Pharmacology & Therapeutics 165 (2016) 114–131

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: M. Birrell

Alkyl ether lipids, ion channels and lipid raft reorganization in cancer therapy

Paul-Alain Jaffrès [a,e], Consuelo Gajate [b], Ana Maria Bouchet [c,e], Hélène Couthon-Gourvès [a,e], Aurélie Chantôme [c,e], Marie Potier-Cartereau [c,e], Pierre Besson [c,e], Philippe Bougnoux [c,d,e], Faustino Mollinedo [b], Christophe Vandier [c,e,*]

[a] CEMCA, UMR CNRS 6521, IBSAM, Université de Brest, 6, Avenue V. Le Gorgeu, 29238 Brest Cedex 3, France
[b] Laboratory of Cell Death and Cancer Therapy, Department of Cellular and Molecular Medicine, Centro de Investigaciones Biológicas, Consejo Superior de Investigaciones Científicas (CSIC), C/Ramiro de Maeztu 9, E-28040 Madrid, Spain
[c] INSERM/University of Tours U1069, Nutrition-Croissance et Cancer (N2C), F-37032 Tours, France
[d] Centre HS Kaplan, CHU Bretonneau, Tours F-37032, France
[e] Network "Ion channels and Cancer-Canceropole Grand Ouest", (IC-CGO), France

ARTICLE INFO

Available online 8 June 2016

Keywords:
Alkyl ether lipids
Lipid rafts
Ion channel
Death receptor
Apoptosis
Cell migration

ABSTRACT

Synthetic alkyl lipids, such as the ether lipids edelfosine (1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine) and ohmline (1-*O*-hexadecyl-2-*O*-methyl-*rac*-glycero-3-β-lactose), are forming a class of anti-tumor agents that target cell membranes to induce apoptosis and to decrease cell migration/invasion, leading to the inhibition of tumor and metastasis development. In this review, we present the structure–activity relationship of edelfosine and ohmline, and we point out differences and similarities between these two amphiphilic compounds. We also discuss the mechanisms of action of these synthetic alkyl ether lipids (involving, among other structures and molecules, membrane domains, Fas/CD95 death receptor signaling, and ion channels), and highlight a key role for lipid rafts in the underlying process. The reorganization of lipid raft membrane domains induced by these alkyl lipids affects the function of death receptors and ion channels, thus leading to apoptosis and/or inhibition of cancer cell migration. The possible therapeutic use of these alkyl lipids and the clinical perspectives for these lipids in prevention or/and treatment of tumor development and metastasis are also discussed.

Contents

Abbreviations: AEL, alkyl ether lipid; Bid, BH3-interacting domain death agonist; CASMER, cluster of apoptotic signaling molecule-enriched rafts; CCT, CTP:phosphocholine cytidylyiltransferase; DISC, death-inducing signaling complex; DMSO, dimethyl sulfoxide; Edelfosine, 1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine or ET-18-OCH_3; FADD, Fas-associated death domain-containing protein; HPLC/MS, high pressure liquid chromatograph/mass spectrometry; IKCa, intermediate conductance calcium-activated potassium channels; JNK, c-Jun amino-terminal kinase; KCa, calcium-activated potassium channels; Kir2.2, isoform 2.2 of potassium inward rectifier; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; Miltefosine, hexadecylphosphocholine; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide; NSCL, non-small cell lung carcinoma; Ohmline, 1-*O*-hexadecyl-2-*O*-methyl-*rac*-glycero-3-β-lactose; PAF, platelet-activating factor; PC, phosphocholine; Perifosine, (1,1-dimethyl-piperidin-1-ium-4yl) octadecyl phosphate; PLC, phospholipase C; PKCs, protein kinase C (different isoforms); RANKL, receptor activator of nuclear factor kappa-B ligand; SKCa, small conductance calcium-activated potassium channels; STIM, stromal interaction molecule; TRAAK, twik-related arachidonic acid-stimulated potassium channels; TREK-1, twik-related potassium channel-1; TRPC, transient receptor transient channels; TWIK, tandem pore domain weak inward rectifier potassium channels.

