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REVIEW ARTICLE

Regulations of Xenobiotics and Endobiotics on Carboxylesterases: A Comprehensive Review

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Abstract Carboxylesterases (CESs) play major roles in catalyzing the hydrolysis of a wide range of ester- and amide-containing compounds. CESs dominate both the biotransformation of numerous therapeutic drugs and the detoxification of environmental toxicants, and the activity alteration of CESs may be a determinant reason for modification of the resultant pharmacokinetic/pharmacodynamic profile when two or more drugs are concurrently used. Herein, we provide a comprehensive review of the current literature involving of induction and inhibition on CESs by both exogenous and endogenous compounds. In particular, the inhibition constant and inhibition pattern of inhibitors on CESs in studies using animal microsomes or human recombinant CESs are summarized. Further studies are needed to clarify the underlying regulation mechanism, and alterations in CESs activity should be taken into consideration for safe clinical therapy.

Key Points

CESs play vital roles in the metabolism of prodrugs.

CESs can be induced and inhibited by both exogenous and endogenous compounds.

Alteration of the CESs activity may lead to unexpected clinical outcomes.

1 Introduction

Carboxylesterases (CESs) are members of the α, β-hydrolase family, which is responsible for the metabolism and detoxification of a wide range of ester- and amide-containing compounds. Of particular clinical relevance, these enzymes participate in the biotransformation of numerous drugs and prodrugs including the antiplatelet drugs aspirin and clopidogrel [1], the ACE inhibitors delapril, imidapril and temocapril [2], and the antitumor drug irinotecan [3], among others. The CESs also play important roles in the detoxification of environmental toxicants, such as pyrethroids, which are a major class of insecticides used worldwide and extensively in the USA [4]. In addition to metabolism, the involvement of CESs in the fields of histochemistry, hematology, toxicology, pharmacology, therapeutics, as well as tumor cell killing, immune surveillance, and malignant diseases, has been greatly emphasized in recent years [5].

Several CES isozymes have been identified in mammals [6]. These isozymes are classified into five groups, denominated CES1 to CES5 according to the homology of their amino acid sequences. Among these groups, CES1 and CES2 are the major isoforms of CES and share 48 % sequence homology. CES1 family can be divided into eight subfamilies from CES1A to CES1H. The CES1A subfamily includes the major forms of human CESs, and the major isoforms of rat, dog and mouse CES [7]. The expression tissues and substrate selectivity of CES1 and CES2 differ. Human CES1 is highly expressed in the liver and may be detected in macrophages and human lung epithelia, heart, and testis [8]. CES1 mainly hydrolyzes substrates carrying small alcohol groups and large acyl groups, such as cocaine, meperidine, and

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delapril, whereas the CES2 enzyme is found in the small intestine, colon, kidney, liver, heart, brain, and testis [9, 10] and efficiently hydrolyzes compounds with large alcohol groups and relatively smaller carboxylate groups, such as heroin and 6-acetylmorphine [11]. CES3 includes ES-male and human CES3. The CES4 family is currently identified as CES family by Miyazaki et al. [12]. The CES5 family includes the 46.5 kDa CES isozymes, which present a structure different from those observed in other CES families [13].

CES activity can be influenced by a variety of compounds. Considering that CES enzymes are considered to be one of the major determinants of the metabolism and disposition of various substrates through their actions in the liver and intestine, alterations in the activity of CES enzymes are often important causes of drug interactions. Inhibition and induction of CES activity may result in modification of the pharmacokinetic/pharmacodynamic profiles of existing drugs via alteration of their half-life or toxicity. Therefore, investigation on the mechanism of CES regulation and exploration of the clinical implications of these compounds are considerably important. This review comprehensively discusses several types of potential inducers and inhibitors of CESs in detail, as well as pharmacogenetics of CESs, and provides ways to achieve the ultimate the goal of therapeutic improvement.

