Biochemical and Biophysical Research Communications 446 (2014) 651–655

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

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

Review

Regulation of the adrenoleukodystrophy-related gene (*ABCD2*): Focus on oxysterols and LXR antagonists

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ARTICLE INFO

Article history:
Available online 27 January 2014

Keywords:
LXR antagonists
Oxysterols
Adrenoleukodystrophy
Peroxisome
ABC transporters
Neurodegenerative disorders

ABSTRACT

The regulation of the *ABCD2* gene is recognized as a possible therapeutic target for X-linked adrenoleukodystrophy, a rare neurodegenerative disease caused by mutations in the *ABCD1* gene. Up-regulation of *ABCD2* expression has indeed been demonstrated to compensate for *ABCD1* deficiency, restoring peroxisomal β-oxidation of very-long-chain fatty acids. Besides the known inducers of the *ABCD2* gene (phenylbutyrate and histone deacetylase inhibitors, fibrates, dehydroepiandrosterone, thyroid hormone and thyromimetics), this review will focus on LXR antagonists and 22S-hydroxycholesterol, recently described as inducers of *ABCD2* expression. Several LXR antagonists have been identified and their possible indication for neurodegenerative disorders will be discussed.

Contents

1. Introduction

Childhood cerebral adrenoleukodystrophy (CCALD) and the adult form called adrenomyeloneuropathy (AMN) are the main clinical phenotypes of X-linked adrenoleukodystrophy (X-ALD, OMIM 300100) [1]. CCALD is characterized by inflammatory demyelination of the central nervous system. AMN is characterized by a non-inflammatory distal axonopathy mainly affecting spinal cord and peripheral nerves. In spite of the success of a gene therapy trial, this fatal disorder is still in search for an efficient therapy that could represent a good alternative to the hematopoietic stem cell transplantation, the unique therapy available for the patients with the cerebral form. From a biochemical point of view, X-ALD is characterized by the accumulation of very-long-chain fatty acids (VLCFA) resulting from a β-oxidation defect caused by mutations in the *ABCD1* gene. *ABCD1* encodes for a peroxisomal half ABC transporter participating in the entry of VLCFA-CoA into the peroxisome, the unique site of their β-oxidation [2]. Overexpression of the *ABCD2* gene [3], the closest homolog of *ABCD1*, has been shown to compensate for *ABCD1* deficiency in X-ALD skin fibroblasts [4,5]. Functional redundancy is also recognized *in vivo* since reversion of the adrenomyeloneuropathy-like phenotype has been observed in *Abcd1* null mice overexpressing *Abcd2* [6]. Therefore, pharmacological induction of *ABCD2* could represent an alternative therapy for X-ALD.

Numerous investigations focused on the transcriptional regulation of *ABCD2* to discover endogenous or synthetic inducers and/or novel molecular regulation pathways have been initiated. These studies faced with different concerns. To limit side effects, it is necessary to find out regulators with an elevated specificity for *ABCD2*. Obviously, a pleiotropic effect may be considered as positive if such inducers lead to an increase in peroxisomal β-oxidation, a decreased elongation of fatty acids, an anti-inflammatory effect or a decrease in the level of oxidative stress. Moreover, pharmacological induction of *ABCD2* should a priori occur in the key tissues

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http://dx.doi.org/10.1016/j.bbrc.2014.01.025
0006-291X/

affected by the disease (adrenals, testis, brain) and specific cell types such as glial (especially oligodendrocytes) or microglial cells. At first glance, it would be necessary that pharmacological inducers were able to enter into the brain. However, it cannot be excluded that pharmacological induction of *ABCD2* in circulating cells would be sufficient to trigger beneficial effects in central nervous system of X-ALD patients. Finally, the ability to overexpress *ABCD2* in a tissue in which expression level is already elevated might be difficult.