* Corresponding author at: INSERM/University of Tours U1069, Nutrition-Croissance et Cancer (N2C), F-37032 Tours, France. Tel.: +33 247366024; fax: +33 247366226.
E-mail address: christophe.vandier@univ-tours.fr (C. Vandier).
URL's: http://www.ic-cgo.fr (P.-A. Jaffrès), http://www.ic-cgo.fr (A.M. Bouchet), http://www.ic-cgo.fr (H. Couthon-Gourvès), http://www.ic-cgo.fr (A. Chantôme), http://www.ic-cgo.fr (M. Potier-Cartereau), http://www.ic-cgo.fr (P. Besson), http://www.ic-cgo.fr (P. Bougnoux), http://www.ic-cgo.fr (C. Vandier).

http://dx.doi.org/10.1016/j.pharmthera.2016.06.003
0163-7258/

1. History

In the early 1960s, it was found that the generation of 2-lysophosphatidylcholine (LPC) by phospholipase A_2 and its accumulation in the macrophage membrane led to activation and enhancement of the phagocytic activity of peritoneal macrophages in vitro and in vivo (Munder et al., 1969; Munder & Modolell, 1973). Thus, LPC was suggested to play a role in the defense mechanism of the immune system through macrophage activation, but LPC was not stable, and was biologically inactivated either by the action of acyltransferase, leading to phosphatidylcholine, or by lysophospholipase, leading to glycerophosphocholine (Mulder and van Deenen, 1965). To circumvent these metabolic changes, LPC analogues with longer half-life times were synthesized as a result of a joint effort of different groups led by Herbert Fisher, Otto Westphal, Hans Ulrich Weltzien and Paul Gerhard Munder in the Max-Planck-Institut für Immunbiologie in Freiburg. A major emphasis was laid on modifications in the positions C1 and C2 of the glycerol backbone in the molecule of LPC (1-acyl-*sn*-glycero-3-phosphocholine), replacing the ester bonds for ether linkages to generate alkyl ether lipids (AELs) that were unable to be metabolized by either acyltransferases or lysophospholipases. As a result, edelfosine (1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine, ET-18-OCH_3), was synthesized by Günter Kny in 1969, making use of the previous experience of Bernd Arnold and Hans Ulrich Weltzien with the synthesis of 1-*O*-alkyl and 2-*O*-methyl derivatives of glycerol. As expected, a number of the newly synthesized ether analogues of LPC were potent immune modulators (Munder et al., 1979), and interestingly enough some of them turned out to exert strong antitumor activity (Tarnowski et al., 1978; Munder, 1982), with edelfosine being the most active of these compounds. Subsequent work conducted in the late 1970s and 1980s by Munder's team and additional groups showed that the antitumor action of edelfosine was due to both an enhanced tumoricidal activity of macrophages and to a direct cytostatic and cytotoxic effect on tumor cells (Munder et al., 1979; Andreesen et al., 1984; Scholar, 1986). Later in 1993, edelfosine was shown independently by researchers in Madrid (Spain) (Mollinedo et al., 1993) and Milan (Italy) (Diomede et al., 1993) to promote apoptosis in cancer cells. Then, in the late 1990s and early 2000s, a number of findings were unveiled by Faustino Mollinedo and Consuelo Gajate's group in Valladolid and Salamanca (Spain) showing edelfosine-induced selective apoptosis in cancer cells, following the preferential drug uptake in tumor cells (Mollinedo et al., 1997; Gajate et al., 2000a, 2000b) as well as the reorganization of membrane raft domains (Gajate & Mollinedo, 2001; Gajate et al., 2004). Thus, these data provided the first evidence for a selective proapoptotic drug and for the involvement of membrane rafts in cancer chemotherapy.