2 CESs Inducers

Both clinicians and researchers have shown considerable interest in the induction of expression of drug-metabolizing enzymes using chemicals, including drugs. CES activity was previously reported to be induced by phenobarbital (PB), Aroclor 1254, polycyclic aromatic hydrocarbons, synthetic glucocorticoids, pregnenolone-16α-carbonitrile (PCN), and clofibrate (CLOF) [14]. A number of new CESs inducers have recently been found. For instance, urethane dimethacrylate (UDMA) is a major dental resin monomer that often used to restore impaired tooth structure after polymerization. UDMA (0–0.25 mM) was found to stimulate CES2 mRNA expression in human dental pulp cells; however, no changes in CES1A1 or CES3 mRNA expression were found even at high concentrations of UDMA (0.1 and 0.25 mM) [15]. Another research reported that *bis*-phenol-glycidyl methacrylate (BisGMA) induced CES2 expression in human cultured dental pulp cells, but to a relatively lesser extent [16]. Hottori et al. [17] reported methylprednisolone hemisuccinate was hydrolyzed to methylprednisolone by CES in rat liver microsomes and that several clinically used glucocorticoids, including dexamethasone, caused a remarkable increase in hydrolytic activity of the compound.

Considering that CES is vital hepatic hydrolases contributing to approximately 80–95 % of the total hydrolytic activity in the liver, microsomal enzyme inducers (MEIs) would be ideal inducers. MEIs exert their effects on target genes through direct or indirect activation of transcription factors, such as the aryl hydrocarbon receptor (AhR), pregnane X receptor (PXR), constitutive and rostane receptor (CAR), peroxisome proliferator-activated receptor (PPAR), and nuclear factor erythroid 2-related factor 2 (Nrf2). Regulation of mRNA expression of CESs by 15 MEIs was previously examined in the liver of male C57bl/6 mice in vivo, and the data obtained demonstrated that the mRNA expression of the CES2 subfamily may be readily induced by the 1,4-*bis*[2-(3,5-dichloropyridyloxy)]benzene, PCN and oltipraz, which are CAR, PXR and Nrf2 ligands, respectively; by contrast, the expression of the CES1 subfamily was generally not altered by most MEIs. Antioxidant sulforaphane,*tert*-butylhydroquinone (tBHQ) and sensitizer trinitrobenzene sulfonate were reported to induce CES1 by activating Nrf2 in HepG2, Caco-2 and HeLa cells [18, 19].

Choi et al. examined whether p53 tumor suppressor, an important regulator of cellular response to chemotherapeutic agents, induces CES2 expression [20] and showed that 5-fluorouracil (5-FU), a p53 activator, induced CES2 expression in two colon carcinoma cell lines expressing wild-type p53. Irinotecan (CPT-11) is a commonly used chemotherapy drug for colon cancer and also a prodrug that is metabolized by CES2 in vivo into an active form SN-38. Increased expression of CES2 was shown to result in enhanced CPT-11-mediated cell-killing effects. Induction of CES2 by p53 exerts implications on the mechanisms of response and resistance to combination chemotherapy regimens including 5-FU and CPT-11.

3 CESs Inhibitors

Understanding and clarifying the mechanism of inhibition of CESs, which is recognized as a prevalent factor influencing drug interactions, is an important endeavor. Previously reported inhibitors of CESs include therapeutic drugs, pharmaceutical excipients and endogenous compounds, among others. The inhibition constant (K_i) values and inhibition type of inhibitors mentioned in the text are shown in Table 1.

3.1 Therapeutic Drugs

3.1.1 Antihyperlipidemic Drugs and Antidiabetic Drugs

In multiple drug therapy, drug interactions are important issues that must be taken into consideration. Given that