2. Regulators of *ABCD2* expression

In 1998, sodium phenylbutyrate (4-PBA), a histone deacetylase (HDAC) inhibitor, was shown to normalize VLCFA levels in human and murine X-ALD fibroblasts by increasing their peroxisomal β-oxidation [4]. In 4-PBA-treated *Abcd1* null mice, VLCFA levels were decreased both in adrenals and brain. Induction of peroxisome proliferation and/or *Abcd2* in brain was hypothesized to be responsible for this observation. In rats and different cell types, 4-PBA was shown to induce peroxisome proliferation and increase peroxisomal β-oxidation by inducing the *Abcd2* gene through its minimal promoter (Fig. 1) [7]. However, while induction of *Abcd2* was observed *in vitro* in glial cells and in the liver of treated-rats, there was no evidence of induction in the brain. A clinical trial in adrenomyeloneuropathy patients failed to demonstrate efficiency probably because of the very short half-life of 4-PBA *in vivo* [8]. Since the proof of concept that molecules involved in chromatin remodeling could be indicated for X-ALD, several studies have been initiated on analog compounds. Valproic acid (a non-specific HDAC inhibitor used in epilepsy) was shown to induce *ABCD2* expression in X-ALD fibroblasts but apparently without decrease of saturated VLCFA levels [9]. Suberoylanilide hydroxamic acid (SAHA) was able to normalize VLCFA (peroxisomal β-oxidation and *ABCD2*/*ABCD3* expression levels are increased while the elongase *ELOVL1* expression is decreased) in X-ALD fibroblasts and to down-regulate the expression of proinflammatory cytokines in *Abcd1*/*2*-silenced mouse astrocytes [10]. Similar results were recently obtained with caffeic acid phenethyl ester [11].

Fibrates are hypolipidemic drugs that induce peroxisomal proliferation and peroxisomal β-oxidation in rodents through PPARα activation. Early studies demonstrated inducibility of *Abcd2* in the liver but not in the brain of rodents [5,12,13]. Up-regulation of *Abcd2* was shown to be dependent on PPARα although no functional peroxisome proliferator response element has been identified in the promoter of *Abcd2* [12]. Indirect regulation involving SREBP2 has been suspected [14] but there is currently no direct proof in favor of this hypothesis. Other potent PPARα activators (GW6867, GW7647) were shown to induce *Abcd2* expression in the liver but not in brain. Similar results were obtained with tetradecylthioacetic acid, another PPARα agonist known to cross the blood–brain barrier [14]. A clinical trial was recently initiated on bezafibrate, a drug shown to reduce VLCFA accumulation in X-ALD fibroblasts contrary to other PPAR ligands but failed to demonstrate induction of *ABCD2* and improvements in adrenomyeloneuropathy patients [15].

Dehydroepiandrosterone (DHEA) and its sulfate ester are the most abundant steroids in humans. DHEA is involved in neuroprotection and neurite growth and exerts anti-oxidant and anti-inflammatory effects through several nuclear receptors including PPARα. *Abcd2* was induced in the liver of male rodents treated with DHEA or its 17β-reduced metabolite ADIOL (5-androstene-3β,17β-diol) independently of PPARα [16]. A clinical study on X-ALD patients showed that DHEA supplementation for 3 months did not lower plasma levels of VLCFA [17]. Other testosterone metabolites were shown to increase peroxisomal β-oxidation and reduce the accumulation of VLCFA in X-ALD fibroblasts [18].

The *ABCD2* promoter contains a DR-4 motif, which is recognized by the thyroid hormone receptors TRα and TRβ and serves as a thyroid hormone response element [19,20] (Fig. 1). Treatment of rodents with thyroid hormone (T3) resulted in *Abcd2* and *Abcd3* induction in the liver but not in the brain [19]. *Abcd2* induction was also observed in T3-treated oligodendrocyte cells but not in astrocytes. In human X-ALD fibroblasts, T3-dependent induction of *ABCD2* was transitory and correlated with an increase of peroxisomal β-oxidation and a decrease of VLCFA levels [19]. GC-1 or CGS23425, two thyromimetics specific of TRβ (avoiding cardiac side effects due to TRα activation), were shown to stably up-regulate *ABCD2* and *ABCD3* genes in human HepG2 cells and X-ALD skin fibroblasts [21]. Further studies in animals would be required to test their therapeutic potentialities.

