular iodine (I_2) supplement, and is a potent activator of peroxisome proliferator-activated receptor type gamma (PPARγ). These observations led us to propose I_2 supplement as a novel coadjutant therapy which, by inducing differentiation mechanisms, decreases tumor progression and prevents chemoresistance. Some kinds of tumoral cells, in contrast to normal cells, contain high concentrations of arachidonic acid, making the I_2 supplement a potential "magic bullet" that enables local, specific production of 6-IL, which then exerts antineoplastic actions with minimal deleterious effects on normal tissues.

Contents

1. Introduction

Epidemiological studies have shown that moderately high iodine ingestion is a protective factor against mammary and prostate pathologies [1,2]. *In vivo* and *in vitro* studies have provided evidence that molecular iodine (I_2) rather than iodide (I^-) is responsible for these antineoplastic effects, and two molecular paths have been proposed: (1) I_2 exerts a direct effect related to the its oxidant/antioxidant properties, which can dissipate the mitochondrial membrane potential thereby triggering mitochondrion-mediated apoptosis [3], and/or I_2 functions as a scavenger and protective antioxidant neutralizing HO• radicals [4], and (2) I_2 exerts an indirect effect through iodolipid formation and the activation of peroxisome proliferator-activated receptors type gamma (PPARγ) which, in turn, trigger apoptotic or differentiation pathways. Here, we review these latter mechanisms that involve the formation of iodo-lactone.

Unsaturated fatty acids (UFAs), in addition to being structural components of biomembranes, are metabolized to reactive products and exert a crucial role in several physio- and pathological processes [5]. Many UFA-derivatives, especially the lactones, can act at different cellular levels, functioning as substrates of

* Corresponding author at: Instituto de Neurobiología, Universidad Nacional Autónoma de México, Campus Juriquilla, Boulevard Juriquilla 3001, Querétaro, CP 76230, Mexico. Tel.: +52 442 2381067; fax: +52 442 2381067.
E-mail addresses: marionava23@unam.mx (M. Nava-Villalba), caracev@unam.mx (C. Aceves).

http://dx.doi.org/10.1016/j.prostaglandins.2014.07.001
1098-8823/

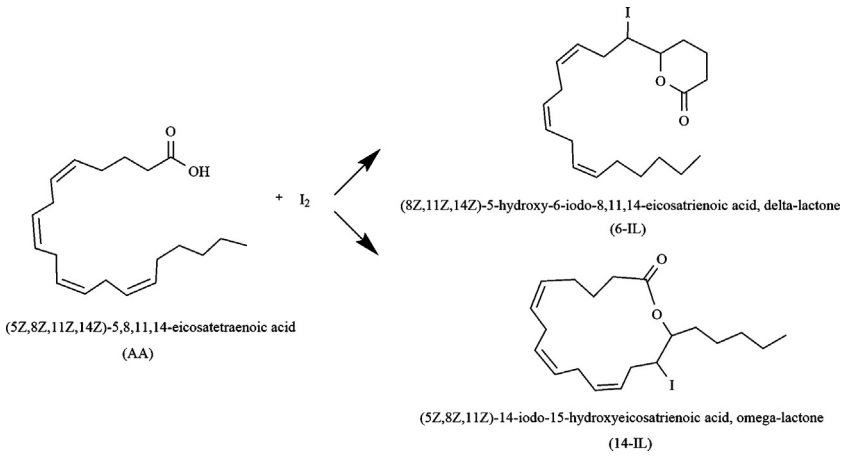

Fig. 1. Chemical structure of iodolactones. The reaction involves the formation from molecular iodine of a positively charged halonium ion at the C-6 or C-14 position of arachidonic acid and the subsequent ring closure by a hydroxyl group at C-5 or C-13 to form the corresponding lactone.

intercellular mediators and also exerting significant intracellular impacts on gene expression and metabolic responses [6–8]. In the thyroid gland, certain iodinated lactones participate in modulating mechanisms that were attributed previously to iodine but could not be explained by thyroid hormone actions. The recent demonstration that some of these iodolactones have effects and can be generated in extrathyroid tissues like mammary gland, may help explain the pleiotropic effects associated with deficient or excess iodine. We propose that I_2 supplement can be used as adjunctive therapy that may be a new "magic bullet" against several cancers capable of iodine uptake.