Table 1 Inhibitors, K_i values and inhibition types for CESs

Inhibitors	CES isoforms	Sources	K_i	Inhibition type	References
Mevastatin	CES1	Human	20.8 ± 8.8 μM	Non-competitive	[21]
Simvastatin	Recombinant CES1A1	Human	0.11 ± 0.01 μM	Mixed	[22]
	CES1 HLM	Human	0.76 ± 0.06 μM	Competitive	
	Recombinant CES2	Human	0.67 ± 0.09 μM	Non-competitive	
	CES2 HLM	Human	1.85 ± 0.28 μM	Non-competitive	
	CES2 HJM	Human	3.67 ± 0.49 μM	Non-competitive	
Troglitazone	Recombinant CES1A1	Human	0.62 ± 0.08 μM	Mixed	
	CES1 HLM	Human	5.64 ± 0.23 μM	Non-competitive	
Fenofibrate	Recombinant CES2	Human	0.04 ± 0.01 μM	Competitive type	
	CES2 HLM	Human	87.7 ± 12.0 μM	Non-competitive	
	CES2 HJM	Human	0.50 ± 0.06 μM	Competitive	
Carvedilol	CES1 RLM	Rat	1.6 ± 0.2 μM	Competitive	[24]
	CES1 RJM	Rat	8.8 ± 0.5 μM	Competitive	
	CES2 HLM	Human	1.6 ± 0.2 μM	Competitive	
Manidipine	CES2 RJM	Rat	0.8 ± 0.1 μM	Competitive	
Nordihydroguaiaretic acid	CES1 HLM	Human	13.3 ± 1.5 μM	Mixed	[24]
	CES1 RLM	Rat	0.4 ± 0.0 μM	Uncompetitive	
	CES1 RJM	Rat	11.0 ± 2.2 μM	Mixed	
Telmisartan	Recombinant CES1A1	Human	0.49 ± 0.09 μM	Competitive	[25]
	CES1 HLM	Human	1.69 ± 0.17 μM	Non-competitive	
Nitrendipine	Recombinant CES1A1	Human	1.12 ± 0.39 μM	Mixed	
	CES1 HLM	Human	1.24 ± 0.27 μM	Competitive	
Diltiazem	Recombinant CES2	Human	0.25 ± 0.02 μM	Non-competitive	
	CES2 HLM	Human	2.89 ± 0.39 μM	Non-competitive	
	CES2 HJM	Human	4.67 ± 2.12 μM	Mixed	
Verapamil	Recombinant CES2	Human	3.84 ± 0.99 μM	Competitive	
	CES2 HLM	Human	11.54 ± 1.20 μM	Non-competitive	
	CES2 HJM	Human	15.75 ± 2.63 μM	Non-competitive	
Nelfinavir	CES1	Human	3.7 ± 0.7 μM	Competitive type	[28]
Tamoxifen	CES1	Human	15.2 ± 2.8 μM	Non-competitive	[21, 30]
	CES	Rabbit	23.3 ± 14.3 μM	Non-competitive	
Vinblastine	CES2	Human	66.1 ± 6.1 μM	Non-competitive	[31]
Procainamide	CES1 HLM	Human	29.3 ± 4.8 μM	Competitive	[24]
Physostigmine	CES2 HLM	Human	0.2 ± 0.0 μM	Competitive	[24]
	CES2 HJM	Human	3.1 ± 0.2 μM	Non-competitive	
	CES2 RJM	Rat	2.5 ± 0.3 μM	Mixed	
Sodium lauryl sulfate	Recombinant CES1A1	Human	0.04 ± 0.01 μg/ml	Competitive	[43]
	CES1 HLM	Human	0.12 ± 0.03 μg/ml	Competitive	
Polyoxyl 40 hydrogenated castor oil	Recombinant CES1A1	Human	0.20 ± 0.09 μg/ml	Competitive	
	CES1 HLM	Human	0.76 ± 0.33 μg/ml	Competitive	
Tween 20	Recombinant CES2	Human	0.93 ± 0.36 μg/ml	Competitive	
	CES2 HLM	Human	2.2 ± 0.55 μg/ml	Mixed	
	CES2 HJM	Human	1.2 ± 0.33 μg/ml	Non-competitive	
Polyoxyl 35 castor oil	Recombinant CES2	Human	4.40 ± 1.24 μg/ml	Mixed	
	CES2 HLM	Human	20.54 ± 3.82 μg/ml	Competitive	
	CES2 HJM	Human	13.2 ± 2.0 μg/ml	Non-competitive type	
Loperamide	Recombinant CES2	Human	1.5 ± 0.14 μM	Competitive type	[38]