The DR-4 motif is also a response element for the liver X receptor (LXR), the nuclear receptor for oxysterols [22] and overlaps with a sterol regulatory element (SRE), which binds SREBP [23,24]. This promoter region is therefore a convergence point for a complex cross-talk involving key players of the lipid metabolism (TR, LXR, SREBP) which are closely associated and whose expression levels and effects are mutually controlled (Fig. 1). Deiodinase 2, which converts T4 to T3, is repressed by natural endogenous LXR ligand 22(R)-hydroxycholesterol (22R-HC) [25]. Unliganded TRβ represses LXRα transactivation [26]. TRβ and LXRα modulate the expression of SREBP [27]. The *ABCD2* gene was found to be up-regulated by cholesterol depletion *via* SREBP in X-ALD fibroblasts [23]. Lovastatin treatment was reported to reduce cholesterol and saturated VLCFA levels in X-ALD patients [28] but failed to demonstrate clinical improvement [29]. Interestingly, cholesterol excess known to induce SREBP1c expression and to activate LXRα, resulted in a reduced hepatic expression of *Abcd2* in mice [24]. LXRα activation with the synthetic agonist T0901317 or 22R-HC was shown to interfere with SREBP1c-mediated activation of the *Abcd2* promoter [24]. Besides, polyunsaturated fatty acids (PUFA) were found to modulate the *Abcd2* hepatic expression in rodents [30]. PUFA are known activators of PPARα and modulators of cholesterol levels acting through SREBP inhibition and by antagonizing the activation of LXRα by oxysterols [31].

From these different results, it became clear that molecules capable of inhibiting the LXR pathway would have an interest in the context of X-ALD. The LXR antagonist GSK(17) (GSK1440233A, compound 17) was identified from a screening of GlaxoSmithKline compound collection [32]. Another LXR antagonist, 22(S)-hydroxycholesterol (22S-HC), was described to reduce lipogenesis and free cholesterol [33,34]. Both molecules were shown to moderately induce the expression of *ABCD2* in HepG2 hepatoma cells and X-ALD skin fibroblasts [35]. This study confirmed that 22R-HC down-regulates *ABCD2* expression in both cell types. Interestingly, both *ABCD3* and *CTNNB1* genes (the gene encoding for β-catenin) were induced by LXR antagonists. β-catenin and TCF-4, important components of the Wnt/β-catenin signaling pathway, were recently described as inducers of the *ABCD2* expression [36]. A functional TCF binding element (TBE) was indeed characterized in the promoter of *ABCD2*. Since the Wnt components are repressed by oxysterols [37,38], the induction of *ABCD2* upon treatment with LXR antagonists could be a direct consequence of LXR antagonization on the promoter of *ABCD2* and/or the result of the indirect activation of β-catenin expression (Fig. 1). Besides, LXR antagonists were shown to decrease oxidative stress in X-ALD fibroblasts while 22R-HC treatment resulted in increased reactive oxygen species production [35]. Oxidative stress changes may result from the moderated alterations observed in monounsaturated fatty acid levels as a direct consequence of the induction of *ABCD2* and stearoyl-CoA desaturase-1 expression. Activation of the Wnt/β-catenin pathway whose role in liver protection against oxidative stress has previously been demonstrated [39] may be considered as an alternative