2. Iodolactonization

Iodolactonization is one of a group of chemical reactions called halo-cyclization, which was described at the beginning of 20th century employing bromine [9]. Shortly thereafter, from 1904 to 1908, Bougault reported iodolactonization as an organic reaction that produces a lactone ring through the addition of oxygen and iodine across a carbon=carbon double bond [10–12]. This reaction can be carried out with any alkene, but of particular interest for biology are the iodolactonizations of UFAs. In fact, Corey used this chemical reaction as a key intermediate step to produce prostaglandins [13], and other researchers have used iodolactonization to synthesize compounds with antitumoral activity such as vernomenin and vernolepin [14], or vibralactone, a pancreatic lipase inhibitor used to treat obesity [15]. Arachidonic acid (AA) is a polyunsaturated, free fatty acid present in membrane phospholipids of all mammalian cells. Pure AA can be iodinated at each of its four double bonds [16]; however, the iodinated products of only the C5,6 and C14,15 double bonds (6-IL and 14-IL respectively) exhibit biological effects [17,18]. The reaction mechanisms involved in the formation of these components begin with the generation of a positively charged halonium ion from molecular iodine at the C-6 or C-14 position of AA; subsequently, the hydroxyl group at C-5 or C-13 is involved in a nucleophilic, intramolecular ring closure that forms the corresponding lactone [19–21]. Iodinated AA derivatives can be obtained enzymatically [16,19], as well as by chemical reactions employing iron/H_2O_2/iodide [22] and acetonitrile/iodide systems [23] (Fig. 1).

3. Role of iodolipids in thyroid physiology

Thyroid function can be regulated by iodide; this is a local mechanism with features distinct from those of the major thyroid regulator: the thyroid stimulating hormone (TSH). When the amount of iodide intake rises above 1 mg/day, iodide ceases to function as a substrate for hormonogenesis, and it is perceived as a homeostatic signal that prevents the installation of thyrotoxicosis [20], a phenomenon called the "Wolff–Chaikoff effect" [24]. This homeostatic regulation is characterized at the molecular level by: (1) inhibition of H_2O_2 generation by dual oxidases, thereby blocking iodide oxidation and organification [24,25]; (2) suppression of sodium-iodide symporter (NIS) expression [26], stopping the entry of iodide and lowering the intracellular iodide concentration; and (3) inhibition of thyroid hormone secretion [27]. In high concentrations of iodide, additional mechanisms are also observed, like reduction of thyroid blood flow [28,29], inhibition of thyroid growth [17,30], and induction of apoptosis [31,32]. Since all these inhibitory effects of iodide can be prevented by blocking iodide uptake with perchlorate (specific inhibitor of NIS) or by inactivating thyroperoxidase (TPO; iodide oxidation enzyme) with methimazole or propylthiouracil, some authors have proposed an iodinated intermediate; this idea has been called the "XI hypothesis" [20,33–35]. A candidate for the iodocompound XI should be formed after an iodide oxidation process and, by itself, it should replicate the inhibitory effects of iodide; a number of candidate molecules have been proposed, but two classes of compounds stand out: iodolipids and iodoaldehydes [20,36,37].

The earliest reports about iodinated components with biological actions in thyroid gland emerged in the 1950s. After incubating subcellular fractions of thyroid tissue, obtained by differential centrifugation, *in vitro* with ^{131}Iodide, Taurog et al. [38] detected an unidentified iodocompound. Although its lipid nature was immediately suspected [39], this was formally confirmed few years later by Vilkki et al. [40] and Mauchamp et al. [41]. During the next two decades it was established that the phospholipids, fatty acids, and neutral lipids could all be iodinated, and it was postulated that these iodocompounds could be intracellular iodide carriers or they could serve as iodine storage for hormone formation [42–44]; later, a strong tendency correlating their presence with hormogenesis began to emerge [41,45–47]. However, only in 1980 did chemical structures of iodinated lipids with physiological actions start to be characterized through gas chromatography–mass spectrometry (GC–MS). Boeynaems et al. [19] first reported the iodolactonization of arachidonic acid (AA): from an incubation of lactoperoxidase with potassium iodide and H_2O_2, the main product was 5-hydroxy-6-iodo-8,11,14-eicosatrienoic acid, δ-lactone (6-IL). Shortly thereafter, the macrolides 14-iodo-15-hydroxyeicosatrienoic acid, ω-lactone (14-IL) and 15-iodo-14-hydroxyeicosatrienoic acid, ω-lactone were also identified [48]. These compounds exhibit an important