Table 1 continued

Inhibitors	CES isoforms	Sources	K_i	Inhibition type	References
27-Hydroxycholesterol	Recombinant CES1	Human	10 nM	Non-competitive	[47]
Arachidonic acid	Recombinant CES1	Human	1.7 μM	Non-competitive	

HLM human liver microsomes, *HJM* human jejunum microsomes, *RLM* rat liver microsomes, *RJM* rat jejunum microsomes, K_i inhibition constant, IC_{50} 50 % inhibitory concentration, *CES* carboxylesterase

patients with diabetes and hyperlipidemia frequently experience hypertension and heart failure, such patients are concurrently prescribed with antihypertensive, antihyperlipidemic and antidiabetic drugs. Fleming et al. [21] found that mevastatin, which is an antihyperlipidemic drug, inhibited o-nitrophenyl acetate hydrolysis by CES1A (K_i: 20.8 μM). Simvastatin, lovastatin and troglitazone have also been reported to inhibit the activity of recombinant human CES1A significantly; in particular, recombinant human CES2 activity was strongly inhibited by lovastatin and fenofibrate. Simvastatin and lovastatin contain lactone rings; stains with an open acid form such as pravastatin and fluvastatin did not show inhibition of CES1A enzyme activity. Thus, study results suggest that the lactone rings in simvastatin and lovastatin are important for inhibiting CES1A enzyme activity [22]. However, in contrast to this in vitro study, the lack of interaction in vivo in humans between enalapril and simvastatin and between ramipril and simvastatin has been reported [23]. In spite of this, the drug interaction should be taken into consideration.

3.1.2 Antihypertensive Drugs

Patients suffering from hypertension disease may be prone to heart failure, hyperlipidemia, or diabetes. These patients are concurrently treated with multiple medications, including antihypertensive, antihyperlipidemic, or antidiabetic drugs. A study in 2009 reported that CES2 activity from rat jejunum microsomes was inhibited by carvedilol and manidipine. Delapril and temocapril caused weak inhibition of CES1 (>50 % of control) in human liver, but over 90 % inhibition in rat liver [24]. We performed systematic studies assessing the potential of 17 antihypertensive drugs to inhibit CES enzyme activity in humans, and found that imidapril hydrolase activities by recombinant CES1A1 and human liver microsomes (HLM) were intensely inhibited by telmisartan and nitrendipine. CES2 activity was also substantially inhibited by diltiazem and verapamil [25].

3.1.3 Anti-Psychotic Drugs

The risk of adverse drug–drug interactions (DDIs) is present when metabolic inhibitors are combined with known or suspected substrates of a given enzyme. Dl-threo-methylphenidate (MPH) is the most widely prescribed medication for treating attention-deficit/hyperactivity disorder (ADHD) in children and also is a selective substrate of CES1. Mostly, ADHD patients receiving MPH regimens are often given other therapeutic drugs concomitantly. Zhu et al. [26] determined aripiprazole, perphenazine, thioridazine, and fluoxetine to be the potent human CES1 inhibitors through in vitro screening using cell lines; in this study, an IC_{50} value of 5.7 μM was obtained for aripiprazole. The results of a subsequent experiment conducted in animals were consistent with the in vitro observations, thus indicating that aripiprazole inhibits CES1. Hence, inhibition of CES1 by a number of agents studied may potentially produce a DDI between MPH and the concurrently administered drugs may contribute to the large variability often observed in MPH disposition, tolerability, and response.

3.1.4 Antiviral Drugs

Polypharmacy and the potential for DDIs are recognized as nearly inevitable consequences and risks associated with the current pharmacological management of HIV patients; thus, patients prescribed with multiple drugs are among the higher risk groups in terms of the potential for significant DDIs despite vigilant monitoring [27]. Nelfinavir was found to exhibit strong inhibition on human CES1 via a competitive mechanism with a K_i value of 3.7 ± 0.7 μM using cell lines over-expressing hCES1. Other protease inhibitors such as amprenavir, atazanavir, ritonavir and saquinavir showed less potent inhibition relative to nelfinavir [28]. Another antiviral drug adefovir dipivoxil was also reported to be an effective and reversible inhibitor in rat intestinal homogenates. This inhibitory action is due to the presence of alkyl esters in the structure as well as carbon chain length/double bonds in the drugs [29]. Clinician awareness and education with regard to drugs associated with clinically significant DDIs may be a critical and ongoing process.