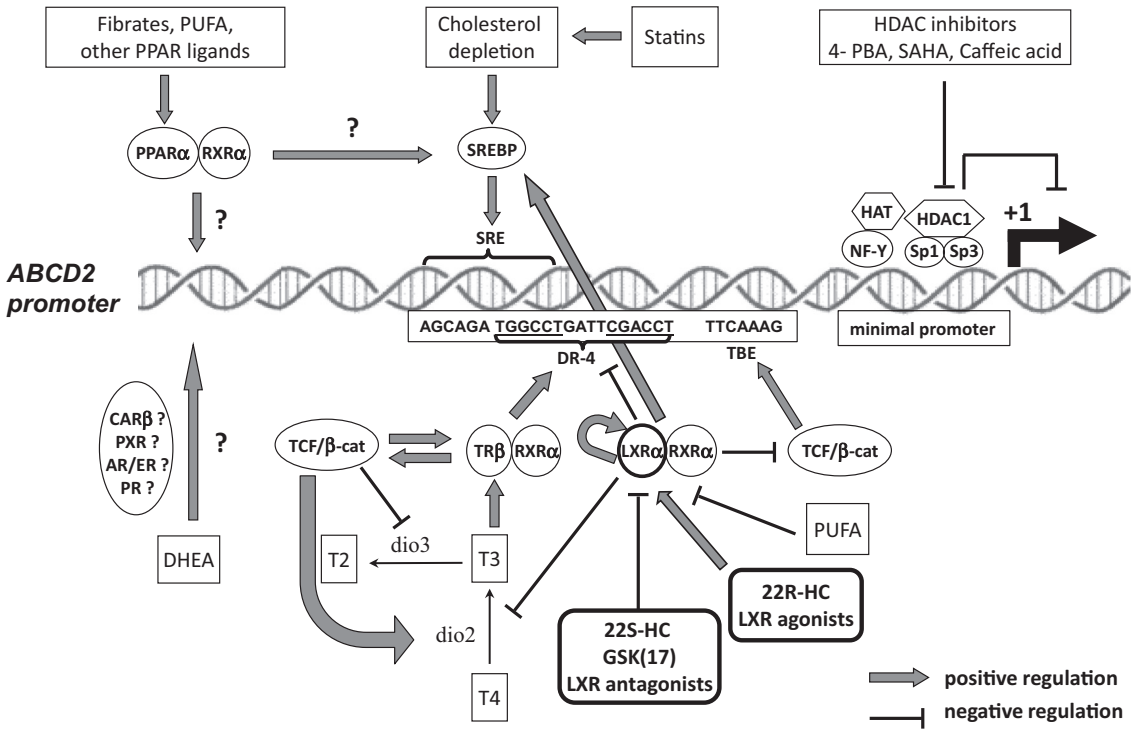

Fig. 1. Schematic representation of the transcriptional regulation pathways occurring on the *ABCD2* promoter and their crosstalks. Hormones, pharmacological and synthetic regulators or endogenous regulators and their associated transcription factors are presented. LXR agonists such as 22R-HC repress the *ABCD2* promoter through the DR4 motif while LXR antagonists (22S-HC, GSK(17)) activate the *ABCD2* promoter.

hypothesis. *In vivo* analyses in rats treated with 22S-HC confirmed the positive effect of LXR antagonists on the expression levels of *Abcd2*, *Abcd3*, and *Ctnnb1* in the liver [35]. Further experiments are needed to analyze the effects in the brain.

3. Endogenous and synthetic LXR antagonists

Given the critical role of LXR in cholesterol metabolism, glucose homeostasis, inflammation and lipogenesis, pharmaceutical companies have focused their efforts on LXR agonists. It is therefore not surprising that very few compounds with antagonistic activity have been identified or developed. Nevertheless, the clinical application of LXR agonists for the treatment of the metabolic syndrome is currently limited by the fact that they activate triglyceride synthesis via LXRα. Combination of LXRα/β agonists with a LXRα-selective antagonist may overcome this side effect.

Therefore, in recent years, increasing efforts have been devoted to discovering LXR antagonists for the potential treatment of fatty liver disease, diabetes, obesity, hypertriglyceridemia and inflammation [40]. Several natural antagonists have been identified. For instance, guttiferone selectively binds to LXRα without provoking the recruitment of co-activators [41]. Riccardin C and F act as LXRα agonist/LXRβ antagonist and LXRα antagonist respectively [42]. Geranylgeranyl pyrophosphate, one of the major products of the mevalonate pathway, possesses an antagonizing activity, which is equally potent to LXRα and LXRβ [43]. Several PUFA, especially arachidonic acid, are competitive natural antagonists of both LXR isoforms [31]. Among cholesterol derivatives, the 5α,6α-epoxycholesterol as well as sulfated oxysterols (5α,6α-epoxycholesterol-3-sulfate and 7-cetocholesterol-3-sulfate) have been described as LXRα antagonist [44,45].