A number of compounds derived from the original AELs have been synthesized, including miltefosine (hexadecylphosphocholine). It is a simplified version of the above AELs and lacks the glycerol backbone (Unger et al., 1988; Eibl & Unger, 1990; Unger et al., 1990). Miltefosine is used in the clinic as a topical treatment (Miltex; Asta Medica, Frankfurt, Germany) for cutaneous metastases in breast carcinoma (Clive et al., 1999; Smorenburg et al., 2000; Leonard et al., 2001). Replacement of the choline head group in miltefosine by a cyclic aliphatic piperidyl moiety yielded another set of compounds with an improved therapeutic index, from which perifosine (1,1-dimethyl-piperidin-1-ium-4-yl) octadecyl phosphate) stood out for its potent and promising antitumor activity against various cancer cell types and it is being currently tested in clinical trials (Richardson et al., 2012). These new compounds are also known as alkylphosphocholine analogues, which together with additional structurally related compounds constitute a family of synthetic compounds collectively named as alkylphospholipid analogues, and include rather heterogeneous chemical structures, including AELs, but edelfosine is still considered as the prototype of this increasing family of alkylphospholipid compounds. Since the late 1990s additional promising compounds have introduced carbohydrates or carbohydrate-related molecules to the AEL chemical leads, leading to the so-called glycosylated phospholipids (Danker et al., 2010; Semini et al., 2014) and the non-phosphorus glycosylated ether lipids (Arthur & Bittman, 2014). Beyond the action of edelfosine and glycosylated phospholipids as proapoptotic drugs, a new mode of action was recently discovered with the observation that, at lower concentration, edelfosine interacted with the SK3 channel (Potier et al., 2011) leading to a reduction of SK3-dependent cancer cell migration. A less toxic analogue of edelfosine was identified, ohmline (1-*O*-hexadecyl-2-*O*-methyl-*rac*-glycero-3-β-lactose (Girault et al., 2011; Chantome et al., 2013) which is a glyco–glycero ether lipid. Because of its apparent lack of general toxicity, its in vivo use revealed its ability to prevent bone metastases in a metastatic breast cancer model (murine experiments). The anticancer action of edelfosine (proapoptotic effect) or ohmline (anti-metastatic effect) is based on different mechanisms of action but, to some extent, they also possess some similarities since they interact selectively with proteins localized at the plasma membrane and more likely in the lipid rafts. The recent insights in the mechanisms of action of both edelfosine and ohmline are further detailed and discussed below, including the potential medical innovations suggested by these original modes of action.

2. Structure–activity relationship of edelfosine and ohmline and their effects on the SK3 channel

The mode of action of edelfosine and ohmline is singular compared to most anticancer drugs. These lipids do not interact with DNA. Because of their amphiphilic nature, they incorporate into cell membranes where they can affect a large number of membrane-embedded proteins. Among them, ion channels and more precisely the SK3 potassium channel was found to be sensitive to AELs (Girault et al., 2011). The SK3 channel belongs to the calcium-activated potassium channel (KCa) family that comprises many channels which differ in their primary amino acid sequences and exhibit different single channel conductance (Wei et al., 2005). KCa channels can be divided into three subfamilies: big conductance (BKCa), intermediate conductance (IKCa) and small conductance (SKCa). IKCa is also named as KCa3.1 or SK4 or IK1. SK3 is a member of the SKCa ion channel family that includes 2 other isoforms SK1 and SK2. The SK3 channel (like SK1, SK2 and IKCa channels), through its high calcium sensitivity (it is activated by submicromolar concentrations of intracellular calcium), plays a role in the regulation of signaling pathways involving calcium, in both excitable and non-excitable cells. In 2010s, Paul-Alain Jaffrès's group in Brest (France) and Christophe Vandier's group in Tours (France) demonstrated the capacity of AELs to reduce cancer cell migration and metastasis development by targeting the SK3 channel leading these groups to propose AELs and derivatives as a new class of anti-metastatic drugs in targeted and personalized cancer therapy (Girault et al., 2011; Chantome et al., 2013). Therefore, the modulation of SK3 channel activity constitutes a