3.1.5 Anticancer Drugs

Tamoxifen is the most widely used anticancer drug in the world, and the rat homolog of human CES1 was found to be one of only four liver proteins that bind tamoxifen with

high affinity. Studies show that tamoxifen is a micromolar affinity inhibitor of both human CES1 and rat CES [30]. Fleming et al. [21] also found that both recombinant human CES1 and rat CES were inhibited by tamoxifen in a partially non-competitive fashion, because the Z-site located directly "above" the active site may act as an allosteric site. Binding of tamoxifen to human CES1 could affect the efficacy of this chemotherapeutic agent.

Another anticancer drug docetaxel, which is not a CES substrate, weakly inhibited the imidaprilat formation in human liver. Vinblastine is a drug used to treat a number of cancer types, including: Hodgkin's lymphoma, non-small cell lung cancer, bladder cancer, brain cancer, and testicular cancer. Vinblastine has also been reported to show potent inhibition of recombinant human CES2 activity in vitro, with an IC_{50} values of 3.6 ± 0.2 μM, but not CES1 [31].

3.1.6 Antiarrhythmic Drugs

Both Bailey and Takahashi et al. found that the activity of CES1 in human liver microsomes was inhibited competitively by procainamide in vitro [24, 32]. A subsequent study conducted in rats reported that the activity of CES1 and the formation of imidaprilat were evidently inhibited by procainamide; these results were in accordance with in vitro findings [33]. Besides procainamide, another antiarrhythmic agent, quinidine, was also found to decrease the metabolism of meperidine through CES1 inhibition [32].

3.1.7 Anticholinesterase Drugs

Owing to the considerable structural similarity between CES and cholinesterase (ChE), physostigmine, a ChE inhibitor, was reported to be a strong CES2 inhibitor [24]. Rivastigmine and tolserine resulted in over 95 and 80 % inhibition of human liver CES in vitro, respectively, and the inhibition patterns observed were irreversible under the conditions employed [34]. Hence, administration of esterified drugs in combination with these carbamates may inadvertently result in decreased hydrolysis of the former, thereby limiting their efficacy.

3.1.8 Dexamethasone

Several researchers have found that the level of microsomal hydrolase activity to *p*-nitrophenyl acetate, the substrate of CES isozymes, was significantly decreased in rat liver microsomes in the presence of dexamethasone [35, 36]. We also found that the activity of CES1 in rat hepatocytes was inhibited by nanomolar amounts of dexamethasone and slightly elevated by micromolar dexamethasone. By contrast, the activity of CES2 was remarkably increased by micromolar dexamethasone [37]. These results may be of profound significance to patients receiving dexamethasone as a combination therapy, especially in a long-term clinical setting.

3.1.9 Loperamide

Loperamide is often required to treat chemotherapy-associated diarrhea, and it has been found to be a potent recombinant human CES2 inhibitor [38, 39]. Loperamide inhibits recombinant human CES2 activity, with a low IC_{50} value (0.1 ± 0.003 μM), but it moderately inhibits CES1 with IC_{50} values of over 100 μM [31]. Several anticancer drugs, such as capecitabine, are prodrugs that are catabolized by CES. Thus, DDIs may be taken into careful consideration when combining therapies with loperamide.

3.1.10 Sulfonamide Analogs

Sulfonamides analogs were previously demonstrated to be specific CES2 inhibitor sand yielded *K*i values for CES inhibition in the low nanomolar range with a partially competitive type in human intestinal microsomes; no inhibition of CES1 was observed at inhibitor concentrations of up to 100 μM [40].