In addition to GSK(17) and 22S-HC, several other synthetic compounds have been found to inhibit lipogenesis and protect against hepatosteatosis such as fenofibrate ester [46], piperine [47] and SR9238 [48]. A series of dual LXRα/β antagonists (benzenesulfonamides) designed by converting an existing agonist using a structure-based approach led to identification of the compound 54, a potent cell-active antagonist [49]. In the same way, a structure-based design, synthesis, and biological evaluation of a novel series of LXR ligands, identified the compound 48 to have a potent trans-repressional activity [50]. Structural development of LXR antagonists derived from thalidomide-related glucosidase inhibitors led to obtain the dual LXRα/β antagonist 5CPPSS-50 [51] and the LXRα-selective antagonist PP2P [52]. A multi-template approach based on thalidomide led to another potent LXRα-selective antagonist (23f) [53].

4. Neurodegenerative disorders and LXR antagonists

To find an indication for neurodegenerative disorders such as X-ALD, LXR antagonists have to cross the blood–brain barrier as it has been shown for 22S-HC [33]. To date, the patent applications for LXR antagonists did not mention any LXR antagonist useful for neurodegenerative disorders [40]. In addition, among the short list of LXR antagonists, a few have been subjected to biological evaluation. On the contrary, several studies have demonstrated the benefits of LXR agonists for neural development [54] and on various inherited or acquired major neurodegenerative diseases [55]. In Alzheimer's disease mice models, LXRs agonists have been shown to decrease amyloidogenesis and neuroinflammation [56]. In NPC1 mice, LXR activation resulted in increased cholesterol excretion from the brain, decreased neuroinflammation, and deactivation of microglia to slow neurodegeneration and extend the lifespan [57]. Altogether, in spite of side effects mainly due to pro-lipogenic effects and context-dependent pro- or anti-inflammatory effects, LXR agonists are considered as potential therapeutic drugs for neurodegenerative disorders [55]. Therefore, it may appear highly speculative to consider that LXR antagonists may

be beneficial in the context of neurodegenerative disorders. However, it has been shown that LXR agonists inhibit peripheral myelin gene expression in Schwann cells by inhibiting the Wnt/β-catenin pathway [38]. Furthermore, the invalidation of LXR in mice enhanced expression of myelin genes in the sciatic nerve. Thus, LXR activation is not always desirable. LXR antagonists induce *ABCD2* and β-catenin expression and reduce oxidative stress [35]. Provided that similar effects were found in brain cells, LXR antagonists may therefore have benefits in the context of X-ALD. Noteworthy, a recent study on the effects of LXR activation either in Schwann cells or in oligodendrocytes and central nervous system showed that LXR activation can lead to opposite effects depending on the cell type [37]. Moreover, the nature of the LXR ligands can trigger unexpected divergent effects depending on the context. For instance, 5α,6α-epoxycholesterol was shown to function as an antagonist on a number of classic LXR responsive genes. It was also shown to trigger agonist and inverse agonist activities in a cell and gene context-dependent manner [44].

5. Conclusion

Strategies aiming at inducing expression of *ABCD2* remain attractive in the context of X-ALD. An increasing number of studies have reported the characterization of novel and potent LXR antagonists that deserve further investigations to see their effects in brain. It is clear that LXR plays a major role in the regulation of *ABCD2* expression as illustrated by the inverse correlation between the expression levels of *ABCD2* and *NR1H3* (LXRα) genes in human tissues [35]. Obviously, it is not a strict correlation and the expression level of *ABCD2* cannot be restricted to a simple and unique dependency to LXRα. LXRβ as well as many other nuclear receptors and transcription factors participate in the regulation of *ABCD2* (Fig. 1). The possibility to combine pharmacological stimulation/inhibition of these regulatory pathways deserves a careful exploration.

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