3.2 Pharmaceutical Excipients

Pharmaceutical excipients are used to guarantee appropriate physicochemical and biopharmaceutical properties. However, these excipients must ideally not affect the intended therapeutic action of the active substance. Excipients such as polyoxyl 35 castor oil (EL35), Tween 80, and PEG 400 have been found to inhibit the activity of CYP3A4 in rat liver microsomes in vitro [41, 42]. Similarly, we tested the inhibitory effects of 25 pharmaceutical excipients on human CES1 and CES2 in vitro, and found that the imidapril hydrolase activities of recombinant CES1A1 and human liver microsomes (HLM) were strongly inhibited by sodium lauryl sulfate and polyoxyl 40 hydrogenated castor oil. Moreover, the enzyme hydrolase activity of recombinant CES2 was substantially inhibited by Tween 20 and EL35 [43]. Thus, additional caution is needed when two or more excipients are used together, or when patients receive more than two medications simultaneously, because such individual excipients may act synergistically.

3.3 Endogenous Compounds

3.3.1 Interleukin-6

Cytokines, such as interleukin-6 (IL-6), have been shown to downregulate the expression of a variety of drug-metabolizing enzymes. In both primary hepatocytes and HepG2 cells, treatment with IL-6 decreased both mRNA and protein expression of human CES1 and CES2 by as much as 60 %. In addition, pretreatment with IL-6 repressed the hydrolysis of various ester therapeutic agents (e.g., clopidogrel) by CES1 and CES2 toward and then altered the cellular responsiveness [44].

3.3.2 Hepatocyte Growth Factor (HGF) and Epidermal Growth Factor (EGF)

Hepatocyte growth factor (HGF) and epidermal growth factor (EGF) induce the differentiation, proliferation, and migration of cancer cells, and are therefore counterproductive to the successful treatment of cancer. A previous study showed that HGF downregulated the expression of cytochrome P450 (CYP) isozymes in human hepatocytes [45]. Similarly, HGF was reported to suppress the formation of SN-38 from CPT-11 in HepG2 cells, which resulted from a decrease in CES2. Thus, HGF may alter the metabolism of CPT-11, thereby resulting in reductions in the cytotoxicity of the drug [46]. A reduction in cytotoxicity attenuates severe adverse effects but leads to poorer prognosis and failure of chemotherapy with CPT-11. Thus, HGF could be useful as a predictor of clinical resistance in CPT-11-based chemotherapy.

3.3.3 Oxysterols and Fatty Acids

CES1 is abundantly expressed in the human liver and monocytes/macrophages, including the THP1 cell line, whereas CES2 is expressed in the liver but not in monocytes/macrophages. The cholesteryl ester hydrolysis activity in human macrophages has been attributed to CES1. Oxysterols are oxidized forms of cholesterol produced both enzymatically and non-enzymatically via the auto-oxidation of cholesterol. Oxysterols and fatty acids are the metabolites of CES catalytic reaction. Crow et al. [47] found that 27-hydroxycholesterol (27-HC) is a potent inhibitor of CES activity ($IC_{50} = 33$ nM) with a partially non-competitive pattern in THP1 whole-cell lysates. By contrast, recombinant CES2 activity was not inhibited by 27-HC. Furthermore, unsaturated fatty acids were better inhibitors of CES1 activity than saturated fatty acids, whereas CES2 activity was unaffected by any fatty acid. Arachidonic acid (AA) was the most potent fatty acid inhibitor of recombinant CES1 with a non-competitive type; when it is not combined to albumin, exogenous AA penetrated intact THP1 cells and inhibited CES1. These findings suggest that CES activity of recombinant CES1, cell lysates, and intact cells can be impaired by naturally occurring lipids, which may compromise the ability of CES1 to both detoxify environmental pollutants and metabolize endogenous compounds in vivo.

3.4 The Chemical Substances and their Homologs

3.4.1 Organophosphate Compounds

CESs, among other serine hydrolases, are inhibited by covalent reaction of the active site serine residue with organophosphate compounds (oxons) [14]. Oxons are the bioactivated metabolites of organophosphorus pesticides and are formed mainly in liver following cytochrome P450 monooxygenase-catalyzed desulfuration. Saboori and Newcombe [48] previously showed that a CES protein, which was purified from human monocytes, could be inhibited by paraoxon treatment. In addition, chlorpyrifos oxon, paraoxon, and methyl paraoxon have been found to inhibit CES1 and CES2 activity in cell lysates in a concentration-dependent manner with nanomolar IC_{50} values [49, 50]. However, CES1 protein expression in cells was unaffected by 24 h paraoxon treat, which suggested that reduced hydrolytic activity may be due to covalent inhibition of CES1 by oxons and not to downregulation of expression [49].

3.4.2 Flavonoid and its Analogs

Wei et al. [51] examined the inhibitory activities of 19 synthesized phosphorylated flavonoids and 10 parent flavonoids against porcine liver CES by determining the rate of hydrolysis of p-nitrophenyl acetate (PNPA). The phosphorylated flavonoids inhibited CES effectively and irreversibly with IC_{50} values in the nanomolar range. Ethyl phosphorylated flavonoids were relatively more potent than the methyl counterparts, whereas naturally occurring flavone glucoside exerted extremely weak to no inhibitory activity on CES. Another flavonoside, flavone-3,4,7-trihydroxy-3-methoxy-7-glucoside, which is isolated from a medicinal plant *Deverra scoparia,* was also found to be a potent competitive inhibitor of porcine liver CES with a K_i value of 16 μM in vitro [52]. Therefore, flavonoids may be utilized as lead compounds in developing new drugs with low toxicity and modulating the activities of esterified drugs.

3.4.3 Nordihydroguaiaretic Acid

Nordihydroguaiaretic acid (NDGA) is an antioxidant compound found in the creosote bush. NDGA is known as

a potent CES inhibitor [53]. Imidaprilat formation from imidapril in rat and human liver was strongly inhibited by NDGA, both with uncompetitive inhibition [24].

3.4.4 Compounds Containing 1,2-Diones

Benzils, isatins, and 1-phenyl-2-pyridinylethane-1,2-diones, which belong to the family of 1,2-diones,are CES inhibitors [54, 55]. Benzil is a novel and potent CES inhibitor with a Ki value of 45 nM for hCE1. The drug was identified during screening to discover compounds that would inhibit CES activity to acid in anticancer drug efficacy [56, 57]. Benzil analogs and natural compounds containing 1, 2-diones also potently inhibit both CES1 and CES2. For example, tanshinones and *Salvia miltiorrhiza* root extracts were found to markedly inhibit human CES from liver and intestine following incubation with both pure compounds and the crude material; hydrolysis of the anticancer prodrug CPT-11 was also significantly reduced [58]. Therefore, remedies containing tanshinones may be avoided when individuals are prescribed esterified agents and patients should be warned of the potential DDIs that may occur with this material.

3.5 Other Substances

The bacterial endotoxin, lipopolysaccharide (LPS), induces the expression of proinflammatory cytokines such as tumor necrosis factor-α (TNFα) and IL-6 in the liver, thereby contributing to altered drug-metabolizing enzymes. Studies on HepG2 cells demonstrated that treatment with LPS decreased both the mRNA and protein expression of human CES1 and CES2. In addition, HepG2 cells pretreated with LPS, showed altered cellular responsiveness to ester therapeutic agents, including clopidogrel and irinotecan [59]. Our following in vivo experiment revealed that the metabolic activities of CES1 and CES2 were remarkably attenuated in immunological liver injury rats induced by LPS [60]. The mechanism for the repression of CES1 and CES2 by LPS is likely to involve activation of the p38MAPK–NF-κB pathway, and disruption of the function of PXR in the regulation of CESs.

4 Pharmacogenetics of CESs

Variations in drug-metabolizing enzymes genes can contribute to adverse drug reaction and increase sensitivity/resistance to drug treatment [61]. The majority of variations at the DNA level (over 90 %) are in the form of single-nucleotide polymorphisms (SNPs). CES1 and CES2 have recently emerged as important pharmacogenetic regulators of drug metabolism [62]. Alterations in CESs sequences could lead to variability in drug metabolism between patients [63]. It has been reported several CES1 SNPs such as rs2244613, rs8192935, rs3785161, rs71647871 and rs71647872, and affect the metabolism of dabigatran etexilate [64, 65], MPH [66], oseltamivir [67, 68], imidapril [69], and clopidogrel [70]. The CES2 SNPs A139T, rs72547531 and rs72547532 have been found to alter the metabolism of aspirin [1] and irinotecan [71]. These findings demonstrate the potential clinical utility of CESs polymorphisms and provide evidence for personalized tailoring of pharmacological therapies.

5 Conclusions

The CES family of enzymes is a key participant in the phase I drug metabolism process, and catalyzes the hydrolysis of a numerous number of structurally diverse drugs.

CESs are considered protective and detoxifying proteins partly because of their expression patterns. CESs tend to be located in the epithelia that are likely to be exposed to xenobiotics, and the plastic nature of the activate site that can accommodate substrates of widely differing structures. Besides their interesting biochemistry, CESs are also vital to the biomedical field; they are involved in the transformation of numerous drugs, conversion of pro-carcinogens into carcinogens, and detoxification of pyrethroids, a major class of insecticides used worldwide and extensively in the US.

Previous studies have reported that the activity of CESs can be affected by numerous compounds. CESs can be induced by PB, PCN, CLOF and several microsomal enzyme inducers. Compared with the induction, CESs were inhibited by numerous kinds of therapeutic drugs, such as anti-psychiatric drugs, antihyperlipidemic drugs, antidiabetic drugs, antihypertensive drugs, antiviral drugs, and anticancer drugs, and pharmaceutical excipients, endogenous compounds such as IL-6, oxysterols, and fatty acids and chemical substances. Considering that a significant number of drugs are metabolized by CESs, alteration of the enzyme activity presents important clinical implications. Drug efficacy can be decreased and the incidence of DDIs may increase when two or more drugs compete for hydrolysis by the same CES enzyme.

Moreover, the presence of functional genetic variants of CES1 and CES2 are reported to influence the pharmacokinetic and pharmacodynamics properties of several drugs, and it also should be taken into consideration to improve clinical pharmacotherapy.

Most available reports do not describe the related mechanism of regulation of CESs activity. Certain factors influence CESs activity, either directly or at the expression

level of enzyme regulation. Several compounds containing the carbamate moiety have recently been developed as pharmaceutical agents specifically targeting individual members of the serine hydrolase family. Thus, inhibition of CESs by these compounds may occur as a result of covalent modification of the active site serine residue of the enzyme. The expression levels of CESs are tightly controlled by nuclear receptor (NR) proteins, PXR and CAR. PXR and CAR proteins are two closely related members of this superfamily. Both proteins function as ligand-activated transcription factors by interacting with retinoid X receptor-a (RXRa, NR2B1) on response elements located at the control regions of specific genes that these proteins regulate. CES enzymes are also regulated by other NR proteins, such as hepatocyte nuclear factor-4a (NR2A1), PPAR-a (NR1C1), and glucocorticoid receptor (NR3C1) [72]. As CES enzymes perform vital functions in the metabolism and disposition of numerous prodrugs through their actions in liver and small intestine, elucidating the mechanism governing the regulation of CES enzymes expression and activity by NR proteins will significantly impact rational drug design and the future development of prodrugs.

Considering that most studies were conducted in vitro and in vivo using animal models, the available clinical reports are still inadequate. Future research may focus on using in vitro experimental data to predict in vivo results, and more clinical studies are needed to provide better information for predicting DDIs based on CESs.

The substrate specificity of CESs toward new prodrugs under consideration may be examined by using a purified CESs mammalian cell expression system, or specific inhibitors and immunochemical inhibition studies. However, considering the sophisticated metabolism of drugs in vivo and the complexity of physiological factors, such in vitro experiments may not be applicable to predictions of in vivo results. Physiological comparisons based on the pharmacokinetic and kinetic parameters of prodrugs among mammalian species must be performed. Further elucidation of inter-individual variations of CESs in clinical human studies will probably provide important information for predicting DDIs based on CESs.

Compliance with Ethical Standards

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Conflict of interest YX, CZ, WH and DL have no conflicts of interest that are directly relevant to the content of this review